Systematic Review of Preconception Risks and Interventions

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Content

List of Acronyms

AEP	Alcohol-exposed Pregnancy
AIDS	Acquired Immunodeficiency Syndrome
ALL	Acute Lymphoblastic Leukemia
ATD	Anti-thyroid Drugs
AMSTAR	Assessment of Multiple Systematic Reviews
BLDS	British Library of Development Studies
BI	Birth Interval
BMGF	Bill and Melinda Gates Foundation
BMI	Body Mass Index
CDC	Centres for Disease Control and Prevention
CDH	Congenital Diaphragmatic Hernia
CF	Cystic Fibrosis
CHD	Congenital Heart Defects
CHNRI	Child Health and Nutrition Research Initiative
CHOICE	CHOosing Interventions that are Cost Effective
CI	Confidence Interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CL/P	Cleft lip with or without cleft palate
CMV	Cytomegalovirus
CPO	Cleft palate only
cRCT	Cluster Randomized Controlled Trial
DALY	Disability Adjusted Life Years
DCP2	Disease Control Priorities in Developing Countries
DM	Diabetes Mellitus
DPT	Diphtheria, Pertusis and Tetanus
D&C	Dilation and Curettage
ETS	Environmental Tobacco Smoke
FASD	Fetal Alcohol Spectrum Disorder
FGD	Focus Group Discussion
FGM	Female Genital Mutilation
FIMK	Fetal and Infant Mortality Review
FSW	Female Sex Worker
GDM	Gestational Diabetes Mellitis
GIV	Generic Inverse Variance
GRADE	Grades of Recommendation, Assessment, Development, and Evaluation
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
HR	Hazard Ratio
HTN	Hypertension
ICU	Intensive Care Unit
IDA	Iron-deficiency anemia
IFA	Iron and Folic Acid
IPI	Inter-pregnancy Interval
IPV	Intimate Partner Violence
IUGR	Intra-uterine Growth Retardation
LBW	Low Birth Weight
LGA	Large for Gestational Age
LiST	Lives Saved Tool

MD	Mean Difference
MESH	Medical Subject Headings
MNCH	Mother, Newborn and Child Health
MNH	Maternal and Newborn Health
MoH	Minstry of Health
MVA	Manual Vacuum Aspiration
NICU	Neonatal Intensive Care Unit
NTD	Neural Tube Defect
NS	Non Significant
OCP	Oral Contraceptive Pills
OFC	Orofacial Clefts
OR	Odds Ratio
PCC	Pre Conception Care
PKU	Phenylketonouria
PMNCH	Partnership for Maternal, Newborn and Child Health
PPD	Post Partum Depression
PPH	Post Partum Hemorrhage
PRoM	Premature Rupture of Membrane
PTB	Preterm birth
RCT	Randomized Controlled Trial
RH	Reproductive Health
RPS	Research Priority Score
RR	Relative Risk
SD	Standard Deviation
SGA	Small for Gestational Age
SIDS	Sudden Infant Death Syndrome
SLE	Systemic Lupus Erythematosus
STD	Sexually Transmitted Diseases
STI	Sexually Transmitted Infections
STROBE	Strengthening the Reporting of Observational studies in Epidemiology
TLD	Trasverse Limb Defects
UNFPA	United Nations Fund for Population Activities
UTI	Urinary Tract Infection
WHO	World Health Organization
WMD	Weighted Mean Difference
WWE	Women with Epilepsy

Core Report

Background

In recent years, there has been increasing awareness of the persistent burden of maternal, newborn, and child mortality globally. Worldwide, over 350,000 women of childbearing age die every year due to complications of pregnancy and child birth, while over 15 million suffer long-term illness or disability.[1] The risks of adverse pregnancy outcomes are much higher in poor countries as compared to developed countries of the world. In Northern Europe, the risk of pregnancy-related maternal mortality is 1 in 30,000 as opposed to 1 in 6 in the developing world. The majority of maternal deaths occur during labor, delivery, and the immediate postpartum period, with obstetric hemorrhage being the main medical cause of death. Other causes of maternal mortality include hypertensive diseases, sepsis/infections, obstructed labor, and abortion-related complications, etc. In sub-Saharan Africa, the combined maternal mortality ratio for severe bleeding, hypertensive diseases, and infections is almost 500 deaths per 100,000 live births, compared with fewer than 300 per 100,000 in South Asia and 4 per 100,000 in developed nations.[2]

Given the burden of maternal mortality and morbidity, it is important to cast light on the global picture of neonatal survival. Every year an estimated 3.6 million newborn infants also die in the first four weeks of life.[3] Of these, maternal health complications contribute to at least 1.5 million neonatal deaths during the first week of life and 1.4 million stillborn babies.[1] Globally, the main direct causes of neonatal death are estimated to be preterm birth, severe infections, and asphyxia. Low birth weight and maternal complications also carry a high risk of neonatal death.[3]

To address Millennium Development Goals 4 and 5, several efforts have been made to identify interventions and strategies to improve maternal and neonatal health indicators and bridge the yawning equity gap between countries and various sections of the population therein. The *Lancet Newborn Survival Series* (2005) principally focused on pregnancy and newborn interventions and identified 16 interventions with proven efficacy on newborn survival, that were combined into packages at various levels of the health system.[4] In the *Lancet Maternal Survival Series* (2006), it was emphasized that although there are numerous outcomes for maternal health it is most important to focus on the outcome of maternal mortality, especially in areas with high burden. In recent years, the focus has shifted from delivering single interventions to delivering packaged treatment strategies with high coverage in the hope of decreasing this growing burden. Considering the epidemiology of maternal deaths, a health centre intrapartum-care strategy can be justified as the best way to bring down high rates of maternal mortality.[5]

Another major cause of concern is undernutrition among women of reproductive age. Maternal short stature and iron deficiency anaemia increases the risk of death of the mother at delivery, accounting for at least 20% of maternal mortality. Attention to nutrition through adequate dietary intake and supplementation with iron, folate, and possibly other micronutrients and calcium are likely to be of value.[6] The *Lancet Maternal and Child Undernutrition Series* (2008) focused on interventions such as promotion of breastfeeding, strategies to promote complementary feeding, micronutrient interventions, general supportive strategies to improve family and community nutrition, and strategies to reduce the burden of infections like malaria in pregnancy. Results revealed that strategies for breastfeeding promotion have a large

effect on survival. Management of severe acute malnutrition according to World Health Organization (WHO) guidelines reduced the case-fatality rate by 55%.[7]

Subsequent series have also attempted to assess the potential of maternal, reproductive health and nutrition-related interventions with an effort to also integrate service delivery at the primary care level. While there have been several efforts at defining strategies for maternal, newborn, and child survival and development in recent *Lancet* series and other publications,[4, 5, 7-9] there have been relatively few efforts to identify synergies and integrate these interventions across the continuum of care.[10, 11] Some reviews in the past have also evaluated the cost-effectiveness of individual interventions[12-14] and intervention packages.[13] Most of these reviews have focused on pregnancy and post-pregnancy preventive and therapeutic interventions for improved maternal, fetal and neonatal health outcomes. Early preconception care has however, not received adequate attention, and in many cases, has remained unaddressed.

There is growing awareness of the importance of the pre-conception period (that aim to identify and modify biomedical, behavioral, and social risks to a woman's health or pregnancy outcome through prevention and management, emphasizing those factors which must be acted on before conception or early in pregnancy to have maximal impact) and efforts have been made to increase awareness and promote health right from childhood and adolescence onwards.[15-23] Recent research has established linkages of preconception interventions with improved maternal, perinatal and neonatal health outcomes and it has been suggested that several proven interventions recommended during pregnancy may be even more effective if implemented before conception. To illustrate, children born 36 to 41 months after their next older sibling have a lower risk of neonatal, and infant death as well as a lower risk of maternal mortality, third trimester bleeding, and premature rupture of the membranes, puerperal endometritis, and anemia compared to births spaced 9 to 14 months apart. Apart from birth spacing, preventing teenage pregnancy is also an important factor for reduced perinatal mortality. Young mothers are not often physically mature enough to deliver a baby, leaving her and her child at risk for death or disabilities from obstructed labor, fistula, premature birth, or low birth weight. Undernutrition is also an important area of concern for women of reproductive age living in developing regions. Maternal short stature and iron deficiency anemia increases the risk of death of the mother at delivery, accounting for at least 20% of maternal mortality. Attention to maternal nutrition through adequate dietary intake in pregnancy and supplementation with iron, folic acid, iodine, and possibly other micronutrients and calcium are likely to be of value.[24] Although the value of peri-conceptional folic acid supplementation for the prevention of neural tube defects is well recognized, relatively few systematic efforts have been made to define the evidence base for key interventions that could be implemented pre-conception and impact on maternal, perinatal and neonatal health outcomes. The findings from our review have generated much needed evidence synthesis in this area, and complemented existing literature.

In the second phase, we will identify key gaps in knowledge and priority areas for research. This information will assist in the development and implementation of an integrated agenda for maternal, perinatal and neonatal health for BMGF and other agencies.

Objectives

The specific objectives of the two phases of this systematic review are to:

In Phase I

- Collate and synthesize relevant information on interventions available during the preconception period by using standard methods to
  - Identify interventions and their effectiveness when delivered during the preconception period on maternal, perinatal and newborn outcomes.
  - Undertake a qualitative evaluation of factors associated with community-based platforms and integrated strategies/packages targeting preconception interventions for improved maternal, perinatal and neonatal outcomes.

In Phase II

- Develop the framework for undertaking cost-effectiveness analyses of such selected preconception interventions for maternal, perinatal and neonatal outcomes.
- With the synthesized preliminary results and interim products, to consult with key stakeholders and experts to vet key findings, assess gaps and ideas for programmatic implementation or research
- Based on the above, development of an analytical summary of current evidence of intervention impact, research gaps and draft recommendations for including preconception care as part of the 'continuum of care' for MNCH and survival (using the Lives Saved Tool (LiST)).

Methods

Conceptual framework for considering risks and potential interventions

We developed a conceptual framework **Figure 1** to identify some of the potential linkages between preconception risk factors and potential interventions that may impact maternal, neonatal and child health outcomes. It proposes a process of delivering direct or indirect health care interventions that have a potential to identify or modify the biomedical, behavioral and social risk factors attached to pre pregnancy, pregnancy, intrapartum, neonatal and childhood illnesses.

In consonance with the advice received during the consultative process leading to this review we have approached the area of preconception interventions using a dual strategy of:

1. Evaluation of identified interventions which have been evaluated in experimental designs of varied configuration
2. Evaluation of clear risk factors for adverse outcome which could be ameliorated in the pre-conception and periconceptional period. As assessment was made of potential benefit if the risk factor(s) could be ameliorated.

Boundaries and Definitions

We defined ***preconception care***, and its boundaries as: "any preventive, promotive or curative health care intervention provided to women of childbearing age in the period before* (at least 2 years) and between consecutive pregnancies, to improve health related outcomes for women (regardless of their pregnancy status), newborns and children up to 5 years of age."

Social, cultural and environmental interventions	
Poverty alleviation	• School education programs • Employment • Cash transfers (conditional and unconditional), microcredit
Cultural	• Behavior modifications programs for community members • Women empowerment • Community support groups
Environmental	• Smoking and alcohol cessation programs • Prevention of drug abuse or amelioration strategies • Control of Indoor air pollution • Prevention of intimate partner violence

RISK FACTORS
Social Poverty, low status of women, illiteracy
Cultural Cultural taboos, dietary restrictions and manual labor
Environmental Smoking, alcohol consumption, crowding, poor ventilation and indoor air pollution, poor water/sanitation
Health system inadequate basic health care service
Biological nutritional deficiencies, high HIV/ AIDS and TB trends

Biomedical interventions	
Biological	• Prevention and Management of STIs and HIV/AIDS • Nutrition education & intervention programs (such as energy-protein supplements, iron and periconceptual folic acid or multiple micronutrients, calcium etc) • Birth spacing and family planning, including prevention of teenage pregnancy • Mental health programs • Life style modification programs (diet, exercise, smoking, and substance abuse cessation programs) • Counseling and management of oral conditions • Vaccinations (tetanus toxoid, influenza, pneumococcal vaccine
Health System Strengthening through training of health worker and upgrading of services	

Figure 1: Conceptual framework on preconception interventions and their impact on maternal, perinatal and neonatal outcomes

Pre Pregnancy Illness	During Pregnancy Illness	Intrapartum complications	Neonatal Illness	Infancy and Childhood illnesses
Poverty & illiteracy Low status of women Lack of health information Insufficient access to nutritious food and essential micronutrient Teenage pregnancy Indoor air pollution Intimate partner violence STIs and HIV/AIDS Smoking and alcohol consumption	Maternal anemia Micronutrient deficiencies during pregnancy Antenatal depression Complications of pregnancy like PIH and diabetes Infections during pregnancy Inadequate maternal health practices and care seeking	Obstetric complications Complications of abortion lack of SBA deliveries and institutional deliveries Perinatal deaths Maternal deaths	Newborn infections and HIV/AIDS Inadequate newborn health practices and care seeking Neonatal deaths	Childhood infections like pneumonia, diarrhea etc. Inadequate care seeking for childhood illnesses Infant deaths Malnutrition (stunting, wasting etc.) in children Impaired cognitive development in children U-5 mortality

*the period before pregnancy has been divided into a proximal and a distal period: by proximal, we mean interventions in the period immediately preceding pregnancy (up to 2 years prior to conception); and by distal, we mean interventions during adolescence or in general a longer time before pregnancy.

During literature appraisal, we also identified studies that delivered interventions during the periconceptional period and aimed to improve women's health and pregnancy outcomes. We included such studies because a few interventions have to be carried forward to after conception in order to extract maximum benefits. In contrast to pre-conception care, we defined ***periconceptional care*** as "any preventive, promotive or curative health care intervention provided to women of childbearing age preceding, including and immediately following human conception to improve health related outcomes for women, newborns and children up to 5 years of age." This definition allows for variability in operationalizing the lower and upper bound of the periconceptional window depending upon the nature of the intervention. It must be recognized that for many interventions spanning the periconceptional period the exact timing of the conception in relation to conception is uncertain. However, based on the interventions reviewed, we limited the lower bound of periconceptional care to 3 months before pregnancy and the upper bound to up to the first trimester.

The literature clearly shows that some maternal risk factors are rooted in childhood and adolescence. For instance, young girls who are undernourished may become stunted, and maternal short stature is a risk factor for obstetrical intervention, maternal mortality and childhood mortality. Therefore it is necessary that preconception intervention begins in adolescence ("distal" intervention) and continues throughout women's reproductive years ("proximal" interventions). Further, most women have more than one pregnancy, and the intervals between pregnancies ("interconception") should also be seen as an opportune time to promote the health of women and any children they might have in the future. **Figure 2** draws these concepts together, illustrating that healthy women are more likely to have healthy babies, who in turn, could become healthy mothers. Preconception care must therefore take a life course perspective and be modeled into the existing continuum of care for women's, maternal and child health.

Figure 3 takes the life course perspective one step further. The evidence shows that very young or advanced maternal age at conception is an independent risk factor for adverse MNCH outcomes, with the risk being minimum between the ages of 20 and 30. This is because certain risk factors predominantly influence women of a certain age- coerced sex is more common among teenage girls and genetic diseases are more likely to occur in women over the age of 35. It must be noted however that many risks and interventions apply to women throughout their reproductive years, such as suboptimal nutrition, infectious and chronic diseases.

In the box below (**Box 1**), we have listed down all the interventions that we targeted to assess their association with the preconception care.

Criteria for considering studies for this systematic review

Types of interventions

We considered all available published and unpublished papers/reports on the impact of preconception care interventions (individual or delivered in packages) on MNCH outcomes among women of reproductive age. Studies were included if (a) identified studies had delivered interventions or observed risk factors in preconception period and if b) the studies reported maternal, fetal or neonatal outcomes.

Figure 2. Defining the parameters of preconception care

Preconception: Preconception health care is recommended for women of child bearing age (14-49 years).
-It starts when a girl child reaches puberty – Distal Period Interventions
-It also includes care before the first pregnancy or between pregnancies (inter-conception care) – Proximal period Interventions

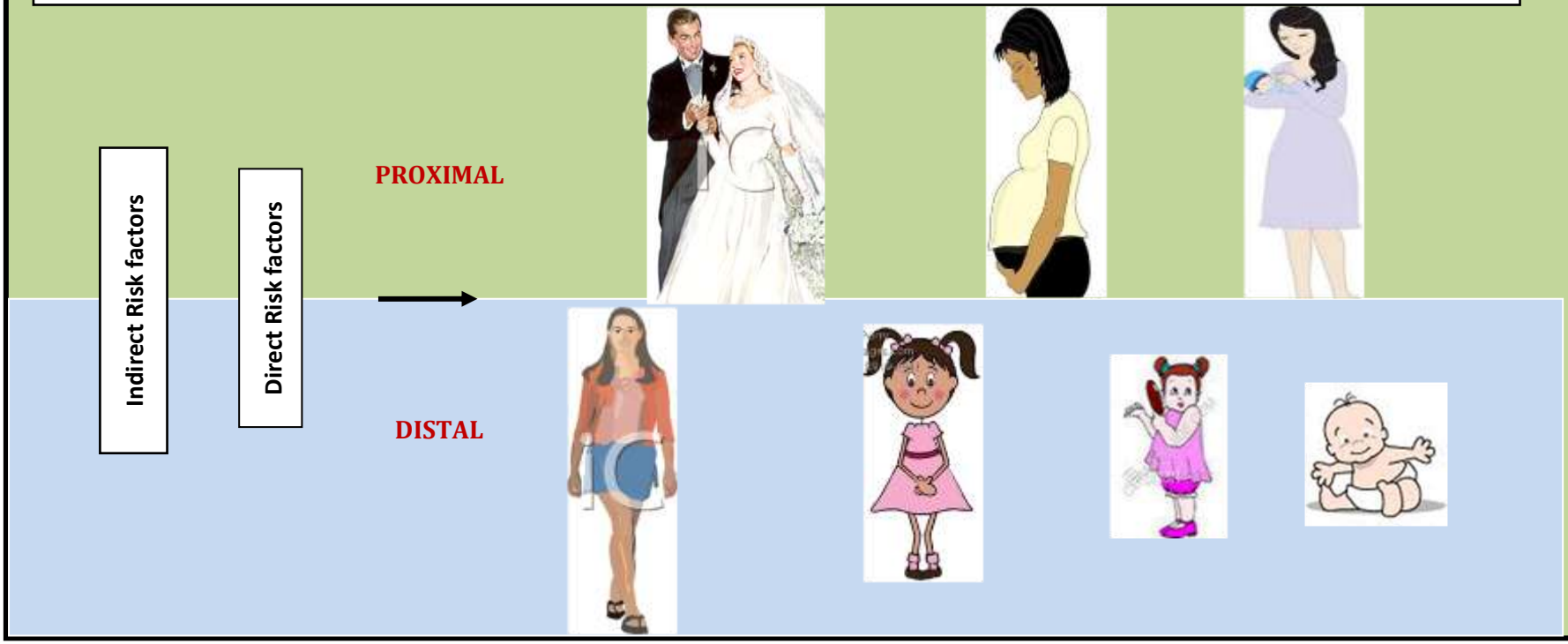
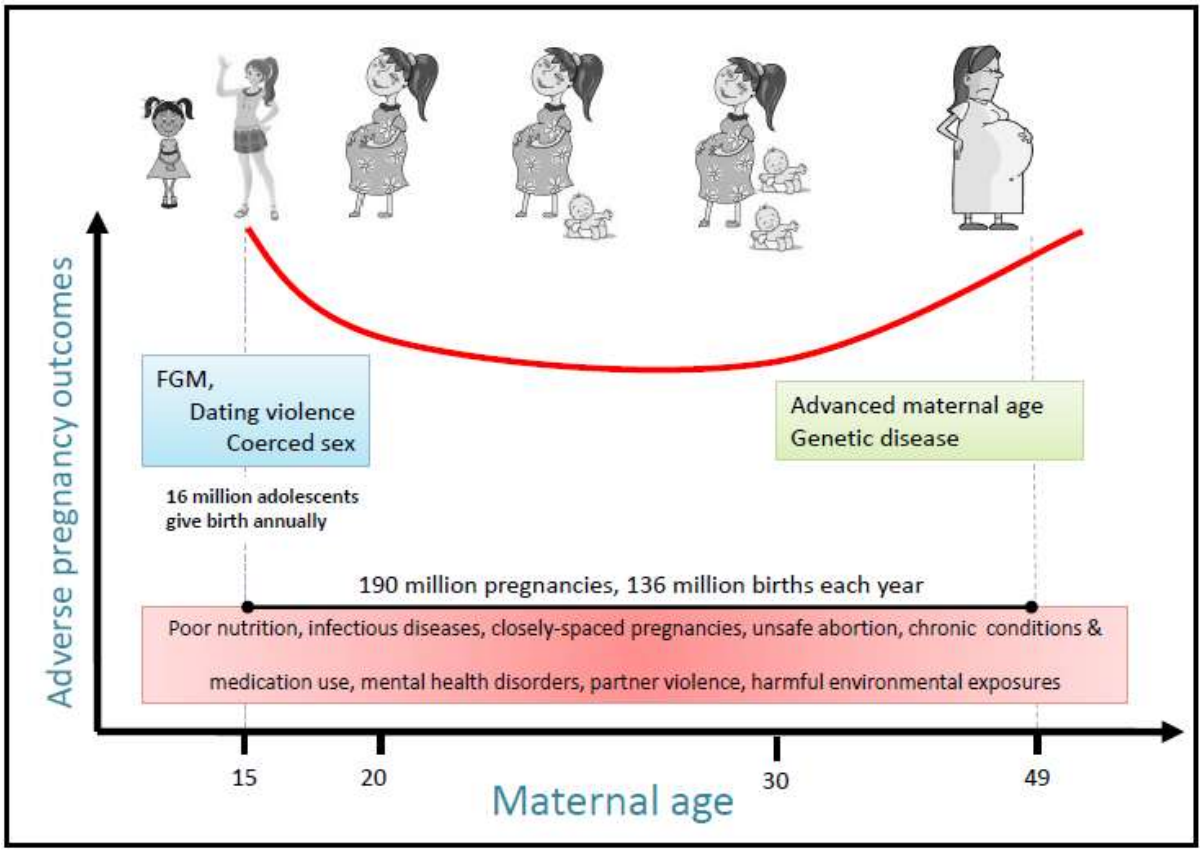


Figure 3: Advanced maternal age and adverse pregnancy outcomes



Our priority was to select existing reviews, randomized, quasi-randomized and before/after trials on the subject to generate effectiveness of preconception interventions. In addition, other less rigorous study designs like observational (cohort and case-control) and descriptive studies were also reviewed to understand the context within which they were implemented, the types of intervention delivered and reported results.

Search strategy

All available evidence for the impact of preconception interventions was systematically analyzed. The following sources of information were used to search literature for review:

1. All available electronic references libraries of indexed and non indexed medical journals and analytical reviews
2. Non-indexed journals not available in electronic libraries
3. Pertinent books, monographs, and theses identified through electronic or hand searching
4. Project documents and reports

The following principal sources of electronic reference libraries were searched to access the available data on preconception period: The Cochrane Library, Medline, PubMed, Popline, LILACS, CINAHL, EMBASE, World Bank's JOLIS search engine, CAB Abstracts, British Library for Development Studies BLDS at IDS, the World Health Organization (WHO) regional databases as well as the IDEAS database of unpublished working

Box 1: List of interventions targeted

Social, cultural and envi Interventions	Biomedical interventions		
Prevention from environment risks • Indoor air pollution • Overcrowding • Lack of water and sanitation • Counseling for teratogen exposure • Mercury exposure • Lead exposure • Soil and water hazards • Occupational/wor kplace exposure **Socio-cultural and financial risks** • Inequity • Poverty alleviation • School education program • Inadequate financial resources Healt**h systems-related ir** public finance strategies to increase access to preconception care	**Nutritional Interventions** • Nutrient intake • Folic acid/ iron / iron + folic acid • Vitamin A • Vitamin D • Calcium • Essential fatty acids • Counseling for obesity • Maternal nutrition • Multivitamins/multiple micronutrient • Iodine supplementation • Pyridoxine (Vitamin B6 supplementation) • Vitamin B12 supplementation • Vitamins (for epileptic mothers) **Prevention and Management of Infections** • Vaccination/immunization (Human papilloma virus – HPV; Hepatitis B; Varicella; Measles, mumps and rubella, influenza, Diphtheria-tetanus-pertussis – DPT)) • Management of STIs such as parvovirus, listerosis, gonorrhea, chlamydia, syphilis, bacterial vaginosis, herpes simplex virus • Management of HIV/ AIDS • Management of Hepatitis C • Treatment of Tuberculosis • Treatment of toxoplasmosis • Treatment of cytomegalovirus • Prevention and treatment of malaria • Treatment of other infections such as asymptomatic bacteruria, group B streptococcus **Contraception and Family planning** • Contraception • Prevention of teenage pregnancy Unwanted pregnancy and post abortion care	**Counseling for couple for detection of disorders** • Genetic screening • Counseling of pts with vasculitis • Couple counseling • Counseling for women with thrombophilia • Pre-conceptional counseling • Pre-conceptional genetic counseling **Interventions for other medical condi** • Management of DM • Connective tissue disease • Heart disease • Counseling with epilepsy/seizure • Thyroid disease • Screening for Cystic fibrosis • Phenylketonouria • Rheumatoid arthritis • Lupus • Renal disease • Thrombophilia • Asthma • Multiple sclerosis • Thalesemia major • Aspirin / Anticoagulants for women with APLA • Counseling for inflammatory bowel disease • Stem-cell and related therapies • Safe use of meds • Periodontal diseases and oral health • Cancer **Life Style Modification** • Reduce tobacco use • Smoking cessation • Illicit drugs • Reduce alcohol consumption • Work and exercise • Weight status • Eating disorders	**Poor prior outcome during pregnancy , birth or post-partum for mother or fetus/neonate** • IVIG in early pregnancy failure • Antenatal screening (for fragile X) • Immunotherapy (for recurrent miscarriages) • Inter-conceptional counseling after fetal loss • Counseling for pre-eclampsia • Prior preterm birth • Prior stillbirth • Prior miscarriages • Prior cesarean delivery **Psychological interventions** • Depression/ anxiety • Bipolar diseases • Schizophrenia • Stress reduction • Drugs (mood-stabilizing agents) • Domestic violence/intimate partner violence I**nfertility** • Lifestyle advice (for people with fertility) **General preconception care** • Routine pre-pregnancy health promotion **Special population** • Immigrants/ refugees • Disabilities **Men**

papers, Google and Google Scholar. Detailed examination of cross-references and bibliographies of available data and publications to identify additional sources of information was also performed. In particular, this search was extended to review the gray literature in non-indexed and non-electronic sources. We have also identified the papers on awareness project by CDC and preconception work by March of Dimes. The bibliographies of books with relevant sections were also searched manually to identify relevant reports and publications.

A broad search strategy was used that included a combination of appropriate key words, MESH and free text terms i.e. ("Preconception Care"[Mesh] OR “pre conception” OR “preconception” OR “prepregnancy” OR “pre pregnancy” OR preconceptional OR periconceptional OR "preconception care" OR "pre conception care" OR "pre pregnancy care" OR "prepregnancy care" OR "preconception health" OR "pre conception health" OR "pre pregnancy health" OR "prepregnancy health" OR “reproductive health” OR “before pregnancy” OR “women’s health”) AND (diabetes OR “heart disease” OR epilepsy OR seizure OR “thyroid disease” OR “connective tissue disease” OR lupus OR

cardiovascular OR nutrition OR weight OR supplement* OR “folic acid” OR folate OR iron OR multivitamin* OR micronutrient OR “prenatal vitamin*” OR obesity OR tobacco OR alcohol OR smoking OR “smoking cessation” OR drugs OR “substance use” OR medication* OR work OR exercise OR “physical activity” OR psychological OR behavioral OR stress OR “mental health” OR infection* OR vaccinat* OR immunization* OR immunization* OR genetic OR contraception OR “family planning” OR “teenage pregnancy” OR “unwanted pregnancy” OR infertility OR “sexually transmitted infection*” OR “sexually transmitted disease*” OR HIV OR AIDS OR periodontal OR “oral health” OR pollution OR “health care” OR healthcare OR “health visit” OR “maternal exposure” OR “environmental exposure” OR "maternal disease" OR "counsel*" OR screening OR "blood group” OR rhesus OR violence OR abuse OR “intimate partner violence” OR “health promotion” OR “health education” OR financial). Studies in languages other than English were included after relevant translation.

We also used the search strategies for individual interventions just to make sure that we captured all the literature pertinent to preconception interventions. Furthermore, vigorous hand search was used to target all published and unpublished work in the field.

Types of outcomes: The following is an illustrative listing of outcomes of interest

Maternal outcomes

- Incidence of antenatal complications: diabetes, pregnancy induced hypertension
- Proportion of neural tube defects and other congenital malformations identified
- Reported maternal behavior change: smoking, diet, alcohol or drug use
- Maternal nutrition status, iron deficiency anemia etc.
- Specific maternal infections in at-risk population (including HIV, other STDs, etc)
- Unwanted pregnancies as well as therapeutic abortion/Unsafe abortion related outcomes
- Maternal mortality
- Preterm birth (<37 weeks of gestation)
- Stillbirths (fetal death after 28 weeks of gestation but before delivery of the baby's head per 1000 total births)
- Post partum outcomes including postpartum hemorrhage, depression, infections and pregnancy within one year of previous childbirth

Neonatal outcomes

- Prematurity and intrauterine growth retardation, reported LBW (<2500g)
- Neonatal mortality (number of neonatal deaths from any cause among total live births)
  - Early neonatal mortality: neonatal deaths in the first week of life
  - Late neonatal mortality: neonatal deaths from 7 to 28 days of life.

Infant and child health outcomes

- Infant and under 5 mortality (where reported)

As contextual and program relevant information, we also specifically evaluated available information on delivery platforms for preconception care; mode of delivery; involvement of community members; involvement of community health workers, their

training, supervision and monitoring; and linkages to the health system, private sector care providers and communities, the role of mass media.

Data extraction: The project team set up a triage process with standardized criteria for evaluating outputs from the search strategy and primary screening. Following an agreement on the search strategy, the abstracts (and the full sources where abstracts not available) were screened by two abstractors to identify studies adhering to our objectives. Any disagreements on selection of studies between these two primary abstractors were resolved in discussion with the senior reviewer. After retrieval of the full texts of all the studies that meet the inclusion/exclusion criteria, each study was double data abstracted into a standardized form. (Data extraction sheets attached in **Annexure I and II**).

Data analysis

Pooled analyses

We performed statistical analysis of randomized, quasi-randomized controlled trials and prospective time series (before/after) studies using the Review Manager software. Data analysis of the outcomes was based on an intention-to-treat principle. For dichotomous data, we presented results as summary risk ratio (RR)/odds ratio (OR) (as quoted in individual studies) with 95% confidence intervals (CI). For continuous data, we used the mean difference (MD) between trials if outcomes are measured comparably. For analyzing and pooling cluster randomized trial data, the entire cluster was used as the unit of randomization and the analysis was adjusted for design.[25] The data of cluster-randomized trials were incorporated using generic inverse variance (GIV) method in which logarithms of RR estimates were used along with the standard error of the logarithms of risk ratio estimates.

Assessment of methodological quality of included studies

Available systematic reviews was assessed using the AMSTAR criteria (Assessment of the methodological quality of systematic reviews).[26] Randomized and quasi-randomized studies was assessed for risk of bias using the Cochrane criteria.[27] We also assessed the quality of prospective time series studies/pre-post trial and observational studies (including cohort, case-control and cross sectional designs) using the criteria adopted from Leovinsohn 1990,[28] and STROBE (Strengthening the Reporting of Observational studies in Epidemiology)[29] respectively. (Data extraction sheets attached in **Annexure I and II**).

Dealing with missing data and heterogeneity

The level of attrition was noted for each study and its impact on the overall assessment of treatment effect was explored by using sensitivity analysis. Heterogeneity between trials was assessed using the I-squared statistic, P value of <0.1 (on chi-square) and by visual inspection of forest plots. When high levels of heterogeneity between trials (exceeding 50%) was identified, further exploration was conducted by subgroup analysis. We initially undertook fixed-effects meta-analysis for combining data where trials examined the same intervention, but then repeated the analysis and applied random-effects meta-analysis as an overall summary because of substantial methodological heterogeneity between and among the studies. The differences in estimates from two sub-group meta-analysis were tested using the method described by Altman and Bland.[30] We performed some disaggregated analysis (quantitative) on

interventions delivered alone versus delivered in combinations, preventive versus therapeutic, interventions involving community mobilization and those delivered in community setup versus those in facility setup.

GRADE analyses

We performed further analysis of the quality of evidence related to each of the key outcomes in each preconception intervention using the GRADE (Grade recommendations for assessment, development and evaluation) approach.[16, 31, 32] Using this approach, we rated the quality of the body of evidence for each key outcome as 'High', 'Moderate', 'Low', or 'Very Low' (**Box 2**). (Data extraction sheets attached in **Annexure III and IV**).

Box 2: Criteria for determining quality of evidence of the included studies for each intervention

Quality of evidence	Study design	Lower quality when:	Higher quality when:
High	Randomized trial	• Serious (-1) or very serious (-2) limitation to study quality • Important inconsistency (-1) • Some (-1) or major (-2) uncertainty about directness • Imprecise or sparse data (-1) • High probability of reporting bias (-1)	• Strong evidence of association – significant relative risk of > 2 (< 0.5) based on consistent evidence from two or more observational studies, with no plausible confounders (+1) • Very strong evidence of association – significant relative risk of > 5 (< 0.2) based on direct evidence with no major threats to validity (+2) • Evidence of a dose response gradient (+1) • All plausible confounders would have reduced the effect (+1)
Moderate	Low-quality randomized trial or high-quality observational study		
Low	Observational study		
Very low	Any other evidence		

The final recommendations were, therefore, made according to the GRADE criteria using a two-step process. First the evidence was graded based on the quality of study design. The second step was to grade the evidence according to the following recommendations:

- **High**: Further research is very unlikely to change our confidence in the estimate of effect.
- **Moderate**: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- **Low**: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- **Very low**: evidence will not be included in our analysis.

Interventions with significant impact estimates for maternal, fetal and neonatal outcomes were assigned a group of A, which signified that the area does not require any further evaluation and can become a part of LiST intervention. While perceonception interventions that have some evidence (limited number of studies) on maternal, fetal, neonatal and their later life were assigned a category of B, which signified that this area still has some gaps and require further exploration and evaluation. We also identified a list of interventions that showed clear benefits during pregnancy and/or are never studied during preconception period and were labeled as C, which signified that these interventions definetly require evaluation during preconception period. We shall target these intervention categorizations for determining further Delphi assessments in Phase2.

Preconception intervention Groups

A	B	C
Interventions with significant impact estimates for maternal, fetal and neonatal outcomes Does not require any further evaluation, can be recommended for implementation	some evidence (limited number of studies) on maternal, fetal, neonatal and their later life were assigned a category of B Still has some gaps and require further exploration and evaluation	interventions that showed clear benefits during pregnancy and are never studied during preconception period Definitely requires evaluation during preconception period

This matrix was developed in order to aid us in identifying the causes and risk factors for maternal, fetal, neonatal, and infant mortality as well as stillbirths, which in turn would allow us to develop efficient and deliverable solutions.

Qualitative/descriptive analysis

The qualitative aspect was covered using Campbell/Cochrane Collaboration standards of systematic review and we employed a theory-based analysis to assess not only which interventions are effective, or not, but why and under what circumstances. Broadly, studies were categorized based on integrated intervention delivery models and then be analyzed on the factors it was built upon. These factors included interventions delivery mode (governmental or non-governmental organization); interventions delivery strategies (direct provision of care, management and referral of morbidities, behavior change communication and community mobilization strategies); and intervention delivery package (in package or alone). This helped us in identifying the components associated with effective models of delivery of integrated community based interventions and the factors associated with the program successes and failures.

Phase II

Cost effectiveness analysis

Several search terms will be combined with our initial search strategy to find literature in the field of cost and cost-effectiveness of preconception interventions for maternal, perinatal and neonatal outcomes. Literature search will be performed using the following thesaurus search terms: 'Costs & Cost Analysis' and 'Cost Benefit Analysis' (all subheadings) combined with 'different interventions' and with free text search (cost*; cost* and effect*; cost* and benefit; cost* and utility) i.e. ("Preconception Care"[Mesh] OR "pre conception" OR "preconception" OR "prepregnancy" OR "pre pregnancy" OR preconceptional OR periconceptional OR "preconception care" OR "pre conception care" OR "pre pregnancy care" OR "prepregnancy care" OR "preconception health" OR "pre conception health" OR "pre pregnancy health" OR "prepregnancy health" OR "before pregnancy" OR "reproductive health" OR "women health") AND (cost OR cost-effectiveness OR "cost effectiveness" OR cost-efficient OR "cost efficient" OR "cost benefit" OR "cost utility" OR benefit OR utility).

We also reviewed Disease Control Priorities Project (DCP2) website for relevant cost-effectiveness papers, and peruse papers on the subject published since. We separately analyzed all the studies pertinent to cost minimization, cost utility and cost effectiveness of preconception interventions. We analyzed the total cost (in USD) of interventions (including of recruiting and training personnel to deliver intervention, conducting sessions) delivered for maternal, perinatal and neonatal outcomes and the

cost per death averted and cost per case averted. We also used a WHO CHOICE model for undertaking a generalized cost-effectiveness analysis.[27]

Proposed Stakeholder consultations and Delphi Process

As the planned consultation process on review outputs and interim products, we undertook a two tiered standardized consultation process with key stakeholders and experts. This consisted of an initial open assessment for setting priorities in preconception health (**CHNRI method**) to elicit specific responses.

CHNRI Methods

The CHNRI methodology for setting priorities in health research investments had four stages: defining the context and criteria for priority setting with input from investors and policymakers; listing and scoring research investment options by technical experts using predetermined criteria (Box 1); weighting the criteria according to wider societal values with input from other stakeholders; and computation and discussion of the scores and agreement between experts.[33-35]

Stage 1: Define the Context and Criteria for Priority Setting

The aim of this particular exercise was to inform key global donors, investors in health research (especially of public funds), and international agencies about research investment policies related to preconception health that were expected to address MDG 4 and 5 in the most effective way. In addition, while focusing on preconception health, there are some expected beneficial effects of investments from such research on related outcomes such as maternal, fetal and neonatal morbidity and mortality and perhaps on the function of health systems and primary health care.

Stage 2: List and Score Research Options Using Predetermined Criteria

These experts in maternal, newborn and child health were carefully selected from around the globe representing key agencies and groups engaged in adolescent, maternal health, reproductive health and newborn care. These included agencies/organizations such as WHO (the departments of maternal, newborn, child and adolescent health, Nutrition), UNFPA, PMNCH, Engender Health, Family Care International, and selected academic experts engaged in generating and synthesizing information on MNH and RH.
A list of research questions were then drafted by our review team. The expert group then reviewed the questions, and added and refined the list. The final questions were sent to each technical group member in an Excel format for scoring.

Based on CHNRI methodology, five scoring criteria were applied: (i) answerability in an ethical way; (ii) likelihood of effectiveness; (iii) likelihood of deliverability, affordability, and sustainability; (iv) maximum potential impact on burden reduction; and (v) predicted impact on equity. The experts made a judgment on each proposed research question by answering the questions presented in **Box 3**.

Stage 3: Solicit Input from Societal Stakeholders to Weight the Criteria

The five criteria for scoring (answerability, efficacy and effectiveness, deliverability, disease burden reduction, and effect on equity) may have be perceived to be of varying importance and the value given to each criterion may have varied with the perspective of stakeholders. For example, women who have experienced a stillbirth may have rated mortality reduction higher than a research funder who may value answerability, or a

Box 3. Questions Answered by Technical Experts to Assign Intermediate Scores to Competing Research Options.

Possible answers: Yes = 1; No = 0; Informed but undecided answer: 0.5; Not sufficiently informed: blank.

CRITERION 1: Likelihood that research would lead to new knowledge (enabling a development/ planning of an intervention) in ethical way.

1. Would you say the research question is well framed and endpoints are well defined?
2. Based on: (i) the level of existing research capacity in proposed research; and (ii) the size of the gap from current level of knowledge to the proposed endpoints; would you say that a study can be designed to answer the research question and to reach the proposed endpoints of the research?
3. Do you think that a study needed to answer the proposed research question would obtain ethical approval without major concerns?

CRITERION 2: Assessment of likelihood that the intervention resulting from proposed research would be effective.

1. Based on the best existing evidence and knowledge, would the intervention which would be developed/improved through proposed research be efficacious?
2. Based on the best existing evidence and knowledge, would the intervention which would be developed/improved through proposed research be effective?
3. If the answer to either of the previous two questions is positive, would you say that the evidence upon which these opinions are based is of high quality?

CRITERION 3: Assessment of deliverability, affordability, and sustainability of the intervention resulting from proposed research.

1. Taking into account the level of difficulty with intervention delivery from the perspective of the intervention itself (e.g., design, standardization, safety), the infrastructure required (e.g., human resources, health facilities, communication and transport infrastructure) and users of the intervention (e.g. need for change of attitudes or beliefs, supervision, existing demand), would you say that the endpoints of the research would be deliverable within the context of interest?
2. Taking into account the resources available to implement the intervention, would you say that the endpoints of the research would be affordable within the context of interest?
3. Taking into account government capacity and partnership requirements (e.g., adequacy of government regulation, monitoring and enforcement; governmental intersectoral coordination, partnership with civil society and external donor agencies; favorable political climate to achieve high coverage), would you say that the endpoints of the research would be sustainable within the context of interest?

CRITERION 4: Assessment of maximum potential of disease burden reduction. As this dimension is considered "independent" of the others, in order to score competing options fairly, their maximum potential to reduce disease burden should be assessed as potential impact fraction under an ideal scenario, i.e., when the exposure to targeted disease risk is decreased to 0% or coverage of proposed intervention is increased to 100% (regardless of how realistic that scenario is at the moment—that aspect will be captured by other dimensions of priority setting process, such as deliverability, affordability and sustainability).

Non-existing interventions*

Maximum potential to reduce disease burden should be computed as "potential impact fraction'' for each proposed research avenue, using the equation: PIF = [S(i = 1 to n) Pi (RRi-1)]/[S(i = 1 to n) Pi (RRi-1)+1]; where PIF is ''potential impact fraction'' to reduce disease burden through reducing risk exposure in the population from the present level to 0% or increasing coverage by an existing or new intervention from the present level to 100%; RR is the relative risk given exposure level (less than 1.0 for interventions, greater than 1.0 for risks), P is the population level of distribution of exposure, and n is the maximum exposure level.

Existing interventions**

Maximum potential to reduce disease burden should be assessed from the results of conducted intervention trials; if no such trials were undertaken, then it should be assessed as for non-existing interventions.

Then, the following questions should be answered:

1. Taking into account the results of conducted intervention trials**, or for the new interventions the proportion of avertable burden under an ideal scenario*, would you say that the successful reaching of research endpoints would have a capacity to remove 5% of disease burden or more?
2. To remove 10% of disease burden or more?
3. To remove 15% of disease burden or more?

CRITERION 5: Assessment of the impact of proposed health research on equity.

1. Does the present distribution of the disease burden affect mainly the underprivileged in the population?
2. Would you say that either (i) mainly the underprivileged, or (ii) all segments of the society equally, would be the most likely to benefit from the results of the proposed research after its implementation?
3. Would you say that the proposed research has the overall potential to improve equity in disease burden distribution in the long term (e.g., 10 years)?

health system planner who may be most concerned with deliverability. Hence, we undertaok an exercise to poll a wide range of stakeholders and to weight the criteria based on values assigned by them.

Stage 4: Compute "Research Priority Scores" and Average Expert Agreement

The overall research priority score (RPS) were computed as the mean of the scores for

the five criteria, weighted according to the input from the stakeholders, according to the formula:
RPS = ((criterion 1 score *0.96) + (Criterion 2 score * 0.86) + (criterion 3 score *0.86) + (criterion 4 score * 1.75) + (criterion 5 score * 0.91))/5
Average expert agreement (AEA) scores were also computed for each research question as the average proportion of scorers who agreed on the 15 questions asked. This was computed for each scored research investment option as:

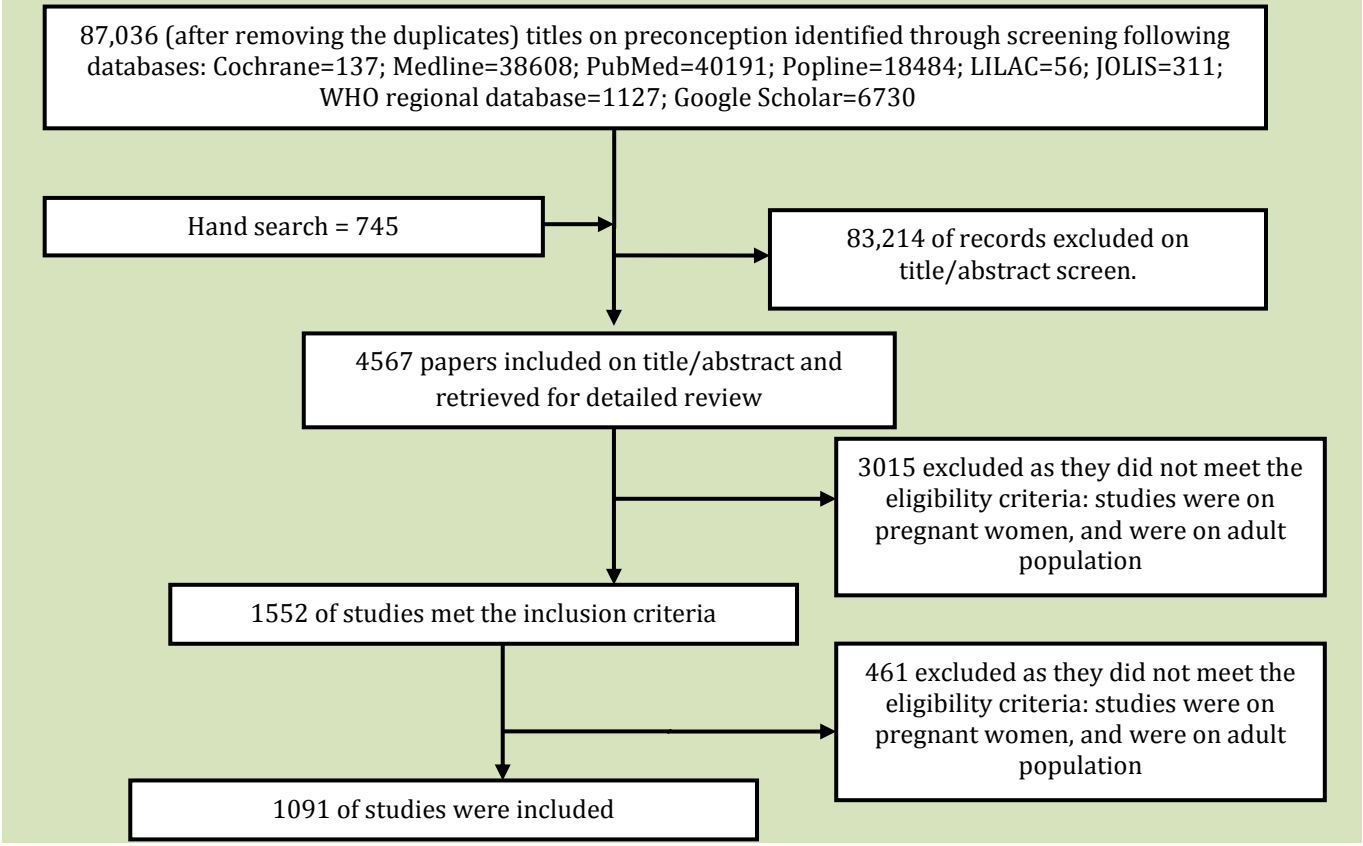
$$\text{AEA (average expert agreement)} = \frac{1}{15} \times \sum_{q=1}^{15} \frac{N \text{ (scorers who provided most frequent response)}}{N \text{ (scorers who provided any response)}}$$

Final Recommendations
Based on the above, we developed an analytical summary of current evidence of intervention impact, research gaps and draft recommendations for including preconception care as part of the 'continuum of care' for MNCH and survival (LiST tool).

Results

The defined search strategy identified 57,036 studies in total (after removing duplicates). We also run a search on identifying data on cost effectiveness and identified 4562 studies in total (after removing duplicates). A further 538 papers were identified on hand search. On initial screening, 4580 papers were identified for full text retrival and on further screening 2059 papers were found eligible and finally 516 were included in this review. Interventions delivered during pregnancy and adult population were excluded from first and second screen (**Figure 3**).

Figure 3: Search Flow Diagram



We found evidence on following components:

Box 4: Found evidence on following preconception interventions

1. Teenage/adolescent health
    a. Female genital mutilation
    b. Teenage pregnancy
    c. Coerced sex/dating violence
2. Birth Spacing and Inter-pregnancy intervals
3. Advanced maternal age
4. Post-abortion care
5. Genetic counseling
6. Preconception care and counseling
7. Nutrition
    a. Pre-pregnancy Weight
    b. Vitamin and mineral supplements
        i. Folic acid and multivitamins
        ii. Iron
        iii. Vitamin A
        iv. Iodine
        v. Other micronutrients
    c. Diet and exercise
8. Intimate partner violence
9. Mental health
10. Infections
    a. STIs
    b. HIV/AIDs
    c. Vaccines
    d. Periodontal disease
    e. Cytomegalovirus
11. Chronic diseases
    a. Diabetes
    b. Hypertension
    c. Anemia
    d. Epilepsy
    e. PKU
    f. Thyroid
    g. SLE
    h. Asthma
12. Substance abuse
    a. Caffeine
    b. Alcohol
    c. Smoking
    d. Illicit drugs
13. Medications use
    a. Oral contraceptives
    b. Weight loss drugs
14. Environment
    a. Radiation
    b. Pesticides
    c. Lead
    d. Other chemicals

PRECONCEPTION RISKS AND INTERVENTIONS

Under this section, we reviewed all possible interventions that can be delivered at preconception and periconception period to improve MNCH outcomes. We have also reviewed some clear risk factors for adverse outcomes which could be ameliorated in the preconception and periconceptional period.

1. Preconception counseling

For detailed review: refer Section I

There is burgeoning interest in preconception care as a means to improve the health of women and children. An evidence base has already been established as to what healthcare for women before pregnancy should entail.[36-43] This review was therefore conducted to determine the specifics of where such care should be provided, who should provide it, and which interventions are most effective in optimizing preconception health. Despite the advocacy for preconception care,[44-49] we found relatively few studies describing the implementation of holistic preconception care and counseling. The interventions were carried out either in health facilities by trained providers a maximum of one year before conception, or in the community by trained facilitators and women's groups.

The community-based studies had randomized controlled designs, and similar outcomes, so we were able to pool their analyses. We found that in developing countries, education on pregnancy and childbirth for women's groups (not during pregnancy) increased the chances that women would seek antenatal care by 39%, however it did not significantly impact specific interventions that would improve the health of women before pregnancy such as being immunized against tetanus (RR 0.98)

or taking iron/folate supplements (RR 1.18). Despite having lower access to quality healthcare, women in community groups were more than twice as likely to use save delivery kits at birth. Overall however, neither maternal mortality (RR 0.95) nor the risk of stillbirths (RR 0.92) was reduced. An encouraging finding was that women were 20% more likely to breastfeed, and would breastfeed sooner, and this may partly account for the drop in neonatal mortality (RR 0.76) in intervention communities.

Interventions carried out in the healthcare setting may provide easier access to couples of reproductive age; however, multiple contacts are required before they respond to invitations to receive preconception care. While many women have multiple risk factors, preconception counseling does not provoke anxiety and risk factors that are identified are more likely to be addressed. Further individual studies show that women who receive preconception care may be more likely to plan and space their pregnancies, quit smoking and alcohol use, and increase their consumption of folic acid.

Following meta-analyses are generated from studies in which counseling was given at mass community level and in the form of support groups.

Important findings

Outcomes	Studies type	No. of studies	Impact estimates	Heterogeneity
Community counseling				
Maternal mortality	Experimental	4	RR 0.95; 95% CI: 0.44-2.06	I^2=68%, P=0.03
Stillbirths	Experimental	4	RR 0.92; 95% CI: 0.80-1.06	I^2=55%, P=0.08
Neonatal mortality	Experimental	5	RR 0.76; 95% CI: 0.66-0.88	I^2=72%, P=0.007
ANC	Experimental	5	RR 1.39; 95% CI: 1.00-1.93	I^2=73%, P=0.005
Iron/Folate	Experimental	4	RR 1.18; 95% CI: 0.98-1.42	I^2=28%, P=0.25
Tetanus toxoid	Experimental	4	RR 0.98; 95% CI: 0.85-1.12	I^2=0%, P=0.70
Clean delivery kit	Experimental	4	RR 2.36; 95% CI: 1.55-3.60	I^2=74%, P=0.009
Breastfeeding	Experimental	4	RR 1.20; 95% CI: 1.07-1.36	I^2=43%, P=0.14
Early initiation	Experimental	3	RR 1.45; 95% CI: 1.20-1.75	I^2=0%, P=0.61
Exclusive (6 wks)	Experimental	2	RR 1.13; 95% CI: 1.04-1.23	I^2=0%, P=0.50

ANC: Antenatal care

Key messages

- Preconception counseling allows women to identify and reduce possible risk factors for poor MNCH outcomes *before* pregnancy. Even though most women have at least one risk factor, and many have multiple risks, preconception counseling does not cause anxiety.
- Women who receive preconception counseling are more likely to change risk behaviors. Therefore, women who receive preconception counseling have better MNCH outcomes
- The content of preconception care has been detailed.[40] Preconception counseling for every woman every time can begin with providers asking two simple questions: "Do you plan on becoming pregnant?" and "Are you currently using any family planning method?"

2. Teenage/Adolescent Health

For detailed review: refer Section II

2.1. Female genital mutilation (FGM)

FGM is a nearly universal practice in certain cultures that causes 100 million women to suffer disastrous health consequences, especially during pregnancy and childbirth.

Although usually carried out between infancy and age 15, FGM is sometimes performed later and many women are reinfibulated after delivery. Observational studies show that in addition to multiple gynecologic problems, women with FGM are at significantly higher risk of stillbirths, and elevated risk of obstetrical intervention.[50] Interventions to encourage cessation of FGM were more successful if they empowered women, used a human rights and development approach, and involved communities and community leaders.[51-54] Such programs of at least one year's duration increased women's resolution to not practice FGM on their daughters 1.9-2.6 times, and the number of community members disapproving the practice by up to 3 times.

Important findings

Outcomes	Studies type	No. of studies	Impact estimates	Heterogeneity
Stillbirths	Observational	2	RR 1.56; 95% CI: 1.15-2.11	I^2=51%, P=0.15
Caesarean section	Observational	3	RR 1.39; 95% CI: 0.93-2.09	I^2=36%, P =0.21
Episiotomy	Observational	2	RR 1.29; 95% CI: 1.29-1.58	I^2=0%, P=0.81
Fetal distress	Observational	2	RR 2.67; 95% CI: 0.14-50.67	I^2=87%, P=0.006

Key messages

- Female genital mutilation leads to difficult labor and childbirth, and has serious health consequences for the mother including increased rates of episiotomies (29% increase) and stillbirths (56% increase).
- Community mobilization and female empowerment can significantly increase the number of parents intending to not practice FGM on their daughters, raise awareness of the adverse health consequences of FGM, and provide a stimulus for community abandonment of the practice.

2.2. Coerced sex and dating violence in adolescence

In this section we aimed to assess how the occurrence of violence amongst adolescents negatively impacted MNCH outcomes. Such violence entailed mainly evidence of dating violence as well as sexual coercion outside of such relationships. We also reviewed projects aiming to bring about improvement in the rate of the aforementioned issues whether by reductions in the acts of violence or a decreased acceptability of aggression or an improved knowledge of consequences attached to such malice.

To date, several dating violence prevention programs have been developed and implemented, with widely varying methods and results. However, so far only one strategy has been demonstrated to be effective in preventing violence, namely school-based programmes for. But the majority of programmes that have been evaluated have been implemented relatively narrowly.

One such dating violence prevention programme was shown to significantly reduce psychological, moderate physical and sexual dating violence perpetration and when evaluated, it showed long-term durability of self-reported decrease in perpetration and ill-treatment[55-58]. Evaluation of a school-based program showed rates of physical dating violence were 2.4% less in the intervention group. A randomized-controlled trial of another school-based intervention showed that the programme had been effective in reducing incidents of physical and emotional abuse and the symptoms of emotional distress for over a year after the programme. One systematic review[59] estimated that on average, universal multi-component programmes reduced violence by 15% in schools that delivered the programmes compared to those that did not. Another review[60] that

examined education programmes for college students on sexual assault found little evidence of the effectiveness of such programmes in preventing such assaults.

Literature on other intervention programs also reports on outcomes associated with a change in the level of knowledge and perceived attitudes post-intervention but not on behaviours and actual prevalence of abuse among adolescents.

Key messages

- Globally, significant numbers of young women have experienced coercive sex
- Females who experienced coercion are more likely to experience both subsequent non-consensual sex as well as risky consensual sexual behaviors.
- They may suffer from poor mental health and this may lead to an increased risk of unintended pregnancies, and STIs.
- During our literature appraisal, we found limited evidence on the effect of coerced sex on MNCH outcomes.
- Interventions like school based programs appear to be effective for the prevention of dating violence in adolescents.
- There is dire need for researchers to examine the longitudinal behavior change that occurs as a result of the prevention programs

3. Maternal age at conception

For detailed review: refer Section III

3.1 . Preventing adolescent pregnancy

Pregnant adolescents have a 50% increased risk of stillbirths and neonatal deaths, as well as higher risk of preterm birth, low birth weight and birth asphyxia. Teenage women are themselves more likely to face intrapartum complications such as obstructed and prolonged labor, vesico-vaginal fistulae, and infectious morbidity.[61]

We conducted a meta-analysis of RCTs that examined any interventions to reduce rates of primary and repeat adolescent pregnancy. Although abstinence-based education has been widely publicized, abstinence-focused sex-education programs insignificantly reduce the risk of pregnancy during adolescence. Expanded sexual-education programs delivered by adults also did not show an effect in preventing adolescent pregnancy.
School- and health center- based interventions to promote contraceptive use also had no effect on preventing teenage pregnancy, regardless of whether the intervention involved free provision, long-acting or emergency contraception, ease of access, or peer counselling.

Comprehensive interventions, such as the "Children's Aid Society Carrera Program" which was carried out in community-centers and provided educational and vocational support, sex education, medical care, sports and arts, free STI testing and condoms are very successful, reducing the risk of teen pregnancy by almost half. Another highly successful program (risk reduction of 57%) focused on youth development through community service, and personal development.[62] The success of combining multiple interventions especially contraception with education, has also been reported in a recent Cochrane review.[63] A conditional cash transfer for girl's dropouts to return to school also showed promising results (11.1% pregnant in intervention group versus 16.2% in control group).

The pooled analysis for all interventions to reduce the incidence of adolescent pregnancies showed only a 15% decrease. Systematic reviews by DiCenso 2002[64] and Corcoran 2007[65] confirm that the evidence for effective teenage pregnancy prevention programs is conflicting.

Successful interventions to prevent ***repeat*** second pregnancies to teenage mothers all include parenting skills training, and encourage teenage mothers to complete their education (risk reduction 59-89%). One particularly successful program (risk reduction 89%) also included comprehensive medical care and referral services for day-care and housing. Another effective program (Second chance club- 84% decreased risk) took a unique approach: it was conducted in high school through individualized case management and group sessions, and focused on school involvement and community outreach, but also provided medical care.

Contraceptive hormonal implants successfully prevented 89% of repeat teenage pregnancies in the pooled analysis. Contraceptive provision to adolescents might be more successful if implemented in school-based health centers with case management provided by an onsite care provider.

Important findings

Outcomes	Studies type	No. of studies	Impact estimates	Heterogeneity
Intervention to prevent repeat pregnancy	Experimental	16	OR 0.63; 95% CI: 0.49-0.82	I^2=74%, P=<0.00001
Contraception to prevent repeat pregnancy	Experimental	3	OR 0.20; 95% CI: 0.03-1.22	I^2=69%, P=0.04
Contraception to prevent teen pregnancy	Experimental	2	RR 1.01; 95% CI: 0.81-1.26	I^2=0%, P=0.65
Intervention to prevent teen pregnancy	Experimental	24	RR 0.85; 95% CI: 0.74-0.98	I^2=54%, P=0.001

Key messages

- Adolescent pregnancy can have serious consequences for the young mother and her child, including obstructed and prolonged labor, high risk of development of vesico-vaginal fistulae, infectious morbidity, stillbirths and neonatal deaths, as well as preterm birth, low birth weight and asphyxia.
- There are social causes and consequences of adolescent pregnancy- lack of education for girls and poverty, for example, are perpetuated since adolescent mothers are often without social support, and unable to finish their own schooling.
- Promising interventions to prevent teenage pregnancy are multifaceted and include communities, schools, health services, and the promotion and distribution of contraceptives; as well as programs that facilitate personal and social development; conditional cash transfers for girls' education must be further explored (risk reductions of 41-57%).
- For adolescents who are already mothers, parental skills training and encouraging them to complete their education, while providing them with medical care, prevents repeat pregnancy during adolescence (risk reductions of 59-89%).

3.2. Advanced maternal age

There is an increasing trend for couples to delay childbearing as a result of numerous personal economic and social reasons. While women of advanced maternal age (over 35 years) may be aware that they face greater difficulty conceiving, and chromosomal abnormalities in the fetus, they are unaware that they are also at a 72% increased risk of Caesarean delivery.[66]

Advanced maternal age is also strongly predisposes to stillbirths (RR 1.62),[67] perinatal mortality (RR 1.44), preterm births (RR 1.29) and low birth weight babies (RR 1.61). It is difficult to determine however, whether maternal age is an independent risk factor, or whether other influences, such as obstetricians exercising increased caution, or a higher rate of maternal chronic disease, are responsible for these elevated risks.[68, 69]

Although hypertension was defined differently in various studies, the risk of hypertension during pregnancy is 3 times higher for women of advanced maternal age versus their younger counterparts. We also found an elevated, but insignificant, risk of pre-eclampsia, which was taken to be a more sensitive indicator than hypertension overall. The risk for placenta previa and gestational diabetes are also 3 times as high in women of advanced maternal age. The greatest risk is for pre-gestational diabetes which is increased six-fold (OR 6.4 and 6.88 in 2 studies) in this population.

Important findings

Outcomes	Studies type	No. of studies	Impact estimates	Heterogeneity
Caesarean section	Observational	25	RR 1.72; 95% CI: 1.59-1.85	I^2=100%, P<0.00001
Stillbirths	Observational	40	RR 1.62; 95% CI: 1.50-1.76	I^2=94%, P<0.00001
Perinatal deaths	Observational	4	OR 1.44; 95% CI: 1.10-1.89	I^2=64%, P=0.04
Preterm birth	Observational	8	OR 1.29; 95% CI: 1.14-1.46	I^2=88%, P<0.00001
Low birth weight	Observational	4	OR 1.61; 95% CI: 1.16-2.24	I^2=60%, P=0.06
Gestational HTN	Observational	8	OR 2.86; 95% CI: 1.53-5.35	I^2=100%, P<0.00001
Pre-eclampsia	Observational	5	OR 2.06; 95% CI: 0.72-5.89	I^2=99%, P<0.00001
Antepartum hemorrhage	Observational	9	OR 3.11; 95% CI: 2.28-4.25	I^2=78%, P<0.00001
Gestational Diabetes	Observational	8	OR 3.00; 95% CI: 2.31-3.89	I^2=89%, P<0.00001

Key message:

- There are many social and personal reasons that couples may choose to delay childbearing. Women of "advanced" maternal age (currently defined as those over age 35 years) are therefore, an increasing obstetric population
- Women who delay childbearing are at a 72% increased risk of Caesarean delivery, and face a higher risk of stillbirths (62% greater), perinatal death (44%), preterm births (29%) and low birth weight babies (61%).
- It is unclear, however, whether this increased risk is solely due to advanced maternal age, or whether other factors, such as parity, mode of conception and pre-existing maternal medical conditions might play a significant role. Further, the literature in this area is quite heterogeneous when defining both the exposure

("advanced" maternal age) and the outcomes (preterm birth, stillbirths).

- Until stronger evidence is available, women who plan to delay childbearing should be counselled regarding increased risks of adverse MNCH outcomes, and quality antenatal care should be provided to those women who do become pregnant during their later reproductive years since appropriate screening and management could ensure better outcomes for them are their newborns.

4. Reproductive Planning

For detailed review: refer Section IV

4.1 . Birth Spacing and Inter-pregnancy intervals

Family planning has a significant role to play in preconception care. Women who are able to decide how many children they wish to have, and use a method to space their pregnancies at least 18-24 months apart, are more physically and emotionally healthy when they do become mothers, which also results in their having healthier children.

Women who have very closely-spaced pregnancies are unable to replete their nutritional reserves,[86, 87] and those who have inter-pregnancy intervals less than 6 months are at substantially higher risk of being anemic (RR 1.32), stillbirths (OR 1.42), premature rupture of membranes (OR 1.42), and puerperal endometritis (RR 1.23). These women are also 3 times more likely to experience uterine rupture during a trial of labor, and are 66% more likely to die during pregnancy and childbirth than women with longer inter-pregnancy intervals. Furthermore, their newborns are at increased risk of being born preterm (OR 1.45), low-birth-weight (OR 1.65), or small-for-gestational-age (OR 1.17).

Conversely, women with extremely long inter-pregnancy intervals (>60 months) have increased risk of third-trimester bleeding (RR 1.11), eclampsia (RR 1.74), and fetal death (RR 1.18). Similarly to women with short intervals, their newborns are likely to be born preterm (OR 1.21), low birth weight (RR 1.37), or small-for-gestational-age (RR 1.18).

While some of our findings must be treated with caution, since the pooled effect sizes are from a low number of studies which employ different methodological criteria, the effect of short and long intervals on neonatal outcomes is confirmed by a previous review.[88]

Important findings

Outcomes	Studies type	No. of studies	Impact estimates	Heterogeneity
Short IPI				
Maternal Anemia	Observational	2	RR 1.32; 95% CI: 1.22-1.43	I^2=0%, P=0.56
Uterine rupture vaginal birth after C-section	Observational	4	OR 3.04; 95% CI: 1.91-4.85	I^2=0%, P =0.97
<6 months	Observational	2	OR 3.27; 95% CI: 1.66-6.47	I^2=0%, P =0.75
<24 months	Observational	2	OR 2.84; 95% CI: 1.50-5.40	I^2=0%, P =0.87
Miscarriage	Observational	2	OR 1.47; 95% CI: 0.30-7.14	I^2=99%, P=<0.001
Fetal death	Observational	3	OR 1.19; 95% CI: 0.95-1.49	I^2=31%, P=0.24
Third-trimester Bleeding	Observational	3	OR 1.38; 95% CI: 0.88-2.15	I^2=90%, P=0.16
PPH	Observational	2	RR 0.99; 95% CI: 0.90-1.08	I^2=0%, P=0.61
GDM	Observational	2	RR 1.01; 95% CI: 0.78-1.30	I^2=0%, P=0.94
Preeclampsia	Observational	2	RR 1.00; 95% CI: 0.93-1.07	I^2=0%, P=1.00
Eclampsia	Observational	2	RR 1.11; 95% CI: 0.70-1.77	I^2=0%, P=0.97

PRoM	Observational	3	OR 1.42; 95% CI: 1.11-1.80	I^2=88%, P=0.003
Preterm birth	Observational	16	OR 1.45; 95% CI: 1.30-1.61	I^2=0%, P=0.61
< 3 months	Observational	2	OR 1.39; 95% CI: 0.91-2.12	I^2=62%, P=0.10
< 6 months	Observational	13	OR 1.47; 95% CI: 1.30-1.66	I^2=94%, P<0.001
< 12 months	Observational	1	OR 1.20; 95% CI: 0.50-2.88	
Puerperal Endometritis	Observational	2	RR 1.23; 95% CI: 1.02-1.48	I^2=69%, P=0.07
Stillbirths	Observational	5	OR 1.42; 95% CI: 1.09-1.86	I^2=45%, P=0.12
Neonatal death	Observational	6	OR 1.31; 95% CI: 0.96-1.79	I^2=59%, P=0.03
LBW	Observational	6	OR 1.65; 95% CI: 1.27-2.14	I^2=96%, P<0.001
SGA	Observational	10	OR 1.17; 95% CI: 1.07-1.27	I^2=83%, P<0.001
Long IPI				
Maternal anemia	Observational	2	RR 1.01; 95% CI: 0.97-1.05	I^2=0%, P=0.86
Fetal death	Observational	2	RR 1.18; 95% CI: 1.06-1.31	I^2=0%, P=0.41
Third-trimester bleeding	Observational	2	RR 1.11; 95% CI: 1.03-1.19	I^2=0%, P=0.80
PPH	Observational	2	RR 0.91; 95% CI: 0.78-1.06	
GDM	Observational	2	RR 1.24; 95% CI: 0.81-1.90	I^2=45%, P=0.18
Preeclampsia	Observational	2	RR 1.43; 95% CI: 0.86-2.36	I^2=96%, P<0.001
Eclampsia	Observational	2	RR 1.74; 95% CI: 1.35-2.25	I^2=0%, P=0.36
PRoM	Observational	3	RR 1.11; 95% CI: 0.94-1.31	I^2=79%, P=0.009
Puerperal Endometritis	Observational	2	RR 1.03; 95% CI: 0.94-1.12	I^2=28%, P=0.24
Preterm birth	Observational	7	OR 1.21; 95% CI: 1.12-1.30	I^2=90%, P<0.001
Stillbirths	Observational	3	OR 1.18; 95% CI: 0.86-1.63	I^2=53%, P=0.12
Neonatal deaths	Observational	5	RR 1.15; 95% CI: 1.06-1.25	I^2=21%, P=0.28
LBW	Observational	5	RR 1.37; 95% CI: 1.21-1.55	I^2=65%, P=0.04
SGA	Observational	8	RR 1.18; 95% CI: 1.05-1.32	I^2=88%, P<0.001

GDM: Gestational Diabetes Mellitus; LBW: Low Birth Weight, PPH: Post-Partum Hemorrhage; ProM: Premature rupture of membranes; SGA: Small for gestational age, IPI: Inter pregnancy interval;

Key messages:

- One third of all pregnancies are unintended and a fifth end in abortion- there is a sizable unmet need for family planning that could prevent the poor maternal and child outcomes resulting from such pregnancies and unsafe abortions.
- Adverse outcomes associated with short intervals include uterine rupture during trial of labor (OR 3.04), stillbirths (OR 1.42), and maternal death (OR 1.66).
- There is an increased risk of neonatal deaths following long intervals (OR 1.15).
- This review also found a significantly increased risk with short and long intervals of preterm birth (OR 1.45 and 1.21 respectively), low birth weight (OR 1.65 and 1.37 respectively), and a slightly increased risk of small-for-gestational age (OR 1.17 and 1.18 respectively).
- After a live birth, women should space their pregnancies with at least 18-24 months before the next conception. Women should not wait longer than 5 years between pregnancies as this may increase the risk of preeclampsia, and maternal and neonatal mortality
- Preconception care should encourage all women to have a reproductive life plan, and to use exclusive breastfeeding and modern contraception so that pregnancies are intended, and women are physically and emotionally healthy before they conceive.

4.2 . Post abortion care

Without access to family planning services, many women risk having unintended

pregnancies and unsafe abortions. Post-abortion care includes emergency treatment of abortion complications, family planning counseling and services, and provision of (or referral to) other reproductive health services regardless of whether the abortion was spontaneous or induced, and has the potential to save the lives of 70,000 women each year.[89] Risk-aversion studies show that women with a previous abortion have greater risks of maternal and fetal complications in subsequent pregnancies,[90-95] hence post-abortion care may be thought of as inter-conception care.

The use of manual vacuum aspiration (MVA) was shown to significantly reduce maternal blood loss and length of hospital stay in one study. Another study demonstrated that training care providers resulted in increased availability of emergency uterine evacuation from 57 to 79% and the use of MVA from 21 to 83%.

The most improvement in number of women receiving/accepting contraception was seen in two interventions. The first included provision of emergency post-abortion treatment, contraceptive counseling, and community-service provider partnerships and increased uptake from 2 to 86.6% in three years. The second intervention comprised training of providers, counseling, free contraception and follow-up. As a result, contraceptive use increased to 96% at intervention site versus 5% at control site, women receiving post-abortion care 3.38 times less likely to have an unplanned pregnancy, and there was an 8% decline in repeat abortion rates versus controls.

An intervention in Russia raised the proportion of women using modern contraception from 50 to 58% and reduced abortions from 49 to 43/1000 women. Another similar intervention showed no effect, however, and attributed this to the number of women undergoing repeat abortions.
Counseling women post-abortion also creates opportunities to involve their partners. Husbands who receive counseling are 1.6 times more likely to support their wives and women who receive support from their partners are nearly 6 times more likely to use family planning methods.

Key messages

- Many women resort to risky abortion practices because they lack access to family planning services, or because of legal issues with induced abortion
- Safe abortion care can prevent half a million maternal deaths, disability, reduce health costs that accrue from the treatment of complications of unsafe abortion, reduce repeat abortions, and possibly lower the prevalence of preterm birth and low birth weight babies
- This review found evidence to support the increased use of contraception in women receiving post-abortion counselling (upto 90%), however better study designs and longer follow-up is necessary to evaluate if this translates to fewer unintended pregnancies, reduces repeat abortions or decreases maternal morbidity and mortality that result from unsafe abortion

4.3. Genetic counseling and screening

We set to look for studies talking about the importance of genetic counseling given to couples planning a pregnancy. Despite an extensive search we found limited evidence[70] identifying the effectiveness of any genetic screening and counseling, provided in the preconception period, in dealing with outcomes in affected pregnancies. Most of the

literature we came across was related to the attitudes and perception of couples regarding the provision of these services and the general attitude of physicians towards genetic counseling and screening in the preconception period. For population-based screening, studies showed that the uptake rates were higher if written information was given,[71] if screening was offered in person by a health professional[72, 73] and if immediate testing was offered.[73, 74] Studies for premarital screening for haemoglobinopathies showed varying results with most reporting couples still proceeding with their marriage plans despite the counseling,[75-78] however it was also reported that many of these couples later sought early prenatal diagnosis.[79-82] In many countries, where population-based screening or premarital programs were effectively implemented, the rates of inheritable genetic disorders have decreased drastically.[70, 83-85]

Key messages

- Premarital screening service for thalessemia provided in Iran, was the only valuable evidence showing a 70% reduction in thalassemia-affected birth post-screening.
- There is otherwise a lack of literature on the provision of comprehensive genetic counseling to couples planning a pregnancy
- A relative lack of literature exists to test effectiveness of preconception genetic screening
- Review of literature for cystic fibrosis shows majority of couples welcome the idea of a pre-pregnancy screening test.
- Attitudes of health professionals regarding preconception cystic fibrosis carrier screening varies considerably. Greatest support to the notion is given by General Practitioners; however this attitude is not translated into practice.

5. Nutrition

For detailed review: refer Section V

5.1. Maternal Pre-pregnancy weight

While obesity is a fast-growing epidemic, women of lower socioeconomic status and young age are also at risk of being undernourished and underweight.

Undernutrition is the indirect cause of one-fifth of maternal deaths during childbirth (Bhutta 2008 Lancet. This review also found a significantly higher risk of preterm births (OR 1.32) and small-for-gestational-age babies (OR 1.64) among women who were underweight before pregnancy (BMI<18.5 kg/m^2 according to WHO guidelines).

Maternal obesity is of great concern since it not only is a direct cause for excess maternal and neonatal morbidity and deaths, but also raises the cost of maternal care. The risk of preeclampsia (OR 2.28) and gestational diabetes mellitus (OR 1.91) approximately doubles with pre-pregnancy overweight, and the effect is even greater for pre-pregnancy obesity although data for maternal obesity was not presented as meta-views. Besides preeclampsia, overweight women are also at increased risk for postpartum hemorrhage (OR 1.18), the other leading cause of maternal mortality. Consistent with previous work,[96-98] this review found that overweight women more often need obstetric intervention (OR 1.53 for induction of labor, 1.10 for assisted delivery, and 1.42 for Caesarean delivery). Overweight status also predisposes to stillbirths (OR 1.40). Furthermore, it contributes to intergenerational obesity, with

babies of overweight women more likely to have macrosomia (RR 1.77) or be large-for-gestational-age (OR 1.65). Overweight women have been shown to have placental dysfunction, which is largely responsible for their adverse MNCH outcomes, however, they also have poor bioavailability of micronutrients that are essential for healthy pregnancy.[96] This means that they may be at increased risk of having babies with congenital birth defects such as congenital heart defects (OR 1.14).

Important findings

Outcomes	Studies type	No. of studies	Impact estimates	Heterogeneity
Underweight				
Preterm birth	Observational	12	OR 1.32; 95% CI: 1.22-1.43	I^2=50%, P=0.02
Stillbirths	Observational	3	OR 1.16; 95% CI: 0.71-1.90	I^2=0%, P=0.69
LBW	Observational	5	OR 1.25; 95% CI: 0.71-2.19	I^2=68%, P=0.01
SGA	Observational	4	OR 1.64; 95% CI: 1.35-2.01	I^2=77%, P=0.004
Overweight				
Hypertensive disorders	Observational	9	OR 1.99; 95% CI: 1.54-2.58	I^2=84%, P<0.0001
Preeclampsia	Observational	12	OR 2.28; 95% CI: 2.04-2.55	I^2=77%, P<0.0001
GDM	Observational	8	OR 1.91; 95% CI: 1.58-2.32	I^2=80%, P<0.0001
PPH	Observational	4	OR 1.18; 95% CI: 1.15-1.21	I^2= 42%, P=0.16
Caesarean delivery	Observational	15	OR 1.50; 95% CI: 1.34-1.67	I^2=94%, P<0.0001
Preterm birth	Observational	15	OR 1.07; 95% CI 0.95-1.19	I^2=89%, P<0.0001
Induction of labor	Observational	5	OR 1.53; 95% CI 1.37-1.71	I^2=94%, P<0.0001
Instrumental delivery	Observational	4	OR 1.10; 95% CI 1.01-1.19	I^2=88%, P<0.0001
Stillbirths	Observational	6	OR 1.40; 95% CI: 1.05-1.85	I^2=82%, P<0.0001
Macrosomia	Observational	11	RR 1.77; 95% CI: 1.54-2.03	I^2=90%, P<0.0001
LGA	Observational	6	OR 1.65; 95% CI: 1.37-2.00	I^2=97%, P<0.0001
CHDs	Observational	3	OR 1.14; 95% CI: 1.06-1.23	I^2=0%, P=0.41
NTDs	Observational	2	OR 0.57; 95% CI: 0.42-0.76	I^2=0%, P=0.80
Limb reduction	Observational	2	OR 1.23; 95% CI: 0.98-1.54	I^2=0%, P=0.65
Congenital Diaphragmatic hernia	Observational	2	OR 0.93; 95% CI: 0.69-1.26	I^2=0%, P=0.69

CHDs: Congenital Heart Defects; GDM: Gestational Diabetes Mellitus; LBW: low birth weight; LGA: Large for Gestational age; NTD: Neural Tube Defects; PPH: Postpartum hemorrhage

Key messages:

- Maternal obesity is a fast-growing epidemic with serious consequences for maternal, pregnancy and child outcomes.
- Pre-pregnancy overweight approximately doubles the risk for hypertensive disorders of pregnancy (OR 1.99), preeclampsia (OR 2.28) and gestational diabetes mellitus (OR 1.91).
- Women who are overweight are 1.5 times more likely to deliver by Caesarean section versus normal-weight women.
- Women who are overweight and obese are more likely to give birth to large-for-gestational age and macrosomic infants (OR 1.63).
- There is some evidence to suggest that birth defects, especially neural tube defects and congenital heart defects, are more common in children born to overweight

women, and that this association becomes stronger with increasing maternal body mass index.
- Data is lacking to suggest an effect of pre-pregnancy overweight on preterm births, instrumental delivery or fetal distress.
- Women who are underweight before pregnancy have a 32% increased risk of preterm birth, and a 64% increased risk of having small-for-gestational age babies.
- We found scarce evidence of an effect of pre pregnancy underweight on stillbirths, low birth weight, operative delivery including caesarean section, or congenital birth defects, although intervention studies of balanced energy protein supplementation during pregnancy do indicate significant benefit. The studies on maternal undernutrition largely focus on maternal short stature as a manifestation of the intergenerational effects of undernutrition, and thus indirectly link undernutrition with adverse MNCH outcomes.

5.2. Diet and Exercise

Since maternal pre-pregnancy BMI has important consequences for pregnancy outcomes, we examined whether interventions to optimize maternal BMI would be successful in improving maternal and neonatal outcomes. A single interventional study[99] demonstrated that a change in the micronutrient-to-energy ratio of food rations in Bhutanese refugee camps (women were underweight) reduced the rate of low birth weight from 16% to 8%, over a period of 2 years.

The interventional trials assessing weight loss interventions in overweight and obese women were rather heterogeneous; however women in the intervention group lost an average of up to 3.5kg. Interventions that combined calorie restriction and physical activity, involved a support system and monitoring, and were sustained over longer periods effected more weight change. This is consistent with previous reviews that have examined interventions for weight loss in adults.[100-102] Since weight loss is difficult to sustain, screening and intervention should begin in adolescence, however there is a need to determine how weight loss interventions might be adapted to young women.[98]

For overall physical activity in the year before pregnancy, there seemed to be a reduced risk of gestational hypertension, however this was not significant (OR 0.65). The evidence of benefit for physical activity on GDM (OR 0.47; 95% CI 0.26-0.85) was more convincing, especially when studies used subgroups based on increased intensity of physical activity or objective measurements of energy expenditure. From studies of work during pregnancy, it can be inferred that exercise of too high intensity or frequency may adversely affect pregnancy outcomes. Further evidence is needed to assess whether improved outcomes are due to exercise or its effect on weight, whether benefit extends to other MNCH outcomes, and what the recommendation for exercise in the preconception period should be.

Key messages

- Evidence for the effect of physical activity or nutritional supplements (such as balanced energy protein) on MNCH outcomes is limited
- With the burgeoning obesity epidemic, a disproportionate amount of maternal and neonatal morbidity could be reduced if overweight women optimized their BMI status before pregnancy.

- Diet and exercise and diet (calorie-restricted) alone are successful interventions for weight loss (average 3 kg) in women (including postpartum). Interventions are more effective when they are more intensified and women must make bigger behavioral changes, and when they have a support group. Programs also have a greater impact if they include regular monitoring of compliance with the intervention and of how much weight loss has occurred. A major issue with such programs however is that initial weight loss is not sustained.

5.3. Periconceptional folic acid and multivitamin supplementation

There is incontrovertible data to support the routine use of vitamins, especially folic acid, by women of reproductive age, to improve their own health as well as their potential mother and child outcomes.

The effect estimates for folic acid supplementation to prevent neural tube defects in our review were similar to those of a recent Cochrane review by Lumley 2009.[103] Folic acid significantly reduced the risk of recurrent NTDs (RR 0.31, 95% CI: 0.14-0.66) when the analysis was restricted to randomized double-blind placebo-controlled studies, however this effect was no longer significant when two observational studies were included (RR 0.43, 95% CI: 0.13-1.40). Likewise, for occurent NTDs folic acid supplementation had a strong protective effect (RR 0.47; 95% CI: 0.34-0.61) (Figure 6.3.2). Although multivitamin supplementation also protected against NTDs (recurrent NTDs RR 0.38, occurent NTDs 0.51), it was difficult to attribute this effect to other vitamins since most of the studies included in this pooled analysis used multivitamins which contained folate.

The findings for neural tube defects prompted researchers to assess whether other congenital defects could also be prevented by folic acid or multivitamin supplementation. For orofacial clefts, neither folic acid nor multivitamin supplementation was shown to be significantly protective, with effect sizes adhering to unity. However, previous reviews[103, 104] have found a modest protective effect when pooling both these sets of data. A study by van Beynum[105] also found that folic acid was beneficial to prevent all subtypes of congenital heart disease. While our analysis did not favor folic acid (RR 1.06), we did find that multivitamin supplementation could significantly decrease the risk of congenital heart defects (RR 0.58). Multivitamin supplementation also is effective in preventing urinary tract defects (RR 0.54), limb reduction defects (RR 0.43), and multiple congenital anomalies (RR 0.57).

After it was found that folic acid could prevent neural tube defects, and that women were not taking the recommended supplements, some countries began to fortify staple food such as flour with folic acid. It was uncertain what impact such widespread supplementation or fortification would have on other pregnancy outcomes. Folic acid fortification did not increase the risk of multiple gestations (RR 0.99). Unfortunately, folic acid also had no impact on the risk of miscarriage (RR 1.07), stillbirths (RR 0.52, 95% CI 0.05-6.01), or ectopic pregnancy (RR0.75, 95% CI 0.24-2.40). Multivitamin supplementation had no effect on preterm birth (RR 0.62, 95% CI 0.20-1.89), however we did find a significant protective effect on preeclampsia (RR 0.73, 95% CI 0.58-0.92).

Given that there is a significant advantage of folic acid supplementation for women in the preconception period, over half of all women in this population do not consume

enough folate. Mass campaigns and personal counseling must be implemented,[106] in those countries where fortification is not practiced, and to target those women who are significantly depleted. Further, women who are at risk of recurrent neural tube defects, or who have other predisposing factors such as epilepsy, may require more intensive interventions.[107, 108]

Important findings

Outcomes	Studies type Heterogeneity	No. of studies	Impact estimates	
Folate versus Multivitamin				
Recurrent NTDs	Experimental I^2=0%, P=0.86	2	RR 0.27; 95% CI: 0.07-1.07	
Folate versus Folate and Multivitamin				
Recurrent NTDs	Experimental	2	RR 0.49; 95% CI: 0.09-2.68	
Multivitamin Alone				
Recurrent NTDs	Experimental	3	RR 0.38; 95% CI: 0.20-0.71	I^2=0%, P=0.43
Occurent NTDs	Exp + Obs	7	RR 0.51; 95% CI: 0.31-0.82	I^2=84%, P<0.001
Cleft lip	Exp + Obs	3	RR 0.70; 95% CI: 0.47-1.50	I^2=0%, P=0.41
Cleft palate	Exp + Obs	3	RR 0.82; 95% CI: 0.43-1.57	I^2=0%, P=0.33
CHD	Exp + Obs	4	RR 0.58; 95% CI: 0.42-0.79	I^2=0%, P=0.95
Urinary Tract Defects	Exp + Obs	3	RR 0.54; 95% CI: 0.35-0.82	I^2=14%, P=0.31
limb reduction Defects	Exp + Obs	3	RR 0.43; 95% CI: 0.23-0.81	I^2=0%, P=0.71
multiple cong Anomalies	Exp + Obs	3	RR 0.57; 95% CI: 0.34-0.97	I^2=57%, P=0.08
Miscarriage	Experimental	2	RR 1.15; 95% CI: 0.98-1.35	I^2=12%, P=0.29
Stillbirths	Experimental	2	RR 0.60; 95% CI: 0.08-4.51	I^2=52%, P=0.15
Preterm birth	Exp + Obs	2	RR 0.62; 95% CI: 0.20-1.89	I^2=89%, P=0.002
Preeclampsia	Observational	2	RR 0.73; 95% CI: 0.58-0.92	I^2=23%, P=0.26
Folate supplementation Alone				
Recurrent NTDs	Exp + Obs	5	RR 0.43; 95% CI: 0.13-1.40	I^2=75%, P=0.003
Occurent NTDs	Exp + Obs	3	RR 0.47; 95% CI: 0.34-0.64	I^2=30%, P=0.24
Cleft Lip	Observational	3	RR 1.01; 95% CI: 0.70-1.46	I^2=0%, P=0.47
Cleft Palate	Observational	3	RR 0.98; 95% CI: 0.61-1.56	I^2=0%, P=0.97
Orofacial clefts	Exp + Obs	5	RR 1.00; 95% CI: 0.76-1.30	I^2=0%, P=0.67
CHDs	Exp + Obs	3	RR 0.88; 95% CI: 0.64-1.23	I^2=70%, P=0.04
Conotruncal CHD	Exp + Obs	4	RR 0.95; 95% CI: 0.58-1.58	I^2=40%, P=0.19
CHDs outflow tract Defects	Observational	2	RR 1.06; 95% CI: 0.83-1.34	I^2=0%, P=0.67
Urinary tract defects	Observational	2	RR 1.23; 95% CI: 0.87-1.73	I^2=0%, P=0.47
Limb reduction Defects	Exp + Obs	4	RR 0.78; 95% CI: 0.37-1.68	I^2=0%, P=0.62
Miscarriage	Experimental	2	RR 1.07; 95% CI: 0.82-1.40	I^2=0%, P=0.61
Stillbirths	Experimental	2	RR 0.52; 95% CI: 0.05-6.41	I^2=56%, P=0.13
Ectopic pregnancy	Experimental	2	RR 0.75; 95% CI: 0.24-2.40	I^2=0%, P=0.63
Folic acid Fortification				
NTDs	Observational	11	RR 0.56; 95% CI: 0.50-0.63	I^2=62%, P=0.003
Multiple gestation	Observational	5	RR 0.99; 95% CI: 0.94-1.05	I^2=58%, P=0.05

Supplementation	Observational	2	RR 0.98; 95% CI: 0.90-1.07	I^2=88%, P=0.003
Fortification	Observational	3	RR 1.00; 95% CI: 0.93-1.07	I^2=0%, P=0.69
Dietary Intake				
Cleft Lip	Observational	6	RR 0.79; 95% CI: 0.62-1.01	I^2=9%, P=0.36
Cleft palate	Observational	4	RR 0.85; 95% CI: 0.50-1.45	I^2=0%, P=0.48

Key messages

- Less than half of all women use folic acid/multivitamins in the periconceptional period despite evidence to support their effectiveness in preventing birth defects and mass campaigns to promote their use in this population
- Folic acid supplementation during the periconceptional period is proven to reduce the risk of neural tube defects- occurent by 16-44% and recurrent by 72-76%.
- Multivitamin supplementation reduces the risk of limb defects (19-76%), congenital urinary tract defects (18-65%).
- This review also demonstrates that periconceptional multivitamin supplementation reduces the risk of multiple congenital anomalies by 43% and preeclampsia by 27%.
- The evidence does not support a significantly increased risk of multiple gestations as a result of folic acid supplementation, RR 0.99-1.02; however a previous review found a pooled annual increase of 4.6% in twinning rates from retrospective cohort studies that merits substantiation pregnancy outcomes.
- Additionally, research is needed to determine the optimal dose of folic acid for fortification of foods, and to demonstrate which interventions to improve the use of folic acid/multivitamin supplements are most effective in women of reproductive age who are at higher risk of birth defects.
- A few observational studies support the role of B-complex vitamins in preventing early pregnancy loss, preterm birth and neural tube defects.
- Multicomponent interventions to increase micronutrient supplementation in women are shown to increase use only transiently and do not achieve universal coverage- however interventions with personal counseling in addition to mass campaigns have been shown to be more effective

5.4. Iron supplementation

Not much has been done with regards to only preconception supplementation, so we also included iron supplementation trials in the general adult population as well as supplementation trials with an iron+other nutrient supplementation.

A single study by Ronnenberg et al. 2004[109] was found on the association of preconception anemia with poor fetal/neonatal effects. This study showed that the risk of low birth weight infants was significantly greater with moderate preconception anemia (OR 6.5; 95% CI: 1.6-26.7). Moderate anemia before pregnancy was also significantly associated with fetal growth restriction (OR 4.6; 95% CI: 1.5-13.5).

Key messages

- There is a huge dearth of literature on the link between preconception anemia and MNCH outcomes.
- The only relevant study cites a significant association between a haemoglobin of less than 95g/L and low birth weight and fetal growth restriction

- Supplementation and fortification studies show a significant improvement in the iron status among women

5.5. Vitamin A Supplementation

Most of the evidence we found was on women of reproductive age with disaggregated data not available for preconception supplementation. Hence we pooled data from trials amongst women of child-bearing age (including those already pregnant). Our analyses failed to show any significant reduction in neither maternal nor fetal/neonatal mortality.

The following meta-analyses show the effect of Vitamin A supplementation on MNCH outcomes.

Important findings

Outcomes	Studies type	No. of studies	Impact estimates	Heterogeneity
Maternal mortality	Experimental	2	OR 0.69; 95% CI: 0.47-1.03	I^2=64%, P=0.06
Neonatal/infant mortality	Experimental	1	RR 1.00; 95% CI: 0.96-1.04	I^2=0%, P=0.47

Key messages

- Current evidence does not prove a beneficial effect of vitamin A supplementation on reducing maternal and/or fetal/neonatal mortality.
- Current evidence mainly comes from trials amongst women of reproductive years (whether currently pregnant or not) where the results cannot be disaggregated to clearly ascertain the role of preconception vitamin A supplementation.
- Future trials need to center on how pre-pregnancy provision of vitamin A supplements could possibly lower adverse pregnancy related outcomes.

5.6. Iodine Supplementation

Iodine supplementation during the preconception period and its effects of preventing MNCH outcomes, related to iodine deficiency, has not been studied sufficiently. Therefore we used evidence from intra-pregnancy supplementation trials and intend to extrapolate their findings to our study period.

One study showed that if the iodine supplement was given before conception the nervous form of endemic cretinism was prevented.[110]

A recent Cochrane review by Mahomed et al. 2007 aimed to assess the effects of iodine supplementation before or during pregnancy in areas of iodine deficiency. However they only found 3 relevant trials which were conducted in pregnant women and no relevant preconception supplementation trial. They showed that supplementation during pregnancy with injectable iodized oil led to a significant 20% reduction in deaths during infancy and early childhood.

Key messages

- Trials on pre-pregnancy supplementation with iodine and their effects on preventing unfavorable pregnancy related outcomes are unavailable.

- Evidence from trials conducted during pregnancy more than highlights the importance of addressing the deficiency states before conceiving, to have the greatest impact in reducing both maternal and fetal/neonatal effects of hypothhyroxemia.
- Future research should aim at the best way of implementing iodine supplementation programs for the general population, especially targeting women of reproductive ages

6. Diagnosis and Treatment of Chronic Diseases

6.1. Diabetes

For detailed review: refer Section VI

Studies have shown that infants of women with pre-existent insulin dependent diabetes mellitus have a 10-fold greater risk of a congenital malformation and a fivefold greater risk of being stillborn than infants in the general population.[111] Significant associations between pre-gestational diabetes and perinatal mortality and congenital malformations, as well as other neonatal and maternal morbidities, were also found in other studies.[112-117] Preconception diabetic care is a multidisciplinary approach with the goal of care being to obtain the lowest possible hemoglobin A1C without significant episodes of hypoglycemia.

We found 23 studies relevant to our intervention under review that looked at various outcomes related to pre gestational diabetes. These studies were mostly cohorts looking at the effectiveness of preconception care for diabetic mothers in reducing adverse pregnancy related effects and only one trial. Meta-analysis of 21 studies showed that preconception care was able to significantly reduce the occurrence of congenital malformations (RR 0.30; 95% CI: 0.22-0.41, a finding that is in conjunction with the results of a review by Ray et al. It was found that preconception counseling plus strict metabolic control had, showed a 71% reduction in the rate of congenital anomalies when compared to mothers receiving standard antenatal care.

Pooled data for the effect of preconception care on the risk of perinatal mortality was also significant (RR 0.31; 95% CI: 0.19-0.53) with preconception counseling plus strict metabolic control again showing a substantial reduction. These figures are comparable to those of a recent review (Wahabi 2010).[118]
Preconception care was effective in reducing pregnancy complications like preterm delivery and caesarean sections, as well as other fetal/neonatal outcomes and macrosomia, but this finding was not significant.

Our data revealed that preconception care was valuable in significantly dropping the level of HbA1C during the first trimester of pregnancy. A single study by Heller 2010[119] showed a weak non-significant effect of preconception insulin in reducing the 1st trimester HbA1C as compared to commencement of insulin in early pregnancy.

The problem however lies in the fact that a substantial number of women with diabetes do not access such preconception care interventions and continue to have unplanned pregnancies with deleterious MNCH results. Since less than 30% of those with diabetes present for preconception care, every office visit of every female diabetic adolescent or woman of childbearing age should be regarded as a preconception care visit. Also with

more women having children in their later years, screening for type 2 diabetes among women of childbearing age becomes more important.

Following meta-analyses are generated from studies looking at MNCH outcomes for preconception diabetic care.

Important findings

Outcomes	Studies type	No. of studies	Impact estimates	Heterogeneity
Congenital malformation	Obs + Exp	21	RR 0.32; 95% CI: 0.23-0.43	I^2=23%, P=0.18
Counseling and glycaemic control	Observational	17	RR 0.31; 95% CI: 0.22-0.42	I^2=21%, P=0.21
Counseling alone	Observational	1	RR 0.25; 95% CI: 0.03-1.94	
glycaemic control only	Observational	3	RR 1.50; 95% CI: 0.30-7.43	
Perinatal mortality	Observational	9	RR 0.31; 95% CI: 0.18-0.54	I^2=0%. P=0.91
Counseling and glycaemic control	Observational	6	RR 0.29; 95% CI: 0.14-0.58	I^2=0%. P=0.77
Counseling alone	Observational	1	RR 0.31; 95% CI: 0.11-0.84	
glycaemic control only	Observational	2	RR 0.73; 95% CI: 0.12-4.66	I^2=0%, P=0.80
Caesarean section	Observational	2	RR 0.87; 95% CI: 0.63-1.20	I^2=77%. P=0.04
Preterm delivery	Observational	4	RR 0.70; 95% CI: 0.55-0.89	I^2=0%. P=0.47
Macrosomia	Observational	2	RR 1.07; 95% CI: 0.56-2.07	I^2=0%. P=0.39
HbA1C in 1st trimester	Observational	7	MD -1.71;95% CI:-2.72,-0.71	I^2=98%. P<0.00001

Key messages

- High level evidence was found for the positive effect of preconception care on reduction of perinatal mortality. The level of evidence of data for the effect of preconception care on the occurrence of congenital anomalies was moderate. Preconception care was found to have a large effect on reduction of both the outcomes
- Preconception care of women with diabetes led to an overall 70% reduction in congenital malformations as compared to children born to women receiving standard antenatal care.
- Preconception care led to a 69% reduction in the occurrence of perinatal mortality associated with preexisting diabetes.
- Better glycaemic control as evidenced by an improved HbA1C in the 1st trimester following preconception care led to significant reductions in the above outcomes.
- Preconception care led to a non-significant 17% decrease in preterm births and a 3% reduction in the rate of C-sections. Pooled data for other fetal/neonatal outcomes did not reach a level of significance either.
- Future research needs to address the gap between provision and availability of preconception care intervention by diabetic women of reproductive age to see similar positive effects in entire populations.

6.2. Epilepsy management in the preconception period

While on the one hand there is extensive support for the pre-conception counseling of all women of child-bearing years suffering from epilepsy, on the other hand there is a

dearth of evidence evaluating the efficiency of such an intervention in dealing with adverse pregnancy outcomes of the disease and its treatment.

A recent review, to determine the effectiveness of preconception counseling in women suffering from epilepsy, found no high-quality studies that optimized pregnancy outcomes among these women.[120] The only study assessing the effectiveness of preconception counseling in women with epilepsy reported that none of the 85 women who were counseled before pregnancy had an abnormal fetus in the subsequent pregnancy as compared to almost 19% of the women who did not receive any preconception counseling (as they were already pregnant) who had an abnormal fetus (with 3 pregnancy terminations). A survey[121] reported that women with epilepsy are not getting the advice they need on issues relating to contraception and pregnancy. This point was also conformed in another study[122] which showed that physicians managing WWE did not place adequate emphasis on preconception care.

What is recommended is a multidisciplinary approach, involving the patient's primary care physician, an obstetrician who specializes in high-risk pregnancies, and a neurologist. Women with epilepsy should be reviewed before planning a pregnancy in order to optimize therapy before conception. Ideally changes in antiepileptic drug therapy should be made at least 6 months before planned conception, if possible. All WWE should be persuaded to begin folic acid supplementation (≥0.4 mg/day) during reproductive years and continue throughout pregnancy.

The current evidence for preconception counseling is encouraging but not conclusive and requires further thorough investigation

Key messages

- Preconception care for women with epilepsy entails re-evaluation of disease status and control, review of current therapy and appropriate changes to doses and regimens and
- Folic acid supplementation well before planning a pregnancy.
- Current evidence for effectiveness of PCC is encouraging but inconclusive.
- Future research should look for effective elements of counseling or mode of delivery

6.3. Management of Phenylketonuria (PKU) and birth outcomes

We intended to accumulate evidence from current literature on the effect of maternal phenylketonuria on the pregnancy outcome, specifically of preconception levels of phenylalanine. Also we looked for any preconception intervention which worked in lowering the MNCH risks associated with poorly controlled phenyalanine levels.

Literature showed that the timing of achieving an optimal Phenlyalanine level was crucial to reducing pregnancy-related adverse outcomes. Rouse et al.[123] in a cohort of women with blood Phenylalanine levels >240umol/L found that mean phenylalanine levels at 4 to 8 weeks gestation predicted congenital heart defect ($P < 0.0001$). They found a significant association for facial abnormalities as well and concluded that each abnormality increased in frequency as Phenylalanine control was delayed: increasing from 19% in offspring of mothers in control before pregnancy to 62% when control was not achieved before 20 weeks' gestational age. Similarly, another study showed that in

women who were preconceptionally treated with good control, microcephaly occurred in only 3.6% of the pregnancies.[124]

Koch et al[124] reported that a preconception Phe-restricted diet led to a 1st trimester PHe level of 500umol/L compared to 641 umol/L in those on a postconception diet. Maillott et al[125] also reported a significant decrease in 1st trimester mean PHe level in those on a preconception diet versus a post-conception diet [248.8 +/-86.6 compared with 493.6 +/- 289.4 mol/L; P < 0.0001].

Our analysis showed that a strict preconception diet was significantly associated with an increment in mean birth weight compared to no dietary restrictions (MD 0.60; 95% CI: 0.39-0.82). The association was also significant for an increase in head circumference (MD 3.20; 95% CI: 2.37-4.03).

Important findings

Outcomes	Studies type	No. of studies	Impact estimates
Mean Birth Weight	Observational	1	MD 0.60; 95% CI: 0.39-0.82
Head Circumference	Observational	1	MD 3.20; 95% CI: 2.37-4.09

Key messages

- Strict dietary control before conception has a strong association with improved growth parameters (birth weight, head circumference).
- Strict preconception phenylalanine restricted diet leads to an improved mean PHe level in the 1st trimester, the period of organogenesis.
- Research into better preconception care plans for women with PKU and more effective implementation of these plans is needed.

6.4. Addressing Thyroid Disorders pre-conceptionally

While literature on the effect of thyroid status on maternal, fetal and neonatal effects is abundant, much work still needs to be done with regards to the effect of preconceptional thyroid status on these outcomes. No literature was available on preconception disease status and its outcomes.
A narrative by Mestman et al.[126] underscores the importance of pre-pregnancy counselling for hyperthyroid women and the use of contraception until achievement of a euthyroid status before conceiving.

A review by Reid et al.[127] on interventions for management of hypothyroidism during pregnancy identified one trial on the effectiveness of levothyroxine treatment in reducing maternal as well as fetal morbidity. It showed a significant 72% decrease in preterm birth (RR 0.28; 95% CI: 0.10-0.80). Browne et al (2009)[128] also reported estimates on association of periconception thyroxine and selected birth defects which were similar to estimates for any thyroid disease Periconception use of Anti-Thyroid drugs was however; shown to significantly increase the rates of selected birth defects (Browne 2009).[128]

Following meta-analyses are generated from studies looking at the effects of thyroid medications on MNCH outcomes

Important findings

Outcomes	Studies type	No. of studies	Impact estimates
Birth defects and ATD	Observational	1	OR 6.11; 95% CI: 2.13, 17.47
Birth defects and thyroxine	Observational	1	OR 1.45s; 95% CI: 1.01, 2.08

Key messages

- Thyroid dysfunction during pregnancy leads to a multitude of maternal and fetal consequences.
- Current literature says attainment of a euthyroid status during the 1st trimester is essential for reducing thyroid related morbidity
- Trials need to be conducted on the effectiveness of comparable treatment modalities when given in the preconception period.

6.5. Systemic Lupus Erythromatoses (SLE)

SLE is a prime example of an autoimmune disease. A number of observational studies look at the effect of active disease in the preconception period on pregnancy related outcomes. Our analysis showed that preconception active SLE was associated with multiple unfavorable maternal and fetal/neonatal outcomes.

An active disease increased the risks of gestational flares by 77% (p=0.04). There was an over three-fold increase in the risk of developing pregnancy induced hypertension if the disease was active (specifically with nephritis) before pregnancy (p=0.002); no association was found with risk of preeclampsia. There was also a significant rise in the preterm deliveries if the disease was not in remission before conception (RR 1.71; 95% CI: 1.18-2.48); this risk was further increased by 13% if the woman suffered from active nephritis pre-pregnancy.

Adverse SLE related fetal/neonatal outcomes in the event of positive disease activity in the preconception period included a significantly increased perinatal mortality (RR 2.42; 95% CI: 1.06, 5.51). No association was seen with either spontaneous abortions or restricted fetal growth. Our results confirmed the findings of Smyth et al.[129]

Following meta-analyses are generated from studies looking at the effect of active disease in the preconception period on MNCH outcomes

Important findings

Outcomes	Studies type	No. of studies	Impact estimates	Heterogeneity
Spontaneous abortion	Observational	2	RR 3.26; 95% CI: 0.58-18.14	I^2=67%, P=0.08
Hypertensions during pregnancy	Observational	2	RR 3.17; 95% CI: 1.56-6.45	I^2=0%, P=0.51
Pretrm delivery	Observational	5	RR 1.71; 95% CI: 1.18-2.48	I^2=0%, P=0.69
Perinatal mortality	Observational	5	RR 2.42; 95% CI: 1.06-5.51	I^2=0%, P=0.54
Flare during pregnancy	Observational	5	RR 1.77; 95% CI: 1.02, 3.07	
Pre-eclampsia	Observational	2	RR 2.38; 95% CI: 0.83, 6.79	
Fetal growth restriction	Observational	1	RR 0.61; 95% CI: 0.16, 2.28	

Key messages

- Evidence supports timing of pregnancy relative to SLE activity. Active disease at conception was associated with hypertension and pre-eclampsia

- Active nephritis per say, was associated with maternal hypertension and premature birth.
- No relevant literature addressing interventions for reducing SLE-related pregnancy outcomes were found.

6.6. Other chronic conditions

Chronic Hypertension and heart disease – pregnancies complicated by chronic hypertension are associated with increased risk of hypertensive disorders of pregnancy and other organ dysfunctions as well as increased fetal risks of preterm birth, intrauterine growth retardation, fetal loss, hypospadias and abruption placenta.[130] Studies show that elevated pre-pregnancy blood pressures lead to increased risk of pre-eclampsia[131] and low-birth-weight babies.[132] periconception use of anti-hypertensives was also found to be positively associated with the occurrence of hypospadias.[130]

Cohort studies demonstrate improved maternal and fetal outcomes when cyanotic heart disease[133] and symptomatic obstructive lesions are corrected prior to pregnancy.[134]

Asthma - research demonstrates that asthma in women with severe asthma prior to pregnancy is more likely to worsen during pregnancy. This reinforces the importance of adequate asthma control prior to conception.[135] It is observed that the dangers of uncontrolled asthma are greater than the risks of indispensable asthma medications. It was found that patients using an inhaled corticosteroid before pregnancy did not have an increase in adverse pregnancy outcomes relative to the group that was not using them.[136] Analysis showed that periconception use of asthma medications was significantly linked to a greater risk of gastroschisis (OR 2.12; 95% CI: 1.39-3.24) especially the use of bronchodilators which significantly doubles the risk.

Headache – frequent prepregnancy headaches were found to be statistically significantly associated with poor mental health in the first 3 months of gestation as well as with antepartum depression.[137]

Important findings

Outcomes	Studies type	No. of studies	Impact estimates
Periconceptional usage of antihypertensives			
Hypospadias	Observational	1	OR 1.90; 95% CI: 1.00-3.60
Periconceptional usage of bronchodilators			
Gastroschisis	Observational	1	OR 2.12; 95% CI: 1.39-3.24

6.7. Medication use

Medication usage among pregnant women and women of reproductive age is common. Medications for chronic conditions are covered in their respective sections. We found studies assessing the effect of use of weight-loss drugs and oral contraceptives.

Analysis of the effect of periconception use of weight-loss drugs showed a significant association with overall higher rates of congenital anomalies (OR 1.59; 95% CI: 1.33-1.89). This association was stronger for congenital heart defects with an 88% increase in incidence of Dextro-TGA and a 58% increase in the incidence of LVOTO (OR 1.88; 95% CI: 1.33-2.65); (OR 1.58; 95% CI: 1.22-2.04) respectively. Bitsko et al.[138] reported

the association with 'Aortic Stenosis' to be highest among the LVOTO defects (OR 1.2; 95% CI: 0.5-3.1).

No significant association was found between pre/peri-conception use of oral contraceptives and maternal complications (gestational hypertension, pre-eclampsia, preterm delivery, and spontaneous abortion) or neonatal complications (LGA, major birth defect or LBW). However, periconception use of oral contraceptive pills (OCP) led to an almost three-fold increase in the risk of Down's in infants.

Werler et al.[139] reported aspirin use in the periconception period to lead to a significantly greater risk of amniotic bands (OR 2.5; 95% CI: 1.4-4.6); vasoconstrictor and decongestant use led to a higher incidence of transverse limb defects (TLD) (OR 1.4; 95% CI: 1.1-2.0); (OR 1.7; 95% CI: 1.2-2.3) respectively.

Following meta-analyses are generated from studies looking at the effect of medications in the preconception period on MNCH outcomes.

Important findings

Outcomes	Studies type	No. of studies	Impact estimates
Weight loss products			
Congenital malformations	Observational	1	RR 1.59; 95% CI: 1.33-1.89
Oral contraceptives – Maternal complications			
Gestational hypertension	Observational	1	OR 0.82; 95% CI: 0.57, 1.17
Pre-eclampsia	Observational	2	OR 0.92; 95% CI: 0.43, 1.95
Spontaneous abortion	Observational	1	OR 0.55; 95% CI: 0.26, 1.16
Preterm delivery	Observational		OR 1.11; 95% CI: 0.38, 3.24
Oral contraceptives – Fetal complications			
Low birth weight	Observational	1	RR 2.80; 95% CI:0.91, 8.61
Large for gestational age	Observational	1	RR 1.67; 95% CI: 0.74, 3.77
Major birth defect	Observational	1	RR 0.86; 95% CI: 0.23, 3.22
Oral contraceptives			
Down's syndrome	Observational	1	RR 2.71; 95% CI: 1.48, 4.95

Key messages

- Periconception use of any weight loss drug was significantly associated with an increased incidence of congenital anomalies in the fetus, especially heart defects.
- Periconception use of oral contraceptives led to no significant increase in spontaneous abortions or any fetal outcomes. However risks of a fetus affected with Down's syndrome increased by almost 3 folds.
- Periconception use of vasoactive substances was linked to limb defects in the fetus.

7. Mental Health

For detailed review: refer Section VII

Mental health conditions are prevalent among women of reproductive age and a substantial proportion goes untreated. There is a deficiency of evidence associating the status of disease and treatment in the preconception period with adverse MNCH effects. From the evidence we gathered, pre-pregnancy depression is significantly related to preterm births (OR 1.04; 95% CI: 1.02-1.07)[180] and adolescent depression was associated with an increased risk of miscarriages (aOR 2.25; 95% CI: 1.12-4.50).[181] When assessing for maternal morbidity, adolescent depression was positively

associated with suffering from intimate partner violence (aOR 3.47) but not STDs (aOR 1.50).[181] Silverman et al concluded that a pre-existing psychiatric condition was one of the best predictors of development of post-partum depression. Literature also showed that a pre- pregnancy psychotic or bipolar illness substantially increased the risk of a postpartum psychotic or bipolar event.[182]

Our analysis showed that there were significant morbidities associated with depression in adolescence (OR: 1.75; 95% CI 1.24-2.46), especially an over 2-fold increase in miscarriages (OR 2.25; 95% CI: 1.12-4.52) and an over 3-fold increase in the occurrence of partner violence (OR 3.47; 95% CI: 1.11-10.83).

Our search for the effect of maternal bereavement on neonatal/infant health revealed that loss of a close relative in the 7-12 months before conception did not increase the risks of autism, epilepsy or febrile seizures in the infant. However, loss of a child or spouse in the 6 months preceding conception was positively associated with ADHD in the male child, childhood obesity and congenital malformation.

Interventions specifically targeting women of reproductive age suffering from a psychiatric condition show that group-counseling[183] and empowerment of women (Hirani)[184] lowered depression in these women but the results so far have not been significant. Interventions teaching coping skills or based on stepwise facilitation seem to significantly lower depression levels and have lasting effects.[185]

Women with serious mental illnesses are at a greater risk of having multiple sexual partners or having been raped and are hence more likely to have unplanned, unwanted pregnancies. Their support system has been reported to be generally lacking. They also have a greater possibility of engaging in risky behavior during pregnancy (substance abuse, suicide attempts). This makes it imperative for their physicians to not only screen vigorously for such cases but also to provide comprehensive family planning and contraceptive counseling as well as attach them to relevant support systems.

Following meta-analyses are generated from studies looking at MNCH outcomes for women and adolescents with mental health disorders

Important findings

Outcomes	Studies type	No. of studies	Impact estimates
Morbidities associated with depression in adolescence	Observational	1	OR: 1.75; 95% CI 1.24-2.46
STD (ever)			OR: ; 95% CI 1.5 0.83-2.71
Induced abortion			OR 1.42; 95% CI: 0.79-2.55
Miscarriage			OR 2.25; 95% CI: 1.12-4.52
Intimate partner			OR 3.47; 95% CI: 1.11-10.83
Counselling and prevalence of depression	Experimental	1	Mean difference: -7.53 (-7.24, 2.18)
Post Economic skill building intervention prevalence of depression	Experimental	1	Mean difference: -2.92 (-13.17, 7.33)

Key messages

- A substantial proportion of mental health conditions in women of child-bearing age remain undiagnosed.
- Adolescent depression significantly increases: the risk of miscarriages by more than two folds; the risk of IPV by more than three-folds.
- Current interventions have not yielded significant impacts on lowering depression in non-pregnant women.
- MNCH effects of preconception disease status and treatment of other psychiatric conditions still needs to be explored.

8. Intimate partner violence

For detailed review: refer Section VIII

Evidence dictates that IPV is a widespread problem and its repercussions, a serious health burden. Most of the studies we reviewed for effect of IPV exposure were risk aversion studies in women in the general population. For outcomes where pre-pregnancy exposure data was not looked at, we took exposure to IPV in women in general.

We found that intimate partner violence positively led to unintended pregnancies; this finding was significant (OR 2.33; 95% CI: 1.25-4.34) and to fetal loss (OR 1.55; 95% CI: 1.40-1.72). A significant increase in gynecologic morbidities was reported in women suffering from IPV (OR 1.45; 95% CI: 1.13-1.85) and rates of STIs were non-significantly raised by almost 2 folds in these women. Gynecologic morbidity increased significantly with any spousal abuse (OR 1.89; 95% CI: 1.23-2.91); combined physical plus sexual violence led to a 72% increase (p=0.04).There was no association between IPV and condom use in women.

IPV had serious detrimental effects on the physical and mental health in those abused. Abused women developed chronic diseases at twice the rate as compared to those not abused (p< 0.001). Ruiz et al.[177] reported that women who had experienced physical, psychological and sexual violence were twice as likely to suffer a chronic disease as those who have not experienced abuse (OR 2.03; 95% CI: 1.18-3.51), especially diseases other than hypertension, diabetes and asthma (OR 2.57; 95% CI 1.38-4.77). IPV leads to a towering five-fold increase in depression among the victims (p<0.00001) and a two-fold increase in impairment of mental health in the past month only (RR 2.08; 95% CI: 1.70-2.55]. Abuse also made these women 7 times more likely to contemplate suicide.

Interventions targeting intimate partner violence have mainly looked at behavioral therapies. These studies have yielded non-significant effects on the occurrence of new events of violence post-treatment. A meta-analysis of 4 trials comparing CBT versus no intervention showed a reduction favoring the intervention group.[178] Behavioral couple's therapy, when compared to gender specific treatment, showed greater reductions in post- treatment aggression and recidivism rates, especially multiple couple's group sessions. A dual intervention targeting both IPV and substance abuse showed decreased rates of both in the intervention group.[179]

Interventions focusing on empowerment of women have been employed to reduce these risks, but their role in decreasing the rate of IPV have so far not been significant. A pilot study on the effectiveness of an intervention to reduce male partner reproductive coercion was associated with a large reduction in pregnancy coercion among

women who had recently experienced IPV (AOR: 0.29; 95% CI: 0.09-0.91).Following meta-analyses are generated from studies looking at MNCH outcomes for Intimate Partner violence in women of reproductive age.

Important findings

Outcomes	Studies type	No. of studies	Impact estimates	Heterogeneity
Gynecological morbidity	Observational	1	OR 1.45; 95% CI: 1.13-1.85	I^2 =33%, P = 0.003
Unintended pregnancies	Observational	2	OR 2.33; 95% CI: 1.25-4.34	I^2 =9%, P = 0.008
STIs	Observational	2	RR 1.89; 95% CI: 0.65, 5.47	I^2 =98%,
Condom use	Observational	3	RR 0.95; 95% CI: 0.61-1.48	I^2=67%, P=0.05
Physical health	Observational	1	OR 2.12; 95% CI: 1.50-3.00	P = 0.003
Depression	Observational	2	OR 4.98; 95% CI: 3.29, 7.55	I^2 =25%, P < 0.00001
Mental health	Observational	2	OR 2.08; 95% CI: 1.70-2.55	I^2=53%, P=0.00001
Suicidal ideation	Observational	1	OR 6.90; 95% CI: 1.90-25.02	P = 0.003
Fetal loss	Observational	1	OR 1.55; 95% CI: 1.40-1.72	P < 0.00001
Post Economic skill building intervention	Experimental	1	RR 0.71; 95% CI: 0.37-1.38	

Key messages

- Women being abused were twice as likely to have an unplanned pregnancy (p=0.008).
- Women suffering from IPV have a >50% risk of fetal loss.
- IPV leads to a significant increase in incidence of gynecologic morbidities (45%) in women
- Women experiencing any abuse in their lifetime are twice as likely to suffer from impaired physical health.
- Women experiencing any abuse in their lifetime are also twice as likely to suffer from impairment of mental functions (p= 0.00001); depression rates are increased almost 5-folds in women abused in the past year; suicidal ideation is raised almost 7-folds in women abused in the past year.
- There was no significant association between IPV and condom use, limited evidence was found on other sexual behaviors.
- An intervention to empower women seemed to have decreased the prevalence of violence by 30% in that community.

9. Infections

For detailed review: refer Section IX

9.1. Sexually transmitted diseases

We aimed to review literature pertaining to the effects of gynecologic infections in women in the preconception period on MNCH outcomes and interventions intended to reduce these infections and hence any associated morbitidy/mortality. Due to a shortage of preconception data being available we also used studies done among the general population. It is imperative to keep in mind the great overlap between interventions targeting STIs, HIV, teenage pregnancies and unwanted pregnancies.

Our analysis showed that post-intervention STI prevalence was significantly decreased by 22%. Behavioral treatments in conjunction with STI management reduced the

incidence of gonorrhea by 57%. For behavioral interventions, re-infection or new STD rates significantly declined (OR 0.65 95% CI 0.53-0.80) at 1 year after the intervention.

Most studies reviewed for interventions for STD control reported outcomes related to safer sexual behaviors entailing efficacious condom use, reduced number of partners. Our analysis showed that such interventions promoted overall safer practices in the subjects especially in terms of a 15% improvement in condom use. This finding is in line with the systematic review (Warner 2006)[140] on effectiveness of condoms in reducing STDs like Chlamydia and gonorrhea. STI rates in Thailand have been successfully reduced through enforced condom use.[141]

Results of another review (Shepherd 2010)[142] on the effectiveness of behavioral interventions for prevention of STIs in adolescents and young adults showed that these programs bring about augment knowledge and self-efficacy and changes in behavioral outcomes to a lesser degree. MNCH outcomes were not studied.
The following meta analyses were generated from studies that looked at the effect of various interventions aiming to reduce STI incidence and prevalence as well as those intending to promote safer sexual behaviors.

Important findings

Outcomes	Studies type	No. of studies	Impact estimates	Heterogeneity
Prevalence of STIs after mass treatment	Experimental	3	OR 0.78; 95% CI: 0.68-0.89	I^2=70%, P=0.001
Syphilis	Experimental	2	OR 0.78; 95% CI: 0.68-0.89	I^2=39%, P=0.20
Gonorrhea	Experimental	2	OR 0.48; 95% CI: 0.30-0.76	I^2=0%, P=0.43
Chlamydia	Experimental	2	OR 1.02; 95% CI: 0.77-1.36	I^2=0%, P=0.43
Trichomoniasis	Experimental	1	OR 0.64; 95% CI: 0.54-0.76	
Bacterial Vaginosis	Experimental	1	OR 0.87; 95% CI: 0.83-0.91	
Safer Sexual behaviors	Experimental	4	OR 1.26; 95% CI: 1.01, 1.56	I^2=83%, P=0.04
Reduced Partner	Experimental	2	OR 1.06; 95% CI: 0.98-1.14	
Condom Use	Experimental	3	OR 2.00; 95% CI: 0.70, 5.72	
Post-intervention re-infection or new STD	Experimental	5	OR 0.65; 95% CI: 0.53, 0.80	I^2=50%, P<0.0001

Key messages

- Reducing the burden of STIs in women of reproductive age could reduce transmission of infections to the newborns, as well as improve the health of women during pregnancy and in the first year after birth.
- Mass treatment of STIs with antibiotics leads to a 22% reduction in its prevalence. (p=0.003), similarly,
- Behavioral/counseling interventions led to a 35% decrease in STI incidence.
- Interventions targeting STIs led to a significant 26% increase in safer sexual behaviors, especially condom use.
- Current interventions need to be put to test in women in the preconception period.

9.2. Preventing transmission of HIV

Women currently comprise the demographic group with the highest incidence of HIV-

those in stable heterosexual relationships are a particularly high-risk group since they may repeatedly experience unsafe sexual behaviors.[143] Women living with HIV/AIDS at present live longer, healthier lives than they were previously able to, and hence many of them desire pregnancy. Although they have higher risks of adverse perinatal outcomes,[144] current prevention of mother to child transmission with, zidovudine intrapartum and immediately after birth is highly effective in preventing the vertical spread of HIV.

Numerous interventions, both distal and proximal, have been carried out to assess their effectiveness in reducing HIV incidence, especially in women and men of reproductive age. The newest approach to preventing transmission involves pre-exposure prophylaxis[145] or antiretroviral therapy as prevention[146] ongoing trials may confirm the effectiveness of this approach in the coming years. Thus far, it seems that interventions that are male-dependent, such as male circumcision (RR for HIV-negative men who are circumcised to become infected 0.49) and condom use (RR 0.15 for consistent use) are more effective than female-dependent methods such as microbicides (HR 0.89, 95% CI 0.73-1.08) in preventing HIV acquisition. Microbicides may in fact increase the risk through genital epithelial injury,[147] whereas condoms have the added benefit of protecting against non-HIV STIs and unintended pregnancy. All serodiscordant heterosexual couples should therefore be advised to use condoms consistently, and interventions must now aim to increase consistent condom use during all sexual exposures.[148]

We did not find conclusive evidence that voluntary counseling and testing would reduce unsafe sexual behavior (OR 1.10), however the data were limited which suggests a need to expand such services and reassess the effect on HIV risk behavior in the future.

There is concrete evidence that other STIs, notably HSV-2, increase the risk for HIV infection.[149, 150] In this review, however, management of STIs (screening, counseling and treatment) had a non-significant impact in lowering HIV risk (RR 1.07) perhaps because we only included arms of factorial trials in which STI management was the only difference from the other trial arms.

Behavioral interventions to reduce the risk of HIV incorporate HIV/AIDS education, condom promotion and skills, peer educators, skills to negotiate safe sexual behavior, address sociocultural barriers and personal risk reduction, counseling and testing. Although these interventions showed a reduction in risky intercourse and STI incidence,[151] they do not seem to impact HIV incidence as significantly. Despite differences in the intervention components and the target populations,[152, 153] it remains unclear whether interventions have more effect if targeted specifically by gender. Amongst IDUs, risk reduction through substitution treatment, harm reduction, and peer education[154-157] is important to prevent transmission to the rest of the population.

It is crucial to note here that interventions which aim to prevent STIs including HIV, and teenage and unintended pregnancies, overlap to a large extent. Surprisingly few trials report public campaigns as an intervention or HIV incidence as an outcome, despite evidence to show the high rates of infection and risky sexual behavior among teens. Further there is a lack of uniform outcome reporting. We therefore pooled intervention trials that reported whether intercourse (especially vaginal) was protected through use

of condoms. Meta-analysis showed that interventions did not significantly affect adolescents' condom use during intercourse (OR 1.04; 95% CI 0.87-1.24) or reduce their risk of unprotected vaginal intercourse (OR 0.96, 95% CI 0.79-1.17).

While it is important to prevent HIV transmission between serodiscordant partners, and from mother to child, it is also necessary to examine whether reduced HIV incidence in endemic regions improves the health outcomes of mothers and newborns. Interventions that are clearly efficacious must now be replicated, with standardized outcome reporting especially of HIV incidence and perinatal outcomes, to demonstrate effectiveness.

Important findings

Outcomes	Studies type	No. of studies	Impact estimates	Heterogeneity
Male Circumcision				
HIV-negative men	Exp + Obs	4	RR 0.49; 95% CI: 0.40-0.59	I^2=0%, P=0.81
HIV-positive men	Experimental	2	RR 1.10; 95% CI: 0.76-1.58	I^2=0%, P=0.045
Microbicides	Experimental	5	HR 0.89; 95% CI: 0.73-1.08	I^2=50%, P=0.08
Consistent condom use	Experimental	4	RR 0.15; 95% CI: 0.09-0.25	I^2=60%, P=0.06
VCT	Experimental	2	OR 1.10; 95% CI: 0.48-2.55	I^2=93%, P=0.0001
Management of STIs	Experimental	5	RR 1.07; 95% CI 0.95-1.19	I^2=89%, P<0.0001

VCT= Voluntary counseling and testing, STIs= Sexually-transmitted infections. For consistent condom use and management of STIs, the effect sizes are presented as rate ratios.

Key messages

- The HIV pandemic contributes significantly to worldwide maternal mortality. Reducing the burden of disease in women of reproductive age could reduce transmission of the virus to newborns, as well as improve the health of women during pregnancy and in the first year after birth.
- Ongoing trials may provide urgently needed evidence as to whether prophylactic or therapeutic use of antiretroviral drugs is safe and effective in women of reproductive age, and improves MNCH outcomes. Thus far, it seems that antiretroviral therapy is successful in preventing transmission to partners and newborns if viral load is significantly suppressed.
- Male circumcision reduces the chances of HIV infection by 51%, but has not been proven to reduce transmission to female partners of HIV-positive men
- Condom use reduces the risk of HIV by 85%. Microbicides and other female-dependent contraceptive methods do not significantly lower risk. Condom use should be promoted among all couples who are serodiscordant or HIV-positive, even during pregnancy. Couples should be made aware of reproductive options that reduce the risk of transmission to their partner and newborns.
- Voluntary counseling and testing does not lower the risk of transmission through unprotected intercourse (RR 1.10, 0.48-2.55). However, public health efforts should still encourage VCT so that people are aware of their HIV-status. Further risk-aversion studies and subsequent trials should assess whether VCT can reduce HIV incidence or risk behaviors in various target populations.
- Management of STIs has been promoted as a risk-reduction strategy, however, we found an insignificant reduction in HIV incidence with improved STI screening and treatment (RR 0.83; 95% CI 0.63-1.09). Comparing outcomes in different populations, or of individual STIs (especially HSV-2) might yield further evidence of effect

- Behavioral interventions show efficacy in high-risk groups such as adolescents. However, replication of successful programs and standardized outcome reporting will be necessary to show consistent effect in reducing high risk behaviors in those populations who are at higher risk or more vulnerable, including adolescents, women and injection drug users.

9.3. Preconception Immunization

Immunization during the preconception period can prevent many diseases which may have serious consequences or even prove fatal to the mother or newborn. Unfortunately, most vaccination trials in the preconception period evaluate efficacy of the vaccine for disease-specific outcomes, and adverse effects.

Vaccination against tetanus is currently given in childhood with booster vaccination during pregnancy. Preconception immunization against tetanus averted a significant number of neonatal deaths (including those specifically due to tetanus) in women receiving more than 1 dose of the vaccine (OR 0.28; 95% CI: 0.15-0.52 and OR 0.02; 95% CI: 0.00-0.28) respectively. This was also true for immunization given as the combined tetanus-diphtheria toxoid (OR 0.52; 95% CI: 0.29-0.91). These findings were confirmed by the results of mass immunization campaigns in three Asian countries.[158-160]

Congenital rubella syndrome is a devastating infection that is preventable. Premarital screening increases the rates of vaccination only when providers advise vaccination and offer it directly after counseling, however routine antibody screening is not recommended because it has a high false-positive rate. National vaccination campaigns for girls and women have been quite successful. Even in the event that immunization (live virus vaccine) occurs within a few months preconception, the risk of the fetus developing congenital rubella syndrome is at most 1.7%. In only one trial was the rate of neonatal death higher in the vaccination arm (1.2% versus 0% in controls).

The HPV vaccine is administered to girls before the onset of sexual activity to prevent against cervical cancer. HPV vaccination provides further advantage, however, to young women and their newborns by reducing the possibility of preterm birth due to cervical incompetence and the rate of laryngeal papillomatosis in the newborn. In clinical trials and surveillance data, the only significant difference in neonatal outcomes was found for miscarriage when Cervarix was administered within 3 months preconception.

Important findings

Outcomes	Studies type	No. of studies	Impact estimates	Heterogeneity
TT versus influenza vaccine				
Neonatal death	Experimental	1	OR 0.52; 95% CI: 0.16-1.70	I^2=87%, P=0.005
Tetanus specific mortality	Experimental	1	OR 0.12; 95% CI: 0.00-7.30	I^2=88%, P=0.004
Tetanus versus Cholera Diptheria				
Neonatal mortality	Experimental	1	OR 0.68; 95% CI: 0.56-0.91	

Key messages

- Neonatal deaths are reduced by 48% by tetanus toxoid given to women of reproductive age. A single dose in preconception period may not be effective in reducing either neonatal death in general or neonatal tetanus-related deaths, 2-3 doses reduce the rates by 72% and 98% respectively.
- Tetanus-diphtheria toxoid significantly reduces overall neonatal tetanus-related mortality by 32% and 4-14 day tetanus mortality by 62%.
- The Rubella vaccine is safe and effective in protecting against congenital rubella syndrome.
- The HPV vaccine when given before pregnancy is safe, but does not reduce the rates of adverse neonatal outcomes (compared to women in the control group)
- Future research should compare the effect of vaccination before pregnancy with vaccination during pregnancy for tetanus and hepatitis B. More evidence is also needed as to whether preconception vaccines have secondary advantages on MNCH outcomes (beyond protection against the specific infection)

9.4. Periodontal disease and dental caries

Offenbacher was the first to suggest that periodontitis could result in preterm birth. Following his lead, many researchers sought to confirm whether maternal periodontal disease could result in preterm low birth weight babies. Systematic reviews that used both epidemiologic and interventional evidence did not consistently support this association, or the association with other adverse MNCH outcomes such as miscarriage, IUGR or preeclampsia.[161-166] Further clinical trials for periodontal treatment during pregnancy found a differential impact on pregnancy outcomes. The lack of a consistent effect is perhaps due to methodological issues; the use of just a single session of treatment; and the possibility that ameliorating this risk might only improve outcomes in a subpopulation.[167, 168]

Treatment of periodontitis during pregnancy may itself introduce into the circulation. We suppose that prevention and/or treatment before pregnancy might help to prevent adverse pregnancy outcomes. Oittinen (2005)[169] was the only study that exclusively focused on prepregnancy periodontal infection and adverse pregnancy outcome (miscarriage and preterm birth not disaggregated) and showed an OR= 5.5 (95% confidence interval 1.4–21.2; p = 0.014). We were unable to include another study (Albert 2011)[170] since periodontal treatment or prevention were not explicitly provided before pregnancy.

Key messages

- Poor oral health has been shown to be a risk factor for adverse pregnancy outcomes, especially preterm low birth weight. However, stronger evidence is needed to define what constitutes “poor oral health” and in which subpopulations prevention and treatment of periodontal disease will be most beneficial.
- Virtually no evidence has been generated to show whether periodontal disease present *before* pregnancy is also a risk for adverse outcomes, or whether treatment at this time could reduce the risk of preterm low birth weight.

9.5. Cytomegalovirus

Congenital cytomegalovirus is a predominant cause of congenital deafness and intellectual disability. In order to develop a vaccine against this infectious disease,

researchers first need to know whether preconceptional immunity in the mother will protect the fetus from acquiring the virus.
In one study,[171] of 46 newborns to women with preconceptional immunity, 16 were infected with CMV. 62% of the mothers with infected infants versus 13% of those with uninfected infants had acquired new antibody specificities. This means that despite immunity, maternal reinfection with a different strain of CMV could still lead to congenital infection.

Fowler (2003)[47] showed that preconceptional immunity significantly lowered the risk (aRR 0.31) of infection in the newborn. Further research attempted to determine whether the timing of the primary infection in relation to conception was a risk factor:[172] Daiminger 2005[173]showed that women with primary infection 2 months to 2 weeks prepregnancy did not have infected infants, whereas women with periconceptional exposure Revello (2002)[174] are more likely to transmit the virus in-utero. The degree of risk may also depend on the endemicity of maternal CMV.

More recently, Revello (2006)[175] showed that of 14 women who had primary CMV infection 2 weeks to 4.5 months before pregnancy, only 1 had an infected newborn (another 1 terminated her pregnancy). Zalel (2008)[176] however, studied 6 women with preconceptional immunity, all of whom had severely infected fetuses, proving that recurrent infection can be as hazardous as primary infection in pregnancy.

Key messages

- Cytomegalovirus is the most common congenital viral infection, and may result in sensorineural hearing loss or intellectual disability in infancy
- Women who acquire **primary CMV infection preconceptionally are at less risk** of transmitting the virus to their newborns than those who become infected during pregnancy. However, women who are **infected at conception or very early in pregnancy or have recurrent infection in pregnancy have a high rate of transmission** to the fetus.
- Women who are planning a pregnancy or already pregnant should be counseled to avoid contact with young children's saliva or urine, and practice strict hygiene if such contact occurs. If women become infected with CMV, they should wait 6 months before attempting to become pregnant.
- Screening and CMV hyperimmune globulin administration have currently been shown as effective only for women with confirmed evidence of CMV infection in pregnancy.
- A vaccine against CMV has not been developed to date, since it is unclear whether immunity before pregnancy would protect the newborn from congenital infection.
- Effective strategies to increase awareness of CMV and the methods to prevent its transmission among women of reproductive age are needed, as well as to improve healthcare providers' counseling regarding the risk of transmission and newborn outcomes

For detailed review: refer Section X

10. Substance Abuse Prevention and Life Style changes

10.1. Reducing periconceptional caffeine intake

Caffeine intake during pregnancy has the ability to increase the risk of adverse fetal outcomes despite consumption being lower than pre-pregnancy levels.[186] We found a

total of six studies that examined periconception caffeine intake as a risk factor for poor fetal outcomes.

Our analysis showed that caffeine intake during the periconception period did not lead to a significant increase in spontaneous abortions (RR 1.77; 95% CI: 0.83, 3.78). However, for an intake of >300mg compared to the referent intake (for all practical purposes we took referent intake <150mg/day) of caffeine per day before conception we found a strong statistically significant association with fetal loss (RR 1.31; 95% CI: 1.08-1.58) and also for an intake of > 420mg/day (RR 6.11; 95% CI:5.12, 7.29).

Following meta-analysis was generated from studies looking at spontaneous abortions for periconception intake of caffeine.

Important findings

Outcomes	Studies type	No. of studies	Impact estimates	Heterogeneity
Spontaneous abortion	Observational	5	RR 1.77; 95% CI: 0.83, 3.78	I^2=98%, P<0.00001

Key Messages

- >300mg/d of periconception caffeine use is associated with a 31% increase in the risk of subsequent fetal loss.
- Individual studies report a non-significant dose-response relation between periconception consumption and fetal loss.
- Highlighted areas of research include conducting a large-scale study with a universal reference intake (not zero) to reconfirm the current evidence and also assess for a relationship between other possible MNCH outcomes, along-with finding a 'safe level'.

10.2. Reducing alcohol intake

Although a positive pregnancy test may lead to a significant decrease in the alcohol use of many women, the intervening time lapse between that and conception is a critical period of fetal susceptibility to alcohol.

We looked into risk aversion studies dealing with both pre- and peri-conception drinking as well as interventions during these same periods to alter drinking behavior among women. Our analysis showed a non-significant 30% increase in the risk of occurrence of spontaneous abortions with preconception alcohol consumption.

One study (Shaw 1996) showed an increase in the rate of NTDs with preconception alcohol intake; however the finding was not significant (OR 1.24; 95% CI: 0.92-1.68). Preconception binge drinking led to a 20% greater risk of NTDs than having >1 drink/day (reference was no alcohol intake).

Periconception consumption was also found to be associated with esophageal atresia +/-tracheoesophageal fistula (RR 1.26; 95% CI: 1.03-1.56). However periconception drinking plus >1 episode of binge drinking compared to drinking without any binge episodes did not yield any association with these gastrointestinal malformations.

Studies evaluating the effect of periconceptional alcohol exposure on the occurrence of congenital heart defects showed no significant associations save with risk of TGA. No

significant association was found between alcohol intake in the periconception period and orofacial defects or congenital diaphragmatic hernias. Periconception alcohol intake was not associated with any adverse pregnancy outcome. However there was a dose response relation between alcohol consumption and these. High alcohol intake (>20 units) led to a significant almost 4-fold increase in very preterm birth and a 2-fold increase in low-birth-weight.

Analysis showed that for depression, the highest rates were seen among alcohol users, whether they used drugs along with it or not (RR 1.94; 95% CI: 1.38-2.73 and RR 1.59; 95% CI: 1.22-2.07 respectively)

Preconception counselling led to a significant decrease in the consumption of alcohol during the trimester (OR 1.79; 95% CI: 1.08-2.97). The association with other drinking behaviours was not significant. Another preconception motivational intervention, consisting of counseling sessions and contraception consultation, led to a highly significant decrement in risk drinking (OR 1.66; 95% CI: 1.36-2.02) with reduction levels being highest in the 3 months post intervention. It also led to a significant increase in the use of effective contraception (OR 2.18; 95% CI: 1.80-2.64) and in so doing, significantly reduced the risk of an alcohol-exposed pregnancy (OR 2.20; 95% CI: 1.81-2.68). This was in conjunction with another similar trial where 74% of women were no longer at risk for alcohol-effected pregnancies at 1 month post-intervention.[187]

Following meta-analyses are generated from studies looking at effects of peri/ preconception alcohol consumption on MNCH outcomes and the effect.

Important findings

Outcomes	Studies type	No. of studies	Impact estimates	Heterogeneity
Spontaneous abortion	Observational	2	RR 1.30; 95% CI: 0.85-1.97	I^2=0%, P=0.74
NTDs	Observational	1	OR 1.24; 95% CI: 0.92-1.68	I^2=0%, P=0.63
EA+/-TEF	Observational	1	RR 1.20; 95% CI: 1.00-1.44	I^2=7%, P=0.30
Depression	Observational	1	RR 1.72; 95% CI: 1.41-2.09	I^2=0%, P=0.66
Adverse pregnancy outcomes			OR 0. 86; 95% CI: 0.78, 0.95	
Preterm birth		1	OR 0.79; 95% CI: 0.65, 0.98	
Very preterm birth		1	OR 1.07; 95% CI: 0.62, 1.86	
Low birthweight		1	OR 0.88; 95% CI: 0.69, 1.13	
Perinatal death		1	OR 0.89; 95% CI: 0.74, 1.07	
Congenital anomalies		1	OR 0.91; 95% CI: 0.80, 1.03	
Periconceptional alcohol And Congenital heart disease	Observational	1	OR 0.96; 95% CI: 0.91, 1.01	
Post motivational intervention	Experimental	1	OR 2.00; 95% CI: 1.79, 2.24	
preconception counseling and reduction in drinking	Experimental	1	OR 1.33; 95% CI: 0.86-2.05	I^2=40%, P=0.19

Key messages

- Pre and periconception alcohol exposure is non-significantly associated with a 30% increase in spontaneous abortion, 24% increase in NTDs and 20% increase in gastrointestinal anomalies.
- Binge episodes during the preconception period lead to a greater incidence of NTDs

- Preconception counselling greatly reduces alcohol intake during the 1st trimester.
- Behavioural interventions lead to a reduction in risk drinking that is highest in the 3 months post-intervention

10.3. Smoking cessation

Our analysis showed that **preconception** smoking was significantly linked to the risk of *preterm births* (OR 2.2; 95% CI: 1.29-3.75). Preconception smoking showed no significant association with *neural tube defects* (OR 0.80; 95% CI: 0.59-1.08) or with *orofacial defects* (OR 0.77; 95% CI: 0.48-1.22). Periconception studies were analyzed separately for different fetal outcomes. Preconception paternal smoking was significantly associated with a greater risk (OR 1.91; 95% CI: 1.09, 3.33) however, maternal was not (OR 0.99; 95% CI: 0.66, 1.47).

Periconception smoking was significantly associated with an almost 3 times increased risk of *congenital heart defects* (OR 2.80; 95% CI 1.76-4.47); light smoking (< 14 cigarettes/day) led to a non-significant 17% lower risk of heart defects than heavy (>25 cigarettes/day). No significant association was found between exposure and *esophageal atresia+/-tracheoesophageal fistula* (RR 0.95; 95% CI: 0.76-1.19) and *congenital diaphragmatic hernia* (OR 1.10; 95% CI: 0.91, 1.33).

Substantial research literature exists for interventions to increase smoking cessation among adults, women in general and pregnant women, however there is a dearth of clinical studies focusing specifically on non pregnant women of childbearing age. When assessing the effectiveness of a preconception counselling intervention versus standard care, one study showed that there was an almost 3 times greater likelihood of women quitting smoking in the post-intervention group, but this was not significant (OR 2.94; 95% CI: 0.70, 12.36).

The following meta analyses are generated from study that looked at the effect of smoking before conception on birth outcomes and of preconception counseling on maternal smoking behaviour.

Important findings

Outcomes	Studies type	No. of studies	Impact estimates
Preconception smoking			
Preterm birth	Observational	1	OR 2.20; 95% CI: 1.29-3.75
NTDs	Observational	1	OR 0.80; 95% CI: 0.59-1.08
Congenital anomalies	Observational	1	OR 0.85; 95% CI: 0.62, 1.16
Leukemia (paternal smoking)	Observational	1	OR 1.91; 95% CI: 1.09, 3.33
Leukemia (maternal smoking)	Observational	1	OR 0.99; 95% CI: 0.66, 1.47
Orofacial defects	Observational	1	OR 0.77; 95% CI: 0.48-1.22
Periconception smoking			
EA+/-TEF	Observational	1	RR 0.95; 95% CI: 0.76-1.19
CHD	Observational	1	OR 0.83; 95% CI: 0.65-1.07
CHD (light smoking vs heavy)	Observational	1	OR 2.80; 95% CI: 1.76, 4.47
Congenital diaphragmatic hernia	Observational	1	OR 1.10; 95% CI: 0.91, 1.33
Preconception intervention			
Counseling and maternal smoking behavior	Experimental	1	OR 2.94; 95% CI: 0.70, 12.36

Key messages

- Preconception smoking increases the risk of preterm births by more than 2 folds
- Pre/peri conception smoking is not significantly associated with congenital defects.
- Preconception couseling leads to an almost 3 fold increase in women quitting smoking before pregnancy.
- ETS exposure was not associated with either congenital heart defects or gastrointestinal anomalies.

10.4. Reducing illicit drugs consumption

In this section we report evidence specifically for illicit drugs including cocaine, marijuana, heroin etc. We found a limited number of risk aversion studies concerned with the MNCH effects of periconception substance abuse. Paternal and maternal usage was analyzed separately. We found that paternal periconception use of illicit drugs did not have an association with the risk of neural tube defects (RR 1.07; 95% CI: 0.81-1.31). When looking at the effect of individual drugs, the only significant association with a greater risk of NTDs was that of paternal heroin use in the periconception period (RR 1.63; 95% CI: 1.23-2.16). Maternal use of recreational drugs during the periconception period did not lead to an increased incidence of occurrence of NTDs (RR 0.91; 95% CI: 0.77, 1.07). Comparing parental use (combined or individual) with no use did not yield any significant association with NTD risk (OR 0.97; 95% CI: 0.72, 1.31).

A strong association was found between recreational drug use in the month in which conception occurred and incidence of gastroschisis (OR 9.60; 95% CI: 1.80-51.20), although this evidence came from a single case-control study.[188]

There was no significant association between substance abuse before pregnancy and maternal depression (OR 1.76; 95% CI: 0.99-3.13).

Two interventional studies on reducing illicit drug abuse were cited. One studied the helath seeking behavior of substance-abusing women using the 'Steps of Change' model.[189] The other studied the effects of behavioral couples therapy vs Individual-Based therapy amongst substance-abusing men on the incidence of partner violence (Stewart 2002)[190]. It reported that post-intervention, male-to-female aggression in the BCT group was lower than in the IBT group (17% vs 43%). Also husbands in the BCT reported fewer days of drug use, longer episodes of abstinence, less drug-related hospitalizations or arrests than husbands receiving individual-based treatment only.

The following meta-analyses are generated from study that looked at the effect of drug use during the month before conception and the following trimester on birth outcomes.

Important findings

Outcomes	Studies type	No. of	Impact estimates
Paternal consumption			
NTDs	Observational	1	RR 1.07; 95% CI: 0.87-1.31
Maternal consumption			
NTDs	Observational	1	RR 0.91; 95% CI: 0.77, 1.07
Gastroschisis	Observational	1	OR 9.60; 95% CI: 1.80-51.20
Depression	Observational	1	OR 1.76; 95% CI: 0.99-3.13
Parental consumption			
NTDs	Observational	1	OR 0.97; 95% CI: 0.72, 1.31

Key messages

- Our results should be interpreted with caution due to a relative scarcity of data on this subject.
- We found no significant association between paternal or maternal periconception use of recreational drugs and NTDs; or between parental drug uses in comparison with no drug use.
- We found a strong positive relation between maternal periconception substance abuse and the risk of gastroschisis.

11. Ameliorating environmental exposure in the pre-pregnancy period

For detailed review: refer Section XI

11.1. Radiation exposure

We looked at studies examining the effects of paternal/maternal preconception radiation on fetal/neonatal effects. Ionizing radiation exposure composed of both, occupation-related exposure as well as non-occupational exposure.

A single study by Doyle et al[191] reporting evidence on the effect of preconception radiation exposures in women on fetal death, showing a significant increase in risk of early miscarriage in mothers who had been employed at or before conception [RR 1.32; 95% CI: 1.04-1.66]. Results for association of still births and 2nd trimester miscarriages with maternal monitoring before conception were not significant.

We found that both paternal and maternal exposure to preconception ionizing radiation at work led to an overall greater risk of childhood cancers but the association reached significance only with maternal exposure (RR 1.29; 95%CI: 1.02, 1.63; RR 1.19; 95% CI: 0.92-1.54 respectively) and although studies may have stated otherwise, our pooled estimate showed a significant association between exposure and outcomes (RR 1.33; 95% CI: 1.06-1.67). Studies looking at the effect of radiation dose on the incidence of childhood hematological malignancies had equivocal results.[192-197]

Non-occupational exposure to ionizing radiation via X-rays led to higher rates of adverse fetal and neonatal outcomes. *Paternal* exposure led to significant decrements in birth weight (MD -73.00; 95% CI: -78.97, -67.03) and intrauterine growth (MD -53.00; 95% CI: -58.21, -47.79). *Parental* X-ray exposure before conception showed a weakly significant positive association with childhood cancers diagnosed in less than 15 years of age (OR 1.13; 95% CI: 1.01-1.26), especially between paternal abdominal exposure and leukemia in the offspring. Because diagnostic x-rays will continue to be widely utilized, knowledge of possible detrimental effects on reproductive outcomes is of practical importance. We postulate that these associations would be stronger with exposures closer to the time of conception. Hence future research should be directed at that *Parental* magnetic field exposures in the periconception period were not found to be associated with development of childhood cancers.

Following meta-analyses are generated from studies looking at MNCH outcomes for pre/periconception radiation exposure.

Important findings

Outcomes	Studies type	No. of studies	Impact estimates
1st trimester miscarriage	Observational	1	OR 1.32; 95% CI: 1.04, 1.66
Stillbirth	Observational	1	OR 1.64; 95% CI: 0.89, 3.00
2nd trimester miscarriage	Observational	1	OR 0.99; 95% CI: 0.59, 1.68
Childhood cancer(maternal exp)	Observational	1	OR 1.29; 95% CI: 1.02-1.63
Childhood cancer(paternal exp)	Observational	1	OR 1.20; 95% CI: 0.94, 1.53
Birth weight (paternal exp)	Observational	1	MD -73.0; 95% CI: -78.97,-67.03
IUGR (Paternal exp)	Observational	1	MD -53.0; 95% CI: -58.21,-47.79
Malignancies in offspring (Parental exposure)	Observational	1	OR 1.13; 95% CI: 1.01-1.26

Key messages

- Occupational radiation exposure in women before conception leads to a significant 30% increase in 1st trimester miscarriages.
- Occupational radiation exposure in women before conception leads to a significant 29% increase in overall childhood cancers.
- Occupational radiation exposure in men before conception leads to a non-significant increase in childhood cancers.
- Paternal X-ray exposure leads to significantly fetal growth restriction and decreased birth weights.
- Future research should be targeted at finding the association between exposure closer to the time of conception and MNCH outcomes.

11.2. Chemical exposure

Parental exposures before conception can result in an array of adverse reproductive effects. We intended to review literature for effects of exposure to toxic chemicals (organic solvents, metals, pesticides, polychlorinated biphenyl [PCB] etc), among either parent in the preconception period, on the subsequent pregnancy and its outcomes. However, we found very limited evidence of toxic forms of exposure and their effects pertaining to MNCH outcomes.

Preconception exposure to pesticides led to a 27% increase in spontaneous abortions ($p < 0.001$); with a 31% increase in early spontaneous abortions ($p=0.0007$) and a 22% increase in late spontaneous abortions (>12 weeks) ($p=0.03$). Paternal exposure to pesticides in the year before conception also showed significant increase in the rates of hematological malignancies in their offsprings.[198-201]

Analysis of a handful of studies on parental exposure to chemicals like paints, solvents, industrial products etc showed a 10% increase in the risk of ALL in subsequent offsprings with paternal exposure and a 44% increase with maternal exposure; both were significant ($p=0.02$; $p<0.00001$ respectively).

With respect to indoor air pollution, we found that women who reported having used wood[202] and/or coal or tires to cook,[203] during the periconception period (3 months before conception till end of 1st month post-conception), had significantly increased risks of having a child with an NTD.

Following meta-analyses are generated from studies looking at MNCH outcomes for pre/periconception exposure to toxic chemicals. These results should be interpreted with caution as only a small amount of relevant studies were pooled and analyzed.

Important findings

Outcomes	Studies type	No. of studies	Impact estimates	
Pesticide				
Spontaneous abortion	Observational	1	OR 1.27; 95% CI: 1.13-1.43	
Paternal exposure				
ALL	Observational	2	OR 1.10; 95% CI: 1.02-1.18	I^2=0%, P=0.67
Solvents	Observational	2	OR 1.05; 95% CI: 0.91-1.22	I^2=0%, P=0.53
Paints/thinners	Observational	2	OR 1.10; 95% CI: 0.93-1.30	I^2=4%, P=0.31
Plastic	Observational	2	OR 1.23; 95% CI: 0.98-1.55	I^2=0%, P=0.70
Oil products	Observational	1	OR 1.10; 95% CI: 0.90-1.34	
Oil/coal products	Observational	1	OR 1.10; 95% CI: 0.90-1.34	
Industrial dust	Observational	1	OR 1.30; 95% CI: 1.00-1.69	
Metal melting	Observational	1	OR 0.90; 95% CI: 0.70-1.16	
Maternal exposure				
ALL	Observational	2	OR 1.44; 95% CI: 1.26-1.64	I^2=0%, P=0.70
Solvents	Observational	2	OR 1.43; 95% CI: 1.16-1.78	I^2=70%, P=0.07
Paints/thinners	Observational	2	OR 1.60; 95% CI: 1.27-2.01	I^2=0%, P=1.00
Plastic	Observational	2	OR 1.74; 95% CI: 0.90-2.50	
Oil products	Observational	1	OR 1.50; 95% CI: 2.11-8.93	
Oil/coal products	Observational	1	OR 1.10; 95% CI: 0.70-1.73	
Industrial dust	Observational	1	OR 1.00; 95% CI: 0.60-1.67	
Metal melting	Observational	1	OR 1.40; 95% CI: 0.80-2.45	

Key messages

- An absolute deficiency of data exists to assess the possible relation between environmental exposures before conception and subsequent pregnancy outcomes
- Limited data shows a 27% increase in spontaneous abortions in those exposed to pesticides in the preconception period ($p < 0.0001$), especially spontaneous abortions in <12 weeks of gestation
- Limited data links living in a lead-polluted area to a 3-fold increase in congenital heart defects
- Limited data points to a 10% increase in the risk of ALL in offsprings of fathers exposed to various chemicals in the preconception period as compared to 44% when the mother was exposed ($p <0.02$; $p< 0.00001$ respectively)

Grading of interventions

Intervention	Group
Teenage/Adolescent Health	
Female Genital Mutilation	A
Prevention of teenage pregnancy	A
Prevention of coerced sex/sexual abuse	C
Advance maternal age	C
Birth spacing and inter pregnancy intervals	A
Post abortion care	C
Preconception counseling	
Genetic counseling and screening	C

General preconception counseling	B
Nutrition	
Maintenance of ideal pre pregnancy weight	A
Diet and exercise	C
Periconceptional folic acid and multivitamin	A
Vitamin A supplementation	B
Iron supplementation	C
Iodine supplementation	C
Balanced protein energy	C
Vitamin D supplementation	C
Vitamin B6 and B12 supplementation	C
Intimate Partner Violence	B
Mental Health	
Depression/ anxiety	C
Bipolar disease	C
Schizophrenia	C
Infections	
Prevention and treatment of sexually transmitted infections	B
Prevention and treatment of HIV/AIDS	B
Immunization such as tetanus	B
Immunization such as hepatitis B, Varicella, Rubella, Influenza, HPV.	C
Prevention and management of malaria	C
Management of tuberculosis	
Management of other infections such as asymptomatic bacteruira, group B streptococcus and toxoplasmosis	C
Chronic Diseases	
Diabetic care and management	A
Heart disease	C
Rheumatoid arthritis	C
Epilepsy management	C
Phenylkenouria	C
Thyroid management	C
SLE	C
Thrombophilia	C
Periodontal disease	C
Medication use	B
Substance abuse	
Smoking cessation	B
Alcohol	B
Caffeine	B
Illicit drugs	B
Environmental exposure	
Radiation	B
Other chemicals	B
Indoor air pollution	C
Over crowding	C
Lack of water and sanitation	C
Interventions to women with poor prior outcomes during pregnancy	
Prior stillbirth	C
Prior miscarriages	C
Prior cesarean section	C

Limitation and research gaps:

1. Ethical concerns have not permitted the feasibility of performing RCTs for certain interventions, e.g., maternal pre pregnancy weight, birth spacing and inter

pregnancy intervals, smoking and other substance abuse cessation and environmental exposures, thereby limiting the data available for meta-analyses on these interventions.
2. For interventions where conducting RCTs was ethically feasible, there was a lack of articles reporting the evidence of impact of similar outcomes, which again restricted the pool of studies for the analysis.
3. Certain outcome measures, such as maternal satisfaction regarding an intervention cannot be quantitatively estimated and are therefore discussed in separate tables.
4. Although we have included data regarding impact of certain interventions individually to women of reproductive age, data on preconception could not be deduced.
5. Furthermore, certain interventions have targeted health care professionals to improve their knowledge and behavior towards certain interventions. However, we have not looked into these at the moment. This is an aspect which can be studied in future in order to refine the findings from this review.
6. A limitation of the meta-analyses is that in majority of the interventions we focused on the comparison of treatment/intervention versus no intervention/ placebo/routine care. For most interventions we have not compared two different interventions against one another e.g. for the intervention of management of diabetes in pregnancy we did not compare insulin versus oral hypoglycemic agents. We feel that this approach was justified as our principal attempt was to gauge the true effects of an intervention without becoming embroiled in the comparison of multiple treatment regimens.

Implications for Policy

Preconception care is symbolic of a strong assurance to optimizing the health of men, women, and children across the lifespan. A substantial body of evidence advocates for preconception care and has laid the groundwork for the content of this care. Clinicians and researchers emphasize that prenatal care is simply too late, and that most interventions effected during pregnancy would achieve greater results if begun before pregnancy. All women of reproductive age, regardless of their dietary intake, must be counseled regarding the importance of taking a folic acid/multivitamin supplement prior to pregnancy to reduce their newborns' risk of congenital birth defects. Women with general medical conditions, especially those with diabetes mellitus, must be counseled regarding their risk, and avoid unplanned pregnancies until intensive therapy and monitoring are able to maintain glycemic control, and optimize their chances of a successful pregnancy. All healthcare professionals who are involved in the care of women of reproductive age must screen women for modifiable risk factors, such as diabetes mellitus, and obesity, realizing that every health visit provides an opportunity to prepare women for pregnancy. Research shows that intensive counseling over time, and even peer support, is necessary and effective in helping women to modify behaviors that put them and their future children at risk. For instance, overweight and obese women may require multiple interventions and multiple attempts to be able to sustain their weight loss and better optimize their body mass index. While such care must be provided to all women who have the potential to become mothers, certain risks are present and therefore, must be addressed as early as adolescence- including female genital mutilation, and risky sexual behavior among teenagers. Together with previous reviews on preconception care, this review reinforces that a change in perspective on women's health cannot result simply from the interaction between provider and

patient; rather behavioral changes such as the consistent use of contraception to prevent teen pregnancy and closely space pregnancies, and the empowerment of communities to abandon the practice of female genital mutilation, must incorporate change on multiple levels of policy and practice to promote the health of women and their future newborns.

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Detailed Analysis of Preconception Risk Factors and Interventions

Section I

Pre-conception Counselling

Background

Preconception or pre-pregnancy care is no longer a new concept- health research since the 1960's has made it clear that since prenatal care improves MNCH outcomes, preconception care is simply a logical extension. It was realized that while prenatal care remains important, intervening at this time is too late to prevent harmful exposures from affecting the developing fetus and that earlier measures to optimize the health of potential mothers (and fathers) would benefit both parents and the newborn. The range of potential interventions extends from the obvious, taking a vitamin supplement for a few months before conception, to birth spacing and preventing adolescent pregnancy. What was remarkable was the difference that resulted just from optimizing women's health *before* pregnancy- ensuring a 2-year spacing between pregnancies, for example, could reduce perinatal mortality by 55%! As significant progress is made towards reducing child deaths worldwide, preconception care is a promising means to improve the lives of women and newborns.

Scope of intervention

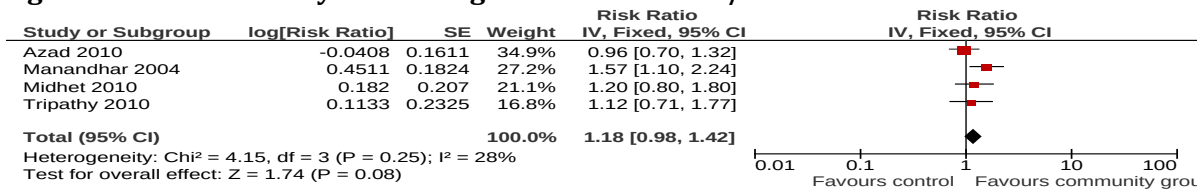
A substantial body of evidence already advocates for preconception care and has laid the foundation for the content of this care.[1,2,3-6] This review was therefore conducted to bridge the research gap between content and implementation- to determine the specifics of where such care should be provided, who should provide it, and which interventions are most effective in optimizing preconception health. To this end, emphasis was placed on trials of intervention that assessed MNCH outcomes and focused on holistic care or counseling specifically before conception.

Impact estimates

Interventions were carried out either in health facilities by trained providers a maximum of one year before conception, or in the community by community women (and their husbands) who had been trained. Community-based studies[7,8,9,10] mainly focused on educating women about pregnancy and child care. Healthcare providers were able to reach women who already attended clinics more easily than through health records. Preconception care and counseling improved women's health behaviors- smoking decreased 30% in one study, and women were 3 times more likely to quit smoking in another study; women were 5-6 times more likely to use folic acid if they had received counseling in a health facility (**Figure 1.1.1**); women were also 20% more likely to breastfeed their newborn (**Figure 1.1.2**), 2.36 times more likely to use safe delivery kits at home births in developing countries (**Figure 1.1.3**), and 39% more likely to obtain antenatal care (**Figure 1.1.4**). MNCH outcomes also showed significant improvement- women were less likely to have an ectopic pregnancy or miscarriage; had lower rates of STIs; and were more likely to identify their pregnancy as intended. Neonatal outcomes were also significantly improved with preconception care/counseling resulting in fewer perinatal deaths, preterm births, congenital defects, small-for-gestational age babies, low birth weight babies, neonatal (RR 0.76) deaths

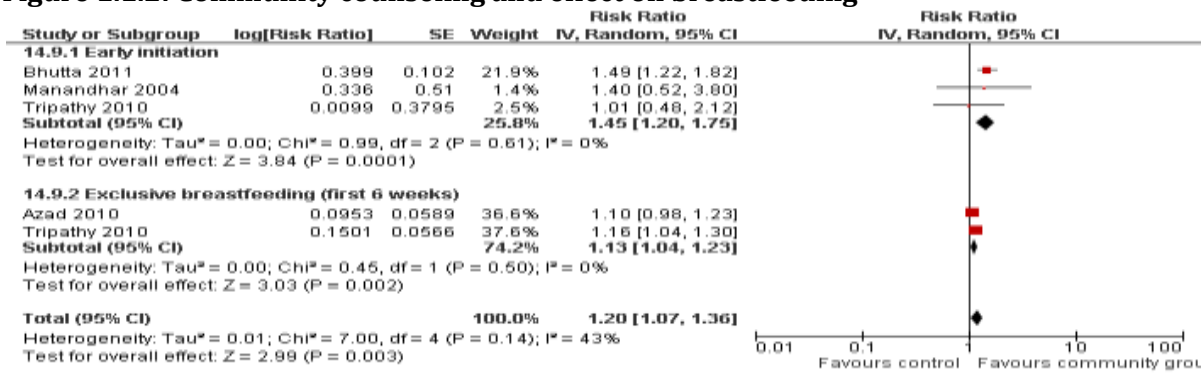
(**Figure 1.1.5**). One study that involving home visits favored the control group, however, this was a low-risk population to begin with.

Figure 1.1.1: Community counseling and effect on iron/folate



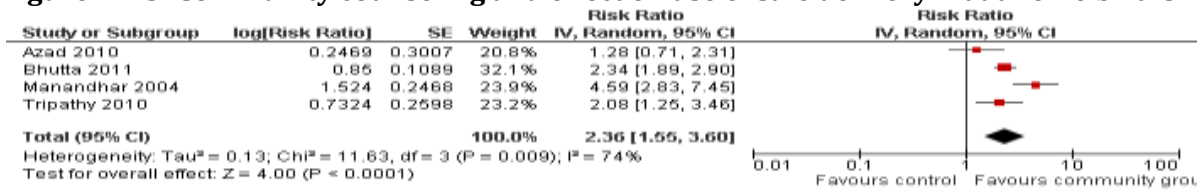
Citation to the included studies:
Azad 2010[7]; Manandhar 2004[9]; Midhet 2010[11]; Tripathy 2010[10]

Figure 1.1.2: Community counseling and effect on breastfeeding



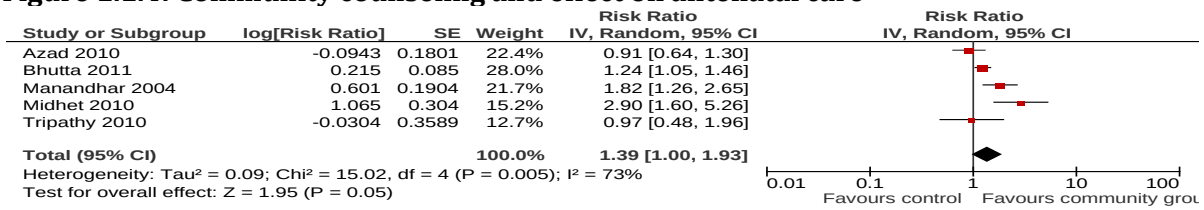
Citation to the included studies:
Azad 2010[7]; Bhutta 2011[8]; Manandhar 2004[9]; Tripathy 2010[10]

Figure 1.1.3: Community counseling and effect on use of safe delivery kit at home births



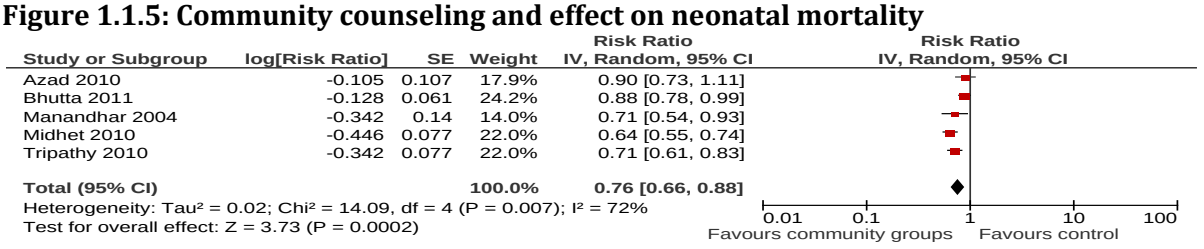
Citation to the included studies:
Azad 2010[7]; Bhutta 2011[8]; Manandhar 2004[9]; Tripathy 2010[10]

Figure 1.1.4: Community counseling and effect on antenatal care



Citation to the included studies:
Azad 2010[7]; Bhutta 2011[8]; Manandhar 2004[9]; Midhet 2010[11]; Tripathy 2010[10]

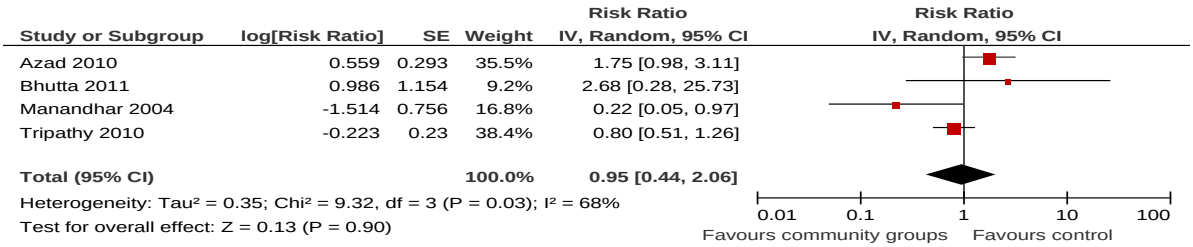
Figure 1.1.5: Community counseling and effect on neonatal mortality



Citation to the included studies:
Azad 2010[7]; Bhutta 2011[8]; Midhet 2010[11]; Manandhar 2004[9]; Tripathy 2010[10]

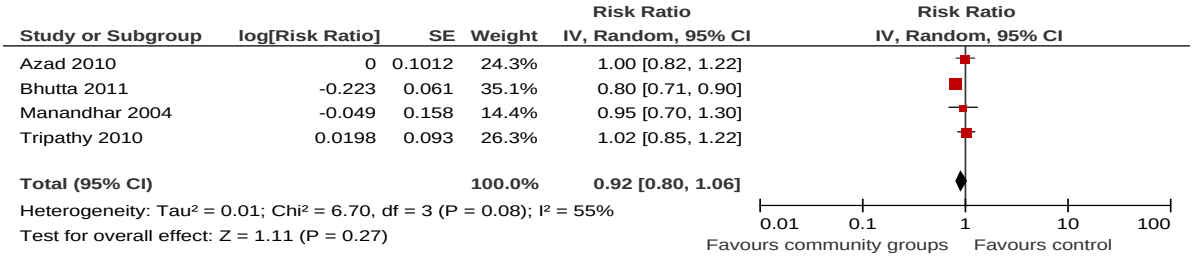
However, no difference were observed for maternal mortality (**Figure 1.1.6**), stillbirths (**Figure 1.1.7**), uptake of tetabus toxoid immunization (**Figure 1.1.8**).

Figure 1.1.1: Community counseling and effect on maternal mortality



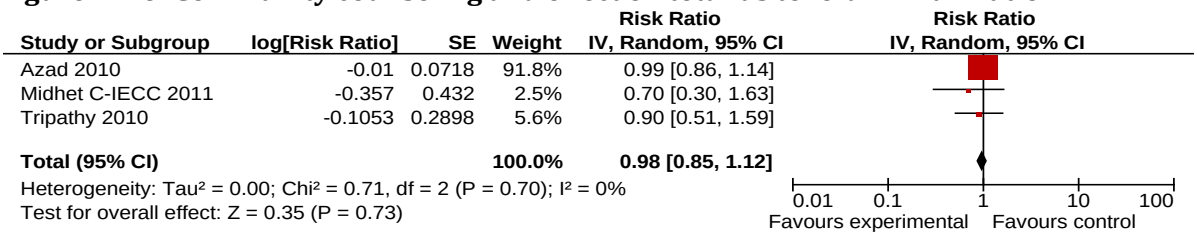
Citation to the included studies:
Azad 2010[7]; Bhutta 2011[8]; Manandhar 2004[9]; Tripathy 2010[10]

Figure 1.1.2: Community counseling and effect on stillbirths



Citation to the included studies:
Azad 2010[7]; Bhutta 2011[8]; Manandhar 2004[9]; Tripathy 2010[10]

Figure 1.1.6: Community counseling and effect on tetanus toxoid immunization



Citation to the included studies:
Azad 2010[7]; Midhet 2010[11]; Tripathy 2010[10]

Table 1.1.1: Interventions for preconception counseling

Preconception Education/Counseling Program	Outcomes
Brochure for patient and letter for primary care physician listing patient's preconception risks and explaining benefits of addressing risks before pregnancy [Jack 1998][1]	36/46 women in the intervention group had at least one risk addressed versus 41/54 women in control group
Prepregnancy clinic- routine assessment and investigations, selected investigations, karyotype of male partner if indicated, consultation and plan for care for future pregnancies [Cox 1992]	Investigations selected specifically were more likely to determine risk. Subsequent pregnancy outcome was unaltered by previous pregnancy history (88% with previous miscarriage had live normal birth, 95% with previous fetal abnormality had live normal birth), but did improve for those women who had chronic maternal disease (81% had a live normal birth, compared to previous live birth rate of 42%, p<0.001)
Mailed invitation to attend preconception counseling at general physician's practice, risk-assessment questionnaire, counseling and specialist referral if necessary [Elsinga 2006[12]& 2008[13] and de Jong-Potjer 2006[14]]	Women attending preconception counseling before pregnancy increased from 8 to 20% Comparison of anxiety levels prior to PCC with the levels afterwards showed an average decrease of 3.6 points (95% CI 2.4 – 4.8). Quit smoking before pregnancy: aOR 2.94 (0.70–8.84)

Table 1.1.1: Interventions for preconception counseling	
Preconception Education/Counseling Program	**Outcomes**
	Quit smoking when discovered pregnancy:aOR1.85 (0.74–4.60) No alcohol use in first trimester:aOR1.79 (1.08–2.97 Preconception folic acid use: aOR 4.93 (2.81–8.66) Use harmful medications in pregnancy: 1.40 (0.66–2.99) Miscarriage:12/145 versus 162/1740 Ectopic pregnancy: 0/145 versus 6/1740 Perinatal death: 1/145 versus 14/1740 Preterm birth: 8/145 versus 124/1740 Low birth weight: 4/145 versus 81/1740 SGA: 1/145 versus 25/1740 Congenital anomalies: 5/145 versus 68/1740
Identification of preconception risks, discussion of timing, planning and preparation for thenext pregnancy, family/genetic history reviewed specialist referrals if necessary, rubella immunization and WAIT, STOP,GO reminder card [Lumley 2006[15], also quoted in Whitworth 2009[2]]	Low birth weight: 25/393 intervention versus 14/394 control, OR 1.85 (95% CI 0.91-3.91) Preterm birth: 24/390 intervention versus 17/391 control, OR 1.44 (95% CI 0.73-2.91) SGA: 40/378 intervention versus 31/382 control Congenital anomaly: 5/392 intervention versus 2/394 control
Six 2-hour group sessions over a 12-week period covering preconception health promotion. Also had a buddy-system (telephone contact) [Hillemeier 2008][16]	Post intervention use of daily folate-containing multivitamin OR= 6.595, meet recommended physical activity level OR= 1.867
Preconception risks identified and managed, referrals if necessary, provision of condoms and multivitamin with folic acid for 3 months before conception, early detection of pregnancy [Czeizel 1999][17]	8837 women, of whom 6060 had a confirmed pregnancy, 7600 accompanied by husband/partner -Genetic counseling: 373/636 couples with genetic risk had informative offspring during study -Of babies born to 53 women with chronic medical conditions, only 1 daughter of an epileptic women had CL/P -Smoking prevalence decreased from 40.3 to 12.4 and then 10% by the time of pregnancy confirmation -Alcohol use declined from 0.2-5.4% to 0-0.8% -Lower rate of ectopic pregnancy: 0.2 compared to 0.8% in general population -Lower rate of major congenital anomalies 20.6 versus 35 per 1000 in general population -Cost per couple for just primary periconceptional care $150
Outreach, education and support for high-risk women with a focus on building resilience to negative social forces through peer mentor-based case management. Self- assessment of needs and abilities, and with peer mentor form a care and goal plan. Case management team (nursing, health education, social worker at the clinic) monitors and coordinates care, works with women. Educational support groups meet monthly, women receive $50 for making progress and staying in program for 6 months [Livingood 2010][18]	-Low birth weight: decreased 10.9% in intervention versus increased 3.2% in control -Infant mortality rate: decreased from 81.3 to 35.7/1000 live births in intervention versus increased from 27.2 to 37.5/1000 live births in control -33.2% in intervention and 31.5% in controls achieved desired birth spacing -After intervention, lower rates of STDs (10.4%) versus controls (16.7%), p=0.02
Brief preconception health promotion at family planning clinic [Moos 1996-abstract only][3]	Women exposed to information on preconceptional health during routine family planning visits had a 51.8% (p = 0.064) greater likelihood of identifying their pregnancies as intended than the group that had been to the family planning clinics but had not been exposed to the program
Women's groups involved in participatory learning and action, with a facilitator, identifying and prioritizing maternal and neonatal problems, and identifying and implementing strategies in the community. [Azad 2010][7]	Neonatal mortality rate: RR 0.93,95% CI 0.80–1.09 Early neonatal mortality rate: RR 0.95,95% CI 0.78–1.16 Late neonatal mortality rate: RR 0.87, 95% CI 0.59–1.29 Stillbirth rate: RR 0.97, 95% CI 0.82–1.15 Perinatal mortality rate: RR 0.96, 95% CI 0.87–1.07

Table 1.1.1: Interventions for preconception counseling	
Preconception Education/Counseling Program	**Outcomes**
	Maternal mortality ratio: RR 2.02, 95% CI 1.11–3.68 >4 antenatal visits: RR 0.74, 95% CI 0.39–1.39 Taking iron tablets: 0.95, 95% CI 0.69–1.30 Maternal tetanus toxoid injection: RR 0.99, 95% CI 0.86–1.14 Safe delivery kit used at home birth: RR 1.29, 95% CI 0.77–2.16 Health system strengthening and training of TBAs was part of both intervention and control Exclusive breastfeeding for 6 weeks: RR 1.10, 95% CI 0.98–1.24 Infant morbidity (cough, diarrhea, fever): RR 0.93, 95% CI 0.74–1.17
Quarterly group education sessions facilitated by lady health workers and community health committees, including promotion of antenatal care and maternal health education, use of clean delivery kits, facility births, immediate newborn care, identification of danger signs, and promotion of care-seeking, using standard materials, flip charts and a video [Bhutta2011][8]	Miscarriage rate: RR 1·12 (0·89–1·40) Stillbirth rate: RR 0·79 (0·68–0·92) Neonatal mortality rate: RR 0·85 (0·76–0·96) Early neonatal mortality rate: RR 0·86 (0·75–0·98) Late neonatal mortality rate: RR 0·83 (0·64–1·07) Perinatal mortality rate: RR 0·83 (0·74–0·93)
A female facilitator convened women's group meetings every month. The facilitator supported groups through an action-learning cycle in which they identified local perinatal problems and formulated strategies to address them [Manandhar 2004][9]	Stillbirth rate: OR 1·06 (0·76–1·47) Neonatal mortality rate: OR 0·70 (0·53–0·94) Maternal mortality rate: OR 0·22 (0·05–0·90) Any antenatal care: OR 2·82 (1·41–5·62) Any iron/folic acid supplementation: OR 1·99 (1·14–3·46) Used clean home delivery kit: OR 4·59 (2·83–7·45) Infant morbidity (fever, cough, diarrhea): OR 0·65 (0·36–1·20) Breastfeeding within 1 hr: 1·40 (0·52–3·79) Discard colostrum: 0·55 (0·27–1·10)
Facilitators used picture books and audio cassettes to educate women's groups on family planning; nutrition; preparation for pregnancy and delivery; and danger signs during pregnancy, delivery and postpartum, over six sessions of 1-2 hours each. Three generations of such groups were formed and separate groups of participating women's husbands as well. [Midhet 2010][11] *women's age not specified	Received routine prenatal care: OR for women's intervention 2.4 (1.4-4.3), for couples' intervention 2.9 (1.6-5.0). Received tetanus immunization: OR for women's intervention 1.8 (1.2-2.9), for couples' intervention 0.7 (0.4-1.1) Took iron/folic acid: OR for women's intervention 1.1 (0.9-1.5), for couples' intervention 1.2 (0.8-1.8) Perinatal death: OR for women's intervention 0.5 (0.3-0.7), for couples' intervention 1.4 (0.9-2.2) Early neonatal death: OR for women's intervention 0.6 (0.4-1.0), for couples' intervention 0.7 (0.3-1.7) Neonatal death: OR for women's intervention 0.7 (0.4-1.0), for couples' intervention 0.9 (0.5-1.6) Using modern contraception: OR for women's intervention 1.6 (1.0, 2.7) 0.7 (0.5, 1.0)
Program components were: organizing women's groups, identifying problems, implementing a "formal action plan" for the problems identified, and training birth attendants and husbands in safe birthing techniques. [O'Rourke 1998][19] *women's age not specified	Perinatal mortality decreased from 117 per 1000 births before the intervention to 43.8 deaths per 1000 births after The proportion of women receiving antenatal care and initiating breast-feeding on the first day after birth was also significantly greater. The number of infants attended to immediately after delivery likewise increased, but the change was not statistically significant.
Facilitator held 20 monthly meetings with women's groups, who identified and prioritized maternal and newborn health problems in the community, collectively selected relevant strategies to address these problems, implemented the strategies, and assessed the results. Used role-play, picture-cards and story-telling[Tripathy 2010][10]	Neonatal mortality rate: OR 0·71 (0·61–0·83) Early neonatal mortality rate: OR 0·63 (0·54–0·75) Late neonatal mortality rate: OR 0·92 (0·67–1·26) Stillbirth rate: OR 1·02 (0·85–1·23) Perinatal mortality rate: OR 0·79 (0·70–0·90) Maternal mortality ratio: OR 0·80 (0·51–1·24) >3 antenatal visits: OR 0·63 (0·37–1·06) Maternal tetanus toxoid injection: OR 0·90 (0·51–1·54) Use of iron supplements: OR 1·12 (0·71–1·76)

Table 1.1.1: Interventions for preconception counseling	
Preconception Education/Counseling Program	**Outcomes**
	Use of safe home delivery kit: OR 2·08 (1·25–3·44) Infant morbidity (any of cough, fever, diarrhea): OR 0·62 (0·37–1·03) Breastfeeding within 4 hours: OR 1·01 (0·48– 2·14) Exclusive breastfeeding for 6 weeks: OR 1·82 (1·14–2·92) Cause-specific mortality for early neonatal deaths (253 in intervention versus 367 in control): -Birth asphyxia 92 versus 142 -Prematurity 85 versus 110 -Septicemia 38 versus 47 -Hypothermia 16 versus 26

Preconception counseling must be tailored to specific high-risk groups. This is especially important for women and couples who have previously had a poor pregnancy outcome, for example a previous pregnancy loss or a recurrent pregnancy loss. Recurrent miscarriage is the spontaneous loss of three or more consecutive pregnancies with the same biological father in the first trimester. Reducing anxiety before the next pregnancy is crucial[20, 21] so that any measures that can be taken to improve subsequent pregnancy outcomes are availed. First, the woman or couple must be counseled regarding their chances of the next pregnancy resulting in a live birth. This probability decreases with number of previous fetal losses, being 80% after the first loss, 70-80% after a second loss, 50-60% after three consecutive losses and subsequently decreasing even further.[21, 22] Women are also more likely to have a live birth if their previous miscarriage was early in gestation (less than 16 weeks). A thorough assessment of possible etiologic factors is recommended for couples who experience recurrent pregnancy loss (defined as 3 or more consecutive losses), which affects about 1% of women. Genetic problems especially chromosomal abnormalities; chronic medical conditions notably thrombophilia; mycoplasma infection; endocrine disorders; substance use especially alcohol or tobacco; anatomical anomalies and immune factors must all be considered in the evaluation of women experiencing pregnancy losses.[20] The most commonly studied interventions have been for thrombophilia associated with antiphospholipid antibodies, factors of immune origin and genetic disorders. Immunomodulation and preimplantation genetic diagnosis are very technical and expensive interventions and thus were not reviewed in detail; however this does not preclude a comprehensive screening and presentation of these options to couples that have experienced the tragedy of recurrent pregnancy loss. The longitudinal studies on women with recurrent pregnancy loss showed that Factor V Leiden (F5) carriers were more likely to have a subsequent loss than non-carriers (odds ratios: 1.93 and 2.03, respectively) and prothrombin G20210A (F2) had similar outcomes as well.[23] At present only low-dose aspirin has been investigated as a periconception intervention for women with recurrent pregnancy loss without a known cause.[24, 25] In recent randomized controlled trials, however, there was no difference in the live birth rate between the group of women given aspiring and those given placebo.[26, 27] Few randomized controlled placebo trials have been conducted for any other risk-reducing

interventions and comprehensive reviews of the causes and management of pregnancy loss indicate that until now the greatest benefit is from supportive care.[28-31]

Grade table

Results from 5 cluster randomized controlled trials were pooled to yield a relative risk of 0.76, 95% CI: 0.66-0.88 for neonatal mortality with preconceptional counseling of women for birth and newborn care preparedness.

Conclusion

Preconception care and counseling show promise as a means to improve maternal and child health. Promoting health before conception can increase antenatal care seeking by 39%, reduce neonatal mortality by 24%, increase the use of safe delivery kits at home births in developing countries by 2.36 times, and increase the likelihood of breastfeeding by 20%. However, further randomized controlled trials are imperative to show which MNCH outcomes preconception care affects consistently and positively, and to delineate where and by whom such care should be provided, how long before conception such care should begin, and which interventions are most successful.

General preconception counseling for reducing neonatal mortality

Patient or population: patients with reducing neonatal mortality
Settings: India, Pakistan, Nepal, and Bangladesh
Intervention: General preconception counseling

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Control	Corresponding risk General preconception counseling	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Neonatal mortality CSG Follow-up: 2.8 years	Study population		RR 0.76 (0.66 to 0.88)	79511 (5 studies)	⊕⊕⊕⊕ high	
	45 per 1000	34 per 1000 (30 to 40)				
	Low risk population					
	24 per 1000	18 per 1000 (16 to 21)				
	High risk population					
	59 per 1000	45 per 1000 (39 to 52)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Key messages

- Preconception counselling allows women to identify and reduce possible risk factors for poor MNCH outcomes *before* pregnancy. Even though most women have at least one risk factor, and many have multiple risks, preconception counselling does not cause anxiety.
- Women who receive preconception counselling are more likely to change risk behaviors (quit smoking before pregnancy OR 2.94, decrease alcohol consumption from 5.4 to 0.8%, 5 times more likely to use folic acid before pregnancy, 39% more likely to seek antenatal care, more than twice as likely to use safe delivery kit at home births)
- Therefore, women who receive preconception counselling have better MNCH outcomes: neonatal mortality 24% risk reduction, 20% more likely to breastfeed.
- The content of preconception care has been detailed. Preconception counseling for every woman every time can begin with providers asking two simple questions: “Do you plan on becoming pregnant?” and “Are you currently using any family planning method?”

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Section II

Teenage/adolescent health

2.1 Female genital mutilation

Background

The number of women living with the consequences of female genital mutilation is estimated to be about 100 million, and the prevalence of this practice is nearly universal in many African countries. Using data from these countries, it is projected that 130 000 life years are lost among women of reproductive age, owing to FGM's association with obstetric hemorrhage.[1] Women with all types of FGM are exposed to the risk of reproductive tract infections, infertility, intractable pain, dyspareunia, urinary and menstrual complications, dermoid cysts, and are postulated to be at higher risk of acquiring HIV.[2] Further, women experiencing childbirth after FGM have a 55% increased risk of stillbirths and neonatal deaths.[3] Women with type III FGM, the most severe form, are 30% more likely to need a caesarean section and 70% more likely to suffer postpartum hemorrhage which puts them at high risk of maternal death. They also face a multitude of other obstetric complications,[4-6] and their newborns are 66% more likely to need resuscitation at birth. FGM is usually performed sometime between infancy and age 15, and occasionally on adult women.

Scope of Intervention

With 2 million girls under the age of 15 at risk of FGM each year, the WHO rejuvenated its efforts to eliminate the practice in 2008, with advocacy, research and public health efforts to motivate communities to abandon FGM, and a global strategy in 2010 to stop the medicalization of FGM. Although FGM is most commonly practiced in childhood, many girls undergo the procedure as adolescents, and many women are reinfibulated after childbirth, with ensuing complications in further pregnancies[7]. This review therefore focuses on a research gap[8] to identify effective interventions to promote the abandonment of FGM in the preconception period, in order to prevent the awful consequences this practice has on maternal, neonatal and child health.

Preconception care for women with FGM
• Women who have undergone FGM should be counseled regarding the increased obstetric and perinatal risks they face, with a view to encourage them to obtain early and regular prenatal care, and to prevent them from being reinfibulated after delivery • Women, and their partners, should also be counseled to encourage them not to carry out the procedure on their daughters

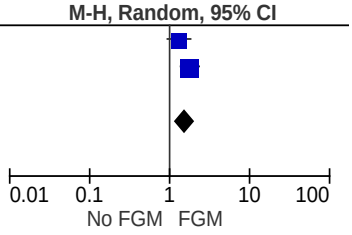
Impact estimates

We only found **observational** studies that have addressed FGM as a risk factor for poor pregnancy outcomes. This review confirms existing evidence that FGM contributes to stillbirths (56% increased risk) (**Figure 2.1.1**), the need for women to undergo an episiotomy during labor (29% increased risk) (**Figure 2.1.2**) and caesarean section (**Figure 2.1.3**), and fetal distress (**Figure 2.1.4**).

Figure 2.1.1: Stillbirths after FGM

Study or Subgroup	No FGM Events	No FGM Total	FGM Events	FGM Total	Weight	Risk Ratio M-H, Random, 95% CI
Morison 2001	81	549	48	427	44.3%	1.31 [0.94, 1.83]
Oduro 2006	91	1466	125	3605	55.7%	1.79 [1.38, 2.33]
Total (95% CI)		**2015**		**4032**	**100.0%**	**1.56 [1.15, 2.11]**
Total events	172		173			

Heterogeneity: Tau² = 0.02; Chi² = 2.05, df = 1 (P = 0.15); I² = 51%
Test for overall effect: Z = 2.88 (P = 0.004)

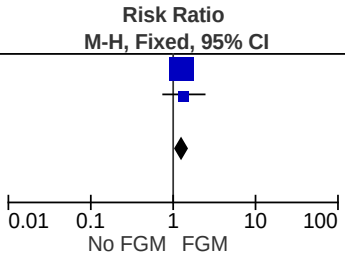


Citations to the included Studies:
Morison 2001[9], Oduro 2006[10]

Figure 2.1.2: Episiotomy after FGM

Study or Subgroup	No FGM Events	No FGM Total	FGM Events	FGM Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Elnashar 2007	150	169	33	47	75.4%	1.26 [1.04, 1.53]
Wuest 2009	24	122	16	110	24.6%	1.35 [0.76, 2.41]
Total (95% CI)		**291**		**157**	**100.0%**	**1.29 [1.05, 1.58]**
Total events	174		49			

Heterogeneity: Chi² = 0.06, df = 1 (P = 0.81); I² = 0%
Test for overall effect: Z = 2.40 (P = 0.02)

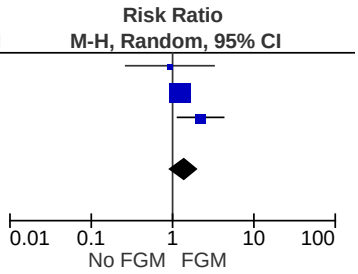


Citations to the included Studies:
Elnashar 2007[11], Wuest 2009[12]

Figure2.1.3: Caesarean section after FGM

Study or Subgroup	No FGM Events	No FGM Total	FGM Events	FGM Total	Weight	Risk Ratio M-H, Random, 95% CI
Elnashar 2007	10	169	3	47	9.3%	0.93 [0.27, 3.23]
Oduro 2006	120	1466	241	3605	64.7%	1.22 [0.99, 1.51]
Wuest 2009	27	122	11	110	25.9%	2.21 [1.15, 4.25]
Total (95% CI)		**1757**		**3762**	**100.0%**	**1.39 [0.93, 2.09]**
Total events	157		255			

Heterogeneity: Tau² = 0.05; Chi² = 3.14, df = 2 (P = 0.21); I² = 36%
Test for overall effect: Z = 1.59 (P = 0.11)

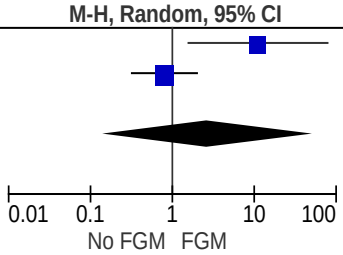


Citations to the included Studies:
Elnashar 2007[11], Oduro 2006[10], Wuest 2009[12]

Figure 2.1.4: Fetal distress and FGM

Study or Subgroup	No FGM Events	No FGM Total	FGM Events	FGM Total	Weight	Risk Ratio M-H, Random, 95% CI
Elnashar 2007	40	169	1	47	45.7%	11.12 [1.57, 78.80]
Wuest 2009	8	122	9	110	54.3%	0.80 [0.32, 2.00]
Total (95% CI)		**291**		**157**	**100.0%**	**2.67 [0.14, 50.67]**
Total events	48		10			

Heterogeneity: Tau² = 3.94; Chi² = 7.47, df = 1 (P = 0.006); I² = 87%
Test for overall effect: Z = 0.65 (P = 0.51)



Citations to the included Studies:
Elnashar 2007[11], Wuest 2009[12]

This review examines **interventional** studies and reaffirms that the education and empowerment of women is critical to successfully abandoning the practice of FGM.[13, 14] We found that such programs carried out over at least a year can increase women's

resolution to not practice FGM on their daughters 1.9-2.6 times post-intervention. This review also reiterates that interventions to stop the practice of FGM are more successful if they employ a human rights and development approach rather than simply increasing awareness of the consequences, [15] use a participatory approach, and involve community leaders and government;[16] overall the interventions increased the number of community members understanding the consequences of FGM and disapproving of the practice by up to 3 times.

Table 2.1.1: Interventions to prevent FGM (as quoted in Denison 2009)[17]

Intervention	Outcome
Training of healthcare workers at 8 sites-3sessions over 2 months including presentation,visual aids, role-playing) [Diop 1998][18]	RR that after intervention healthcare workers: -Know long-term complications of FGM = 0.99 (95% CI 0.79-1.26) -Believe that FGM poses no health risks if done hygienically = 1.54 (0.91-2.60) -Wish to educate their patients about FGM = 1.07 (0.93-1.23)
2 hour-long educational sessions for university students about reproductive health including the dangers of FGM (health talk, group discussion, role play, use of educational aids, handouts) [Mounir 2003][19]	Mean difference in knowledge score after intervention= 0.75 (95% CI 0.63-0.87)
17-21 months Community education and advocacy in refugee camps including introduction to FGM abandonment practices (educational events, community meetings, theatre performances, video sessions, mass media activities) delivered by many groups [Chege 2004][20]	RR that after intervention significant difference in Ethiopian community: -Knowing adverse health consequences of FGM = 1.37 (95% CI 1.26-1.49) -Believing that FGM compromise women's human rights = 2.21(95% CI 1.75-2.79) -Supporting abandonment of FGM in their community = 2.16 (95% CI 1.78-2.62) -Intending to NOT practice FGM on their daughters = 2.62 (95% CI 1.96-3,49) RR that after intervention difference in Kenyan community: -Knowing adverse health consequences of FGM = 1.02 (95% CI 0.99-1.06) -Believing that FGM compromise women's human rights = 0.77(95% CI 0.67-0.89) -Supporting abandonment of FGM in their community = 1.21 (95% CI 0.99-1.48) -Intending to NOT practice FGM on their daughters = 0.94 (95% CI 0.75-1.17) Outcomes in Kenya did not strongly support the intervention, although this was a program expansion- versus a program introduction in Ethiopia
Year-long Community mobilization, advocacy, mass media delivered by women's groups. Tier 1: Community meetings and groups formed which designed action plans. Tier 2: visited local leaders and discussed FGM/C at tribal meetings and town forums. State level: newspaper columns, radio call-in shows, public forums [Babalola 2006][21]	RR that after intervention significant difference in women: -Encouraging others not to practice FGM = 2.68 (95% CI 1.76-4.08) -NOT believing there are benefits of FGM = 1.04 (95% CI 0.95-1.15) -Disapproving of FGM = 1.21(95% CI 1.11-1.13) -Believing that the community favors discontinuation of FGM = 3.50 (95% CI 2.58-4.76) -Having self-efficacy to resist husband's pressure to perform FGM on their daughters = 1.71(95% CI 1.47-1.99) -Intending to NOT practice FGM on their daughters = 1.13(95% CI 1.02-1.26) RR that after intervention significant difference in men: -Encouraging others not to practice FGM = 1.19 (95% CI 0.71-2.01) -NOT believing there are benefits of FGM = 1.17 (95% CI 1.02-1.33) -Disapproving of FGM = 2.57 (95% CI 2.06-3.20) -Believing that the community favors discontinuation of FGM = 1.76 (95% CI 1.25-2.47) -Having self-efficacy to resist husband's pressure to perform FGM on their daughters = 2.20 (95% CI 1.85-2.61) -Intending to NOT practice FGM on their daughters = 1.11 (95% CI 0.97-1.27)

Table 2.1.1: Interventions to prevent FGM (as quoted in Denison 2009)[17]	
Intervention	**Outcome**
Village empowerment through educationalProgramme (sessions in human rights, problem solving, environmental hygiene, women's health) [Diop 2004][22]	RR that after intervention girls < = 10 yrs old had had FGM 0.77 (95% CI 0.64-0.93) RR that after intervention significant difference in women: -Knowing consequences of FGM = 2.92 (95% CI 2.28-3.74) -Believing FGM is unnecessary = 2.18 (95% CI 1.82-2.61) -Disapproving of FGM = 2.10 (95% CI 1.76-2.51) -Believing that husband disapproves of FGM = 1.87 (95% CI 1.60-2.18) -Regretting practicing FGM on daughters = 1.55 (95% CI 1.37-1.76) -Intending to not practice FGM on their daughters =1.91(95% CI 1.64-2.23) RR that after intervention significant difference in men: -Knowing consequences of FGM = 3.10 (95% CI 2.28-4.23) -Believing FGM is supported by religion = 0.71 (95% CI 0.51-0.99) -Intending to not practice FGM on their daughters = 1.97(95% CI 1.65-2.36)
Village empowerment through educationalProgramme (sessions in human rights, problem solving, environmental hygiene, women's health) [Ouoba 2004][23]	RR that after intervention girls < = 10 yrs old had had FGM = 0.74 (95% CI 0.33-1.66) RR that after intervention significant difference in women: -Discussing FGM with others = 1.40 (95% CI 1.27-1.55) -Knowing consequences of FGM = 1.18 (95% CI 1.08-1.29) -Believing FGM is unnecessary = 1.02 (95% CI 1.00-1.05) -Disapproving of FGM = 1.04 (95% CI 1.01-1.08) -Believing that husband disapproves of FGM = 1.03 (95% CI 1.00-1.06) -Regretting practicing FGM on daughters 1.26= (95% CI 1.14-1.40) -Intending to not practice FGM on their daughters = 1.01(95% CI 0.99-1.03) RR that after intervention significant difference in men: -Discussing FGM with others = 1.22 (95% CI 1.13-1.33) -Knowing consequences of FGM = 1.47 (95% CI 1.31-1.64) -Believing FGM is unnecessary = 1.06 (95% CI 1.02-1.11) -Disapproving of FGM = 1.10 (95% CI 1.05-1.15) -Intending to not practice FGM on their daughters = 1.05 (95% CI 1.01-1.09)
Navrongo women's groups- 1. Education and community events (including radio, school and clinics); 2. Livelihood skills and development activities; 3. Above interventions combined IntraHealth Ethiopia- networking with policy makers, training, community mobilization, public declarations Tostan community empowerment program [Feldman-Jacobs 2006][24]	Education and combined interventions led to a significant 93-94% decrease in risk of FGM versus control (baseline prevalence of FGM very low) 2,252 community members agreeing to ban FGC at public declarations. Women: 16/333 approve FGM intervention versus 60/200 control, 12/333 intend to practice FGM on daughter intervention versus 54/200 control. Men: 13/82 approve FGM intervention versus 56/198 control, 20/82 prefer a woman who has had FGM intervention versus 63/198 control. 83% of communities had abandoned FGM

Table 2.1.2: Summary of impact estimates for female genital mutilation			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
Klouman et al (2005)[25] report only a higher rate of bacterial vaginosis among women with FGM, and no difference for all other STIs and urogenital infections. Okonofua et al (2002)[26] report higher prevalence of symptomatic urogenital infections among women with FGM OR for genital ulcers= 4.4 <u>HIV:</u> OR 2.38, 95% CI 0.59–9.69 [Brewer 2007 CS][27] <u>STIs:</u> 26/219 versus 0/3 women with no FGM [Elmusharaf 2006 CC- participants were pregnant or infertile women][28] HSV 2: aOR 4.71, 95% CI 3.46-6.44, p< 0.001[Morison 2001 CS][9] <u>Bacterial vaginosis:</u> aOR 1.66, 95% CI 1.25-2.18, p<0.001[Morison 2001 CS][9] <u>Depression:</u> 30.1±7.31 (mean score and SD) versus 29.9±4.63 women with no FGM[Elnashar 2007 Obs][11] <u>Anaemia:</u> aOR 1.31, 95% CI 1.02-1.68 [Morison 2001 CS][9]	<u>Caesarean section:</u> OR 1.24, 95% CI 0.98-1.57 [Oduro 2006 Obs][10] 10/169 versus 3/47 women with no FGM [Elnashar 2007 Obs][11] FGM I: aRR 1.03, 95% CI 0.88–1.21 FGM II: aRR 1.29, 95% CI 1·09–1·52 FGM III: aRR 1·31, 95% CI 1.01–1.70 [WHO 2006 Coh][29] 27/122 versus 11/110 women with no FGM (p=0.0012 for emergent C-section) [Wuest 2009 CC][12] <u>Instrumental delivery:</u> 14/122 versus 10/110 women with no FGM [Wuest 2009 CC][12] <u>Stillbirths:</u> OR 1.84, 95% CI 1.38-2.45 , p=0.000 [Oduro 2006 Obs][10] aOR 1.16, 95% CI 0.78-1.73 [Morison 2001 CS][9] <u>Episiotomy:</u> 150/169 versus 33/47 women with no FGM, p<0.001[Elnashar 2007 Obs][11] 24/122 versus 16/110 women with no FGM [Wuest 2009 CC][12] <u>Difficult delivery:</u> OR 2.28 [Jones 1999[4], quoted in Obermeyer 2005 SR][30] <u>Perinatal tears:</u> OR 1.43 (comparing type II FGM to none) [Larsen 2002[31], quoted in Obermeyer 2005 SR][30] 21/122 versus 51/110 women with no FGM (p<0.0001 for 1st degree	<u>Low birth weight:</u> OR 0.96, 95% CI 0.81-1.14 [Oduro 2006 Obs][10] FGM I: aRR 0.94, 95% CI 0.82–1.07 FGM II: aRR 1.03, 95% CI 0.89–1.18 FGM III: aRR 0.91, 95% CI 0.74–1.11 [WHO 2006 Coh][29] <u>Fetal distress:</u> 40/169 versus 1/47 women with no FGM, p<0.001 [Elnashar 2007 Obs][11] OR 2.6 [Vangen 2002[32], quoted in Obermeyer 2005][30] 8/122 versus 9/110 women with no FGM [Wuest 2009 CC][12] <u>Infant resuscitation</u>: FGM I: aRR 1.11, 95% CI 0.95–1.28 FGM II: aRR 1.28, 95% CI 1.10–1.49 FGM III: aRR 1.66, 95% CI 1.31–2.10 [WHO	<u>Death:</u> 9/169 versus 0/47 women with no FGM [Elnashar 2007 Obs][11]

	tear) [Wuest 2009 CC][12] <u>Fetal death:</u> OR 2.5 [Vangen 2002[32], quoted in Obermeyer 2005][30] <u>PPH:</u> FGM I: aRR 1.03, 95% CI 0.87–1.21 FGM II: aRR 1.21, 95% CI 1.01–1.43 FGM III: aRR 1.69, 95% CI 1.34–2.12 [WHO 2006 Coh][29] <u>Extended maternal hospital stay:</u> FGM I: aRR 1.15, 95% CI 0.97–1.35 FGM II: aRR 1.51, 95% CI 1.29–1.76 FGM III: aRR 1.98, 95% CI 1.54–2.54 [WHO 2006 Coh][29]	2006 Coh][29] <u>Perinatal death:</u> FGM I: aRR 1.15, 95% CI 0.94–1.41 FGM II: aRR 1.32, 95% CI 1.08–1.62 FGM III: aRR 1.55, 95% CI 1.12–2.16 [WHO 2006 Coh][29] No association [Essen 2002 Obs][33]	

Conclusion

Community mobilisation and empowerment can significantly increase the number of parents intending to not practise FGM on their daughters, by increasing the number of community members who know the adverse health consequences of FGM, disapprove of FGM and think that it is unnecessary, and support community abandonment of the practice. Further research is needed to assess whether women who undergo reversal of the procedure have improved MNCH outcomes, and whether counselling in the healthcare setting and context of pregnancy might provide another avenue to encourage abandonment of FGM.

Key messages

- Female genital mutilation leads to difficult labor and childbirth, and has serious health consequences for the mother including increased rates of episiotomies (29% increase) and stillbirths (56% increase).
- Community mobilization and female empowerment can significantly increase the number of parents intending to not practice FGM on their daughters, raise awareness of the adverse health consequences of FGM, and provide a stimulus for community abandonment of the practice.

2.2 Coerced sex and other abuse in adolescence

Background

Sexual coercion includes coerced or forced intercourse, unwanted sexual touching, verbal harassment, and transactional sex. It was perceived to be a normal part of intimate relationships by Ugandan adolescents.[34] In India 12% of married young women experienced unwanted sex frequently.[35] In other countries, it was found that premarital sexual interactions are a norm and premarital child-bearing tolerable.[36]

Between 7-48% of adolescent girls report that their debut sexual experience was forced.[37, 38] Adolescent girls are more likely to be pressured into sexual activity and are less likely to be in a position to use contraception leading to unintended pregnancies. Females who experienced coercion are more likely to experience both subsequent non-consensual sex as well as risky consensual sexual behaviors. Such coercion may lead to non-use of condoms and an increased risk of unintended pregnancies and STIs.[39, 40] Unequal power relations between genders as well as a big age divide between young women and their partners, greatly contribute to both unwanted sex and subsequent unwanted pregnancy.[41]

Domestic workers are more likely to have been coerced into having sex (OR 1.8). Erulkar et al.[42] cited social exclusion led to significantly higher odds of coerced first sex (OR 2.0). According to a study[43] women who were given alcohol or drugs at coerced sex were almost two times more likely to report multiple sex partners (aOR 1.47; 95% CI: 1.01-2.13) and substance abuse (aOR 1.64; 95% CI: 1.10-2.42) compared to those not given alcohol or drugs. Early experiences of coercion are also associated with poor psycho-social effects like depression, low self-esteem and isolation.[44, 45]

Another area which provides disturbing evidence is that of dating violence. In the past several decades dating violence has emerged as a significant social and public health problem. Teen dating violence is a considerable problem not only because of its

disquieting prevalence and physical and mental health consequences,[46, 47] but also because it transpires at a phase of life when patterns of interaction are discovered and these may carry over into later life.[48] Dating violence is likely a vital context for sexual risks among teens as has been shown in literature which links physical and sexual victimization to sexual risk behaviours as well as sexual health concerns like condom non-use,[49, 50] pregnancy,[49] multiple partnering[51, 52] and STD/HIV diagnosis.[53] Rates of dating violence in high school samples have been found to be as high as 57%.[54]

Scope of the intervention

Adolescence is an age of exploration, transition, and social development. In many parts of the world adolescence is typified by socially approved freedom and sexual experimentation for both genders. In this section we aimed to assess how the occurrence of violence amongst adolescents negatively impacted MNCH outcomes. Such violence entailed mainly evidence of dating violence as well as sexual coercion outside of such relationships. We further reviewed projects aiming to bring about improvement in the rate of the aforementioned issues whether they are reduced acts of violence or decreased acceptability of aggression or improved knowledge of consequences attached to such malice.

One study found that sexual violence was associated with significantly increased chances of reporting of lifetime experience of ever feeling depressed, suicidal ideation, suicide attempts, unwanted pregnancy, pregnancy complications or miscarriages, sexually transmitted diseases, difficulty sleeping, and alcohol consumption.[55]

Content of care for adolescents suffering from dating violence and sexual coercion includes educating them about their rights, informing them about the implications of such acts of violence on their health and, in the case of a pregnancy, on the health of their unborn child. It should inculcate in them safer sexual behaviors and instill in them the ability to stand up for their cause.

Impact estimates

Dating violence prevention programmes have been the most evaluated. To date, several prevention programs have been developed and implemented, with widely varying methods and results (**Table 2.2.1; Table 2.2.2**). Prevention programs can be broadly divided into two subtypes: those which aim to evade violence in dating relationship before it occurs (primary prevention) and those designed to attend to violence that is already occurring in a relationship (secondary prevention). One such dating violence prevention programme was shown to significantly reduce psychological, moderate physical and sexual dating violence perpetration and when evaluated, it showed long-term durability of self-reported decrease in perpetration and ill-treatment.[56-59] Evaluation of a school-based program showed rates of physical dating violence were 2.4% less in the intervention group, however this decrease in self-reported violence was evident in boys and not girl.[60] A randomized-controlled trial of another school-based intervention showed that the programme had been effective in reducing incidents of physical and emotional abuse and the symptoms of emotional distress for over a year after the programme. One systematic review[61] estimated that on average, universal multi-component programmes reduced violence by 15% in schools that delivered the programmes compared to those that did not. A systematic review[62] that examined education programmes for college students on sexual assault found little evidence of the

effectiveness of such programmes in preventing such assaults but reported an increased knowledge about rape and a favourable change of attitudes towards it. Literature on other intervention programs also reports on outcomes associated with a change in the level of knowledge and perceived attitudes post-intervention but not on behaviours and actual prevalence of abuse among adolescents.[63-65]

Conclusion

Many adolescents and young females in developing countries have experienced forced sex, either at commencement of sexual activity or subsequently there forth. Coercive sexual incidents are seen to be associated with severe and long-standing consequences in the lives of young females who are more likely to have unwanted pregnancies, abortions, infection.

So far only one strategy has been demonstrated to be effective in preventing intimate partner violence, namely school-based programmes for adolescents to prevent violence within dating relationships. The majority of programmes that have been evaluated so far have been implemented relatively narrowly and it is time to act and implement these on a large scale to reap maximum benefits before the situation gets even more out of hand.Future researchers should consider designing programs that include a significant skill-building component, in addition to addressing possible misconceptions of the causes and contributory factors relating to dating aggression.

Key messages

- Globally, significant numbers of young women have experienced coercive sex
- Females who experienced coercion are more likely to experience both subsequent non-consensual sex as well as risky consensual sexual behaviors.
- They may suffer from poor mental health and this may lead to an increased risk of unintended pregnancies, and STIs.
- During our literature appraisal, we found limited evidence on the effect of coerced sex on MNCH outcomes.
- Interventions like school based programs appear to be effective for the prevention of dating violence in adolescents.
- There is dire need for researchers to examine the longitudinal behavior change that occurs as a result of the prevention programs

Table 2.2.1: Impact estimates of Intimate partner violence				
Maternal	**Pregnancy**	**Newborn**	**Infant**	**Others**
Mental health: No sexual violence vs sexual violence before age 18- Feeling depressed: 346/639 (54·0% [48·3–59·6])vs 338/418 (80·6% [75·4–85·0]) aOR 2·30 95%CI(1·70–3·11) p<0·0001 Suicidal ideation: 74/639 (10·2% [8·0–13·1]) vs 118/418 (25·3% [20·4–30·9]) aOR 2·31 95%CI(1·57–3·40) p=0·0001 Attempted suicide: 16/639 (2·3% [1·3–4·0]) vs 32/418 (6·0% [4·0–9·1]) aOR 2·03 95% CI(0·97–4·25) p=0·0583 Diffi culty sleeping: 170/639 (26·8% [23·5–30·2]) vs 200/418 (45·3% [38·6–52·1]) aOR 1·78 95% CI(1·32–2·40) p<0·0004 [Reza 2009]^^[55] **Unwanted pregnancy:** No sexual violence vs sexual violence before age 18- 105/639 (16·2% [12·3–21·1]) vs 174/418 (40·4% [35·4–45·7]) aOR 2·92 95% CI (1·87–4·55) p<0·0001. [Reza 2009]^^[55] **Sexually transmitted infections:** No sexual violence vs sexual violence before age 18- 12/639 (1·7% [0·9–3·2]) vs 30/418 (7·6% [5·3–10·8]) aOR 3·69 95% CI (1·78–7·66) p=0·0009. [Reza 2009]^^[55]	**Pregnancy complications or Miscarriages:** No sexual violence vs sexual violence before age 18- 8/639 (1·3% [0·5–3·5]) vs 23/418 (5·4% [3·4–8·6]) aOR 3·54 95% CI (1·47–8·55) p=0·0061. [Reza 2009]^^[55]			**Substance abuse:** Cigarette use: 11/639 (1·6% [0·8–3·2]) vs 12/418 (2·7% [1·4–5·3]) aOR 1·22 (0·58–2·57) p=0·5860. [Reza 2009]^^[55] Alcohol consumption (more than a few sips): 37/639 (5·4% [3·6–7·9]) vs 68/418 (17·3% [12·5–23·4]) aOR 3·02 (1·68–5·44) p=0·0005. [Reza 2009]^^[55] **Condom use:** Conflict in Adolescent Dating Relationships Inventory (CADRI) mean score- Consistent condom use 1.58 (1.07-3.10) vs Inconsistent Condom use 1.87 (1.10-3.42), p=0.045. CADRI subscales- Physical IPV: - Never- (consistent condom use vs inconsistent condom use) 13/24 vs 11/24; Sometimes/often14/31 vs17/31, p=0.591. Verbal/emotional abuse:- Never/sometimes 19/34 vs15/34; Often 8/21 vs 13/21. Multiple logistic regression showed that for each point increase in the $\log_e$-transformed CADRI total mean score, the teen was 12 times more likely to practice inconsistent condom usage, odds ratio (OR) = 12.35, 95% CI = 1.21, 126.16. [Teitelman 2008][66]
^^ In 26.2% of the cases, the perpetrator was the boyfriend or the husband				

Table 2.2.2: Impact estimates of sexual abuse	
Intervention details	**Behavior modification**
The *Choose Life!* Program uses edutainment – drawing on stories and drama to entertain and at the same time educate – to encourage the adoption of healthy behaviors among Batswana youth. *Choose Life!* Integrates health and development issues into radio and television dramas and full-color, easy-to-read booklets. *Choose Life!* Aimed to address issues of gender-based violence via both the print and radio materials. The material intended to sensitize people about the effects of gender-based violence and encouraged abuse victims to take action – to talk to someone trusted, see a doctor and find out how the law can help them end the abuse. [Nkwe 2009][63]	Most adults in the sample (around 90%) knew that forcing someone you know to have sex is still rape; over 80% disagreed with the statement that women sometimes deserve to be beaten, and over two thirds felt that their community could do something about violence against women. Despite these high underlying levels of knowledge and positive attitudes, *Choose Life!* was associated with an increase in positive knowledge and attitudes on each of these measures, particularly among more educated women. In 2003, around one third of boys and one quarter of girls said that if an adult touched their private parts they would tell the perpetrator to stop. In 2007, the percent saying that they would do this had increased to 39% of boys and 33% of girls. For both boys and girls, the percent saying they would take positive action (scream to attract attention, tell a parent or teacher, call a helpline) increased between 2003 and 2007. 29% of those who had read the *Choose Life!* Booklet *Enuff is Enuff*, said that they would phone a helpline if an adult touched their private parts, compared to 21% of those who had not read the booklet. [Nkwe 2009][63]
THE KENYA ADOLESCENT REPRODUCTIVE HEALTH PROJECT [Askew 2004][64] the Population Council's Frontiers in Reproductive Health Program (FRONTIERS) and the Program for Appropriate Technology in Heath (PATH) Kenya office collaborated with three Government of Kenya ministries – the Ministry of Education, Science and Technology (MOEST), the Ministry of Health (MOH) and the former Department of Social Services (now within the Ministry of Gender, Sports, Culture and Social Services (MOGSCSS) – to design and implement a multi-sectoral project with the following ultimate goals: • To improve knowledge about reproductive health and encourage a responsible and healthy attitude towards sexuality among adolescents; • To delay the onset of sexual activity among younger adolescents; • To decrease risky behaviors among sexually active adolescents. Interventions included: 1. supportive environment at the community level 2. health facility interventions (strengthen the health system's ability to meet the reproductive health information and service needs of adolescents) 3. school-based components (educating school children and sensitizing parents on reproductive health issues and services) The study used a quasi-experimental design to determine the relative effectiveness and cost of the interventions. Sites A & B were 'experimental' sites. Site C was the 'control' site	There are increasing proportions of girls (in sites A and C) and boys (in sites A and B) reporting that the first time they had sex it was wanted, as opposed to them being persuaded or forced. For girls in suite A, there were also significant decreases in the proportions reporting persuasion or force, down overall from 39 percent to 11 percent; non-significant decreases were also found in sites B and C (from 34% to 23%, and 43% to 34% respectively). Girls in site B were significantly more likely to report being sweet-talked after the intervention, however, again perhaps reflecting the emphasis in the school-based activities on abstinence. Some quite dramatic and significant decreases in the proportions of adolescents supporting the view, that it was ever justifiable for a man to beat his wife or girlfriend, can be seen by the time of the endline survey, and in all three sites. (But as some of the largest changes were seen in the control sites this would seem to reflect a community-wide change in attitude rather than changes brought about by the interventions.)

Table 2.2.2: Impact estimates of sexual abuse	
Intervention details	**Behavior modification**
The intervention had four components: community activities; teacher-led, peer-assisted sexual health education in years 5–7 of primary school; training and supervision of health workers to provide 'youth-friendly' sexual health services; and peer condom social marketing [Ross 2007][67]	Attitudes to sex: • If a man or youth wants to have sexual intercourse (make love) with a girl, can she refuse to have sexual intercourse (make love) with him if he is older than her? (Yes) • If a man or youth wants to have sexual intercourse (make love) with a girl, can she refuse to have sexual intercourse (make love) with him if he is her lover? (Yes) • If a girl accepts a gift from a boy, must she agree to have sexual intercourse (make love) with him? (No) Adjusted RR (young men) for all 3 correct responses in intervention group compared to control group 1.77 (1.42, 2.22) Adjusted RR (young women) for all 3 correct responses in intervention group compared to control group 1.42 (1.11, 1.81)
Dating violence interventions	
Safe Dates Project Included school and community activities aimed at changing attitudes about violence and gender stereotyping, conflict management, and providing support for help seeking when violence occurred. Participants in the control condition were exposed to only community activities, which included special services for adolescents in violent relationships and community service provider training. Schools assigned to the treatment condition were exposed to the above community activities as well as a series of school activities, which included a theater production, 10-session curriculum provided by a trained presenter, and a poster contest. [Foshee 1996, 1998, 2000, 2004][56-59]	follow-up indicated that the Safe Dates programwas effective in preventing psychological, physical,and sexual abuse perpetration against dating partners as well as in changing mediating variables suchas attitudes about violence, gender stereotyping,conflict resolution, and awareness of communityservices for dating violence. The behavioral effects of the program faded at a one-yearfollow-up. data collected 1 month after program activities, revealed 25% less psychological abuse perpetration, 60% less sexual perpetration, and 60% less physical violence perpetrated in the treatment schools than in the control schools
A five-session prevention curriculum intended to change attitudinal correlates of dating violence that was implemented with both male and female high school students. It was designed to address both perpetration and victimization of dating aggression in a didactic, skills-based forum. [Avery 1997][68]	Boys and girls in the treatment group were significantly less accepting of aggression in the context of a dating relationship comparedto pre-treatment levels, and that this effect was not evident for the control group.
Compared two prevention programs, a short and a long form, whichaddressed various aspects of dating aggression, including sexual, psychological, and physical aggression. The shortform of the program consisted of two classroom sessions, designed to target issues of control in relationships andunderstanding an individual's rights in a dating relationship. The longer form of the program included two additional activities, namely, watching afilm about dating violence and writing fictional letters to a perpetrator and victim of dating violence. [Lavoie 1995][69]	both a short and longer versionof a primary prevention program can be effective in altering attitudes supporting dating violence, and to some degree,knowledge of factors related to dating aggression.
an 18-session program that used a health-promotionapproach to preventing violence by focusing on positive alternatives to aggression. The intervention used both, skill andlearning based approaches as well as addressing patriarchal values	Over time, treatment participants evidenced a significant reduction in physical abuse, all forms of victimization,and reports of emotional distress compared to the control group

Table 2.2.2: Impact estimates of sexual abuse	
Intervention details	**Behavior modification**
believed to contribute to dating violence. Thecurriculum incorporated three components: education and awareness of abuse and power dynamics in closerelationships, skill development, and social action. [Wolfe 2003][70]	
Two schools presenteda half-day prevention program, consisting of an auditorium presentation and a classroom discussion, and two schools employed a full day intervention. The primary goals of this program were to increase knowledge about violence againstwomen in intimate relationships, address sexist attitudes that may underlie violent behavior, increase knowledge ofwarning signs of potential abuse, and provide information regarding community resources available for perpetratorsand victims of aggressive behavior. [Jaffe 1992][71]	Results of this program revealed significant positive changes in knowledge, attitude, and behavioral intentions atpost-test, and most changes were maintained at the delayed follow-up testing. females demonstrated more positive attitudes and stronger behavioral intentions than the maleparticipants. Additionally, for males only, there was a proportion of scores that changed in the undesired directionfollowing the intervention, which may suggest that some males experienced defensiveness as a result of the program, oralternatively, that some males were already engaged in abusive relationships and the program amplified their negativeresponses, and thus required secondary, rather than primary, prevention
[Jones (1987, 1991)][72, 73]	at post-test, thosestudents exposed to the program demonstrated statistically significantly improved scores. Additionally, theexperimental group was somewhat more knowledgeable about general resources available to address issues of datingaggression following the intervention. However, there were no significant differences on attitude items between thecontrol and treatment groups, suggesting that the program was not effective in altering attitudinal correlates to datingaggression. Additionally, this study, like the research discussed previously, found a significant gender difference acrossgroups, with female students more frequently responding in the desired direction on the attitude items
*Skills for Violence Free Relationships*is a multi-session curriculum foradolescents, which uses a gendered perspective,i.e., it is an adaptation of programs for batteredwomen and focuses on males as perpetrators andfemales as victims. (Levy, 1984)[74]	Did not demonstrate change instudents' attitudes toward use of violence.
In Touch with Teens is an eight session curriculumcovering such topics as roots of violence, power andcontrol, cycle of violence, and building blocks of agood relationships [Aldridge, 1993)[75]	Change on severalitems pertaining to knowledge regarding healthyrelationships and knowledge regarding sexualharassment and sexual assault.
'Building Relationships inGreater Harmony Together (BRIGHT)' -Skill-based program focusing on attitudechange, skill enhancement, and support for help-seeking based on a five-session dating violenceprevention curriculum. (Avery Leaf1997)[68]	students in the treatmentgroup showed significant reductions in their attitudes justifying dating violence as well as a significantincrease regarding intention to seek help comparedto those in the no treatment group
a 5-session relationship violence prevention program involving a middle school. A composite measure assessed changes in knowledge, attitudes, and methods of dealing with relationship violence. (Macgowan 1997)[76]	Results indicated that treatment group scores were significantly higher than control group scores at posttest ($p < .001$) and treatment group posttest scores were significantly higher than pretest scores ($p < .001$). Improvements were made in knowledge about relationship violence and attitudes about nonphysical violence. No changes were seen in attitudes about physical violence or in methods of dealing with relationship violence.
Didactic prevention program for women at risk for datingviolence victimization. Participants were high	Theprogram was acceptable, and that participants subjectively noted positive changes in their ability to deal

Table 2.2.2: Impact estimates of sexual abuse	
Intervention details	**Behavior modification**
school and college-aged women. It consisted of nine one-hour group sessions. It designed to identify various types of violent behaviors that occurin dating relationships, explore the negative consequences of aggression, and develop improved interpersonal,empowerment, and self-esteem skills. [Rosenn 1996][77]	withviolent situations. No control group was utilized making conclusions regarding this program tentative.
The Dating Violence Intervention Program (DVIP), a prevention program for teens, included three educational sessions in the context of health classes, several school-wide activities, educatorand administrator education, and a theater presentation. [Sousa 1991][78]	Subjective datasuggest that students demonstrated idiosyncratic behavior changes following theprogram, like confronting peers about abuse,distributing paraphernalia advocating the end of violence, and spontaneously speaking to students and media regardingthe program. However, although these findings are promising, in the absence of a control condition and empirical outcomedata, it is difficult to evaluate the effects of the programs
A coeducational program for teenagers on preventing sexual coercion in dating situations. Students examined individual and social attitudes underlying coercive sexual behavior and learned communication skills aimed at preventing or dealing with unwanted sexual advances. Instruction was enhanced by video and an interactive video "virtual date." [Pacifici 2001][79]	Students in the treatment group with initial coercive attitude scores at or above the mean benefited significantly more than students with the same range of scores in the control group.
A 21-lesson curriculum delivered during 28 hours by teachers with additional training in the dynamics of dating violence and healthy relationships. Dating violence prevention was integrated with core lessons about healthy relationships, sexual health, and substance use prevention using interactive exercises. Relationship skills to promote safer decision making with peers and dating partners were emphasized. Control schools targeted similar objectives without training or materials. [Wolfe 2009][80]	The Preventing Dating Violence was greater in control vs interventionstudents (74/754, 9.8% vs 72/968, 7.4%; adjusted odds ratio, 2.42; 95% confidence interval, 1.00-6.02; *P*=.05). A significant group x sex interaction effect indicated that the intervention effect was greater in boys (PDV: 7.1% in controls vs 2.7% in intervention students) than in girls (12.1% vs 11.9%). Main effects for secondary outcomes were not statistically significant, not even for condom use (control 138/255 (54.1%) vs intervention 200/364 (55.0%), OR, 1.04; 95% CI, 0.51-2.12; *P*=.91); however, sex x group analyses showed a significant difference in condom use in sexually active boys who received the intervention (114 of 168; 67.9%) vs controls (65 of 111 [58.6%]) (*P*<0.01). The cost of training and materials averaged CA$16 per student.

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Section III

Maternal age at conception

3.1 Prevention/avoidance of teenage pregnancy

Background

Ten percent of girls become mothers by the age of sixteen in sub-Saharan Africa and south and south-east Asia. Globally, 16 million girls between the ages of sixteen and nineteen give birth; many more become pregnant but seek induced abortion. These girls are themselves not physically mature, and many enter pregnancy with depleted nutrition reserves and anemia.[5] Adolescent pregnancy is dangerous for both the mother and the child- girls younger than nineteen have a 50% increased risk of stillbirths and neonatal deaths, as well as preterm birth, low birth weight and asphyxia.[10] These health risks further increase for girls who become pregnant at less than age fifteen, and are somewhat reduced for older adolescents age 18-19.[12-15] While many unmarried adolescent girls become pregnant, equally, adolescent pregnancies are the result of child marriages. Adolescent pregnancies are also more common among disadvantaged women.[19] Beyond health risks, adolescent mothers also have social disadvantages,[21] being socially isolated, often without partners or family support, and usually unable to complete their education; thus they may perpetuate socioeconomic and behavioral risks with their own children.

Scope of Intervention

Much research has focused on the poor pregnancy and infant outcomes to adolescent mothers.[25, 26] Adolescents are especially prone to complications of labor and delivery, such as obstructed and prolonged labor, vesico-vaginal fistulae, infectious morbidity, preterm birth and low birth weight.[25] This review instead focuses on what interventions are effective in preventing teen pregnancy and repeat pregnancy in adolescence. Since randomized controlled trials yield more accurate results of effect of interventions,[31] the meta-analyses were limited to these trials, and observational studies were only shown in the table of impact estimates.

Additional Resources for Adolescent Sexual and Reproductive Health
• Population Council • International Planned Parenthood Federation • The Guttmacher Institute • National Campaign to Prevent Teen Pregnancy • United Nations Population Fund

Preconception care in adolescence
• All adults, including healthcare providers, have the opportunity to prevent adolescent pregnancy- preconception counseling should be made available especially in schools, community centers and adolescent health centers • Sexually active young women should be made aware of the risks of teen pregnancy— nutritional anemia, low birth weight babies, maternal mortality, perinatal and infant mortality rates are much higher in adolescents, and the risk increases with decreasing age • Adolescent pregnancy results from the interplay between many contextual influences. The care of

pregnant adolescents and programs to prevent adolescent pregnancy must therefore be responsive to these factors, holistic, and sensitive to the adolescent's needs. "Addressing the adolescents' educational, social, economic, nutritional, psychological, as well as medical needs is more likely to result in better pregnancy outcomes for the mother and child, and also broadens the adolescents' life options." (WHO 2007)[25]

- Adults involved in the care of adolescents should promote access to sexual and reproductive health services for adolescents and school-based reproductive education. They should encourage teens to complete their education and join youth development programs
- Encouraging teenage mothers to return to school, develop parenting skills, and providing them and their young children with comprehensive care prevents repeat pregnancy in adolescence.
- Encourage teens to use long-acting contraception, or provide other means to increase the efficacy of contraceptive protection. Promote condom use
- Adolescent sexual and reproductive health should include counseling, reproductive planning and contraception, screening and management of STDs (including HIV).
- Teens should receive comprehensive education and time to practice interpersonal skills and negotiate safe sexual behaviors

Impact estimates

The combined results for all interventions showed a 37% effect on decreasing the rate of repeat teenage pregnancies (**Figure 2.3.1**).

Three trials focused on preventing teen pregnancy through abstinence-focused education- the strategies that appeared to be successful included sex-education in an after-school program delivered by teachers,[7, 42] however their estimated reduction in risk was non-significant (**Figure 2.3.2**) (**Figure 2.3.3**). The only study in which physicians provided the intervention in their clinics appeared to be very successful (OR 0.17 Boekeloo 1999),[17] however this result was also insignificant.

Expanded sexual-education programs delivered by adults did not show an effect in preventing adolescent pregnancy,[24, 36, 44, 46] except in one study in Chile.[22] One study that delivered such a program, but also included career counselling, family options, and cultural values, delivered by peer counsellors in neighbourhoods cannot be commented on since there were very few participants followed up, and there were no pregnancies in either the intervention or control groups.

Interventions to promote contraceptive use also had no effect on preventing teenage pregnancy, regardless of whether the intervention involved free provision,[51] long-acting or emergency contraception with ease of access,[3, 54] or peer counselling.[38]

The comprehensive intervention "Children's Aid Society Carrera Program" carried out in multiple community-centres that provided educational and vocational support, sex education, medical care, sports, and arts, free STI testing and condoms[47] was actually successful, reducing the risk of teen pregnancy by 41%. Another highly successful program (risk reduction of 57%) focused on youth development through community service, and personal development.[2] Studies not included in the pooled analysis with comprehensive interventions including community activities, school-based education, peer-counselling, adolescent-friendly health services and condom distribution showed mixed results.[55, 56] The success of combining multiple interventions especially contraception with education, has also been reported in a recent Cochrane review.[57] A conditional cash transfer for girl's dropouts to return to school also showed promising results (11.1% pregnant in intervention group versus 16.2% in control group).Another

possible avenue to improve the sexual health of adolescents, including preventing adolescent pregnancy, might be through technological developments such as text messaging.[58]

The pooled analysis for all interventions to reduce the incidence of adolescent pregnancies showed only a 15% decrease. Systematic reviews by DiCenso 2002[59] and Corcoran 2007[60] confirm that the available evidence in this area is conflicting (**Figure 2.3.4**).

Successful interventions to prevent repeat second pregnancies to teenage mothers all include parenting skills training, and encourage teenage mothers to complete their education, regardless of whether they are carried out in health centres, in support groups, or during home visits (risk reduction 59-89%). One particularly successful program (risk reduction 89%)[43] also included comprehensive medical care and referral services for day-care and housing. Another very successful program (Second chance club- 84% decreased risk Key 2001)[27] took a unique approach: it was conducted in high school through individualized case management and group sessions, and focused on school involvement and community outreach, but also provided medical care.

From studies evaluating contraception, it was found that hormonal implants are extremely successful in preventing repeat teenage pregnancy, causing an 89% risk reduction.[16] Contraceptive provision to adolescents might also be more successful if implemented in school-based health centres with case management provided by an onsite care provider.[61]

Conclusion

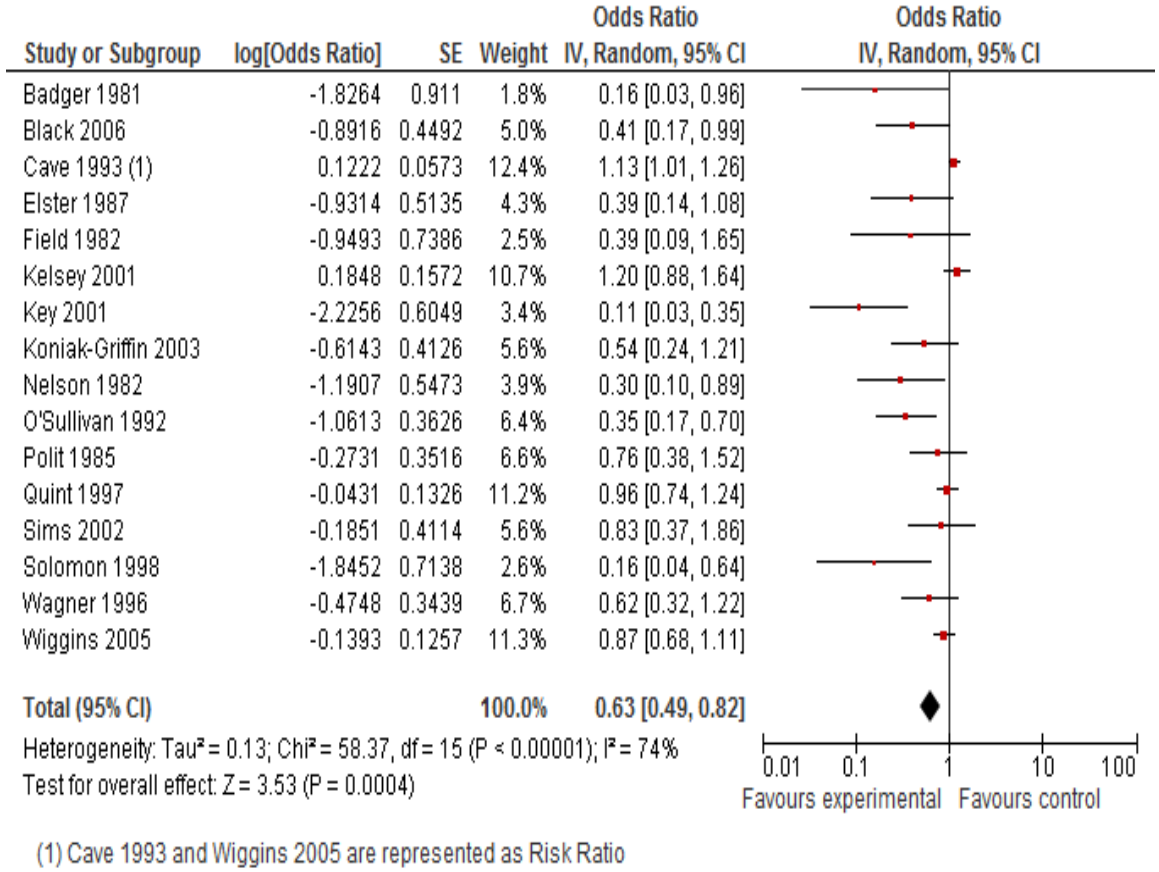
Teenage pregnancy is a health and social problem, with more than 16 million adolescent girls becoming pregnant each year. Although reasons for and rates of adolescent pregnancy vary across regions, adolescents especially those less than 18 years of age, suffer serious maternal and perinatal health consequences, with the risk increasing for the youngest girls.

Abstinence education, expanded sexual health education delivered by adults, and contraception alone, are not effective in reducing the incidence of teenage pregnancy. Comprehensive interventions that address communities, sexual and reproductive health services, contraceptive provision and school-based education; and youth development programs which promote personal development, completion of education, and community service are highly effective in reducing the risk of teenage pregnancies (41% and 57% respectively).[62] Another prospective intervention is conditional cash transfers to encourage girls to stay in school.

Successful interventions to prevent repeat adolescent pregnancy include parental skills training and encouraging young mothers to finish school, as well as comprehensive medical care. Emergency and oral contraception were not successful in reducing repeat teen pregnancies, however hormonal implants might be promising in this population.

Finally, for those adolescents who do become pregnant, a recent meta-analysis shows that comprehensive prenatal care can reduce many of the risks for pregnancy complications faced by teenage women.[63]

Figure 2.3.1: Interventions to prevent *repeat* pregnancy in teen mothers (Adapted from Harden 2006 & Corcoran 2007)



(1) Cave 1993 and Wiggins 2005 are represented as Risk Ratio

Citation to the included studies:
Badger 1981[1], Black 2006[8], Elster 1987[18], Field 1982[20], Kelsey 2001[23], Key 2001[27], Koniak-griffin 2003[29], Nelson 1982[33], O'sullivan 1992[35], Polit 1985[37], Quint 1997[39], Sim 2002[41], Solomon 1998[43], Wagner 1996[45]
Cave 1993[11], Field 1982[20], Polit 1985[37], Quint 1997[39], Solomon 1998[43], Wiggins 2005[48]

Description of support programs for teen mothers:

Postnatal classes on mother-infant interaction (Infant Stimulation/ Mother Training) **[Badger 1981][1]**

Home visits from mentors focusing on teen interaction with her mother, teen mother-infant interaction, preventing second birth (Three Generation Study) **[Black 2006][8]**

Comprehensive educational and employment support, and transport, childcare and counselling(Jobstart) **[Cave 1993][11]**

Comprehensive health services, relationship counseling and educational and financial support (Teen Mother and Child Program) **[Elster 1987][18]**

Daycare and employment training, home-visitation and mother-infant interaction counseling **[Field 1982][20]**

Home visits to strengthen welfare-to-work programs forteenage parents on cash assistance (Teenage Parent Home VisitorServices Demonstration**)[Kelsey2001][23]**

High school intervention focusing on school involvement, medicalcare and community outreach through individualized case management andgroup sessions. (Second chance club)**[Key 2001][27]**

Home visits including:health, sexuality and family planning, maternal role and skills, and educational/vocational support (Public Health Nursing EarlyIntervention Program) **[Koniak-Griffin 2003][29]**

Comprehensive group support for parenting, familyplanning, and completion of education.(Teen-Tot Clinic) **[Nelson 1982][33]**

Counseling by several healthcare providers during well-baby visits (no programmatic intervention) **[O'Sullivan 1992][35]**

Comprehensive individualized medical care, vocational training, and parent skills training through role models and peer-groups (Project Redirection) **[Polit 1985][37]**

Comprehensive educational and employment support, and free healthcare and childcare (New Chance Demonstration) **[Quint 1997][39]**

Home visits including information on services in the community, emotional and instrumental support, andencouragement to complete school and limit further childbearing. (Family Ties) **[Sims 2002][41]**

Comprehensive medical care, short-term recreational activities and transportation, home visits, family and parenting support, referral to services foreducation, daycare, housing (Family Growth Center) **[Solomon 1998][43]**

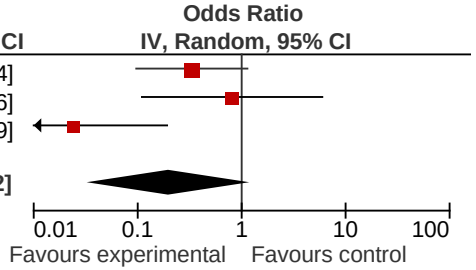
Parent skills education, homevisits, support groups, and child assessments(Teen Parents as TeachersDemonstration**) [Wagner 1996][45]**

Comprehensive support with issues such as housing, health care, education, childcare and parenting skills through group activities and individual advisor (Sure Start Plus) **[Wiggins 2005][48]**

Figure 2.3.2: Contraception for teen mothers and risk of *repeat* pregnancy (adapted from Corcoran 2007 and Lopez 2010)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Belzer 2003	-1.1026	0.6278	39.8%	0.33 [0.10, 1.14]
Gilliam 2004	-0.2107	1.0186	30.6%	0.81 [0.11, 5.96]
Stevens-Simon 1999	-3.7297	1.0609	29.6%	0.02 [0.00, 0.19]
Total (95% CI)			**100.0%**	**0.20 [0.03, 1.22]**

Heterogeneity: Tau² = 1.74; Chi² = 6.40, df = 2 (P = 0.04); I² = 69%
Test for overall effect: Z = 1.75 (P = 0.08)



Citation to the included studies:
Belzer 2003[4], Gilliam 2004[6], Stevens-simon 1999[16]

Provision of emergency contraception **[Belzer 2003][4]**

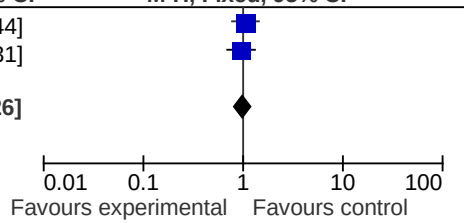
One-time postpartum counseling with written material/videotape aboutOCs **[Gilliam 2004][6]**

Young women using hormonal implants for contraception **[Stevens-Simon 1999][16]**

Figure 2.3.3: Contraception to prevent teen pregnancy

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Raine 2005	66	826	85	1124	50.7%	1.06 [0.78, 1.44]
Raymond 2006	67	746	70	744	49.3%	0.95 [0.69, 1.31]
Total (95% CI)		**1572**		**1868**	**100.0%**	**1.01 [0.81, 1.26]**
Total events	133		155			

Heterogeneity: Chi² = 0.20, df = 1 (P = 0.65); I² = 0%
Test for overall effect: Z = 0.06 (P = 0.96)

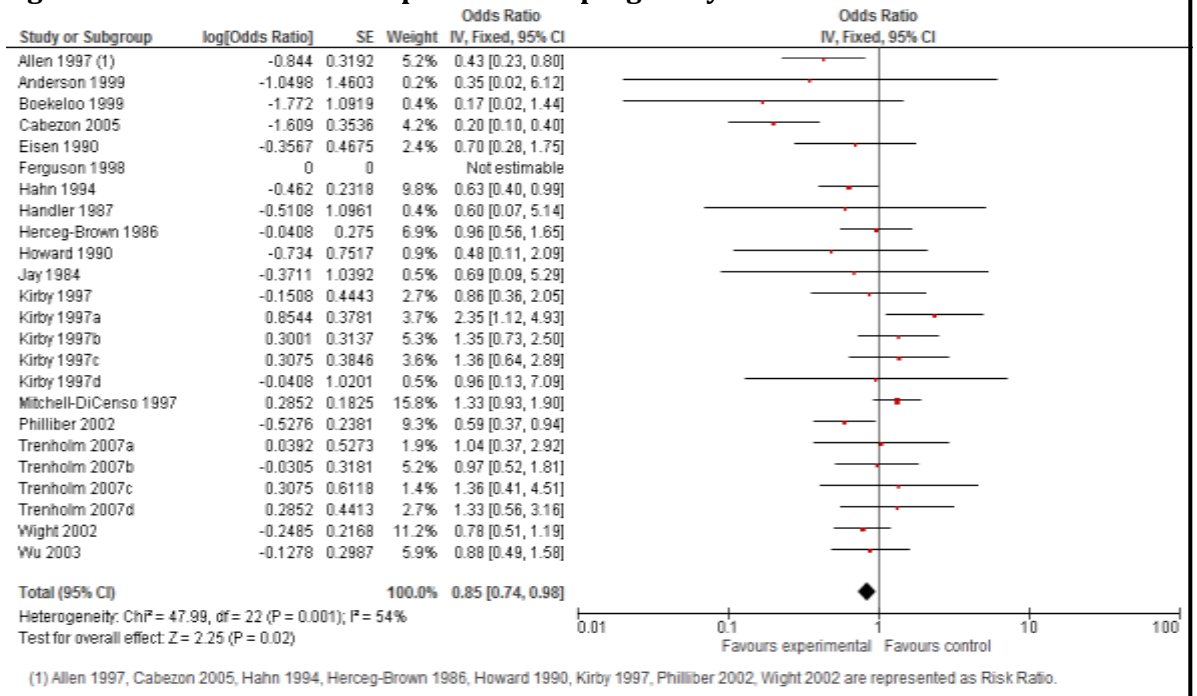


Citation to the included studies:
Raine 2005[3], Raymond 2006[9]

Pharmacy versus advance provision versus clinic access for levonorgestrel **[Raine 2005][3]**

Advance supply of contraceptive pills versus usual method of access **[Raymond 2006][9]**

Figure 2.3.4: Interventions to prevent teen pregnancy



(1) Allen 1997, Cabezon 2005, Hahn 1994, Herceg-Brown 1986, Howard 1990, Kirby 1997, Philliber 2002, Wight 2002 are represented as Risk Ratio.

Citation to the included studies:
Anderson 1999[7], boekeloo 1999[17], Eisen 1990[24], Ferguson 1998[28], Handler 1987[32], Jay 1984[38], Kirby 1997a-d[42], Mitchell-Dicenso 1997[44], Trenholm 2007a-d[49], Wu 2003[52]Allen 1997[2], Cabezon 2005[22], Hahn 1994[30], Herceg-Brown 1986[34], Howard 1990[36], Kirby 1997[40], Philliber 2002[47],Wight 2002[50]

Community service and personal/social development (Teen Outreach Program) **[Allen 1997][2]**

Parent-teen communication and reproductive health **[Anderson 1999][7]**

Pediatrician's office: counseling on sexual and other risk behavior, printed material for parents (ASSESS) **[Boekeloo 1999][17]**

School-based sex education **[Cabezon 2005][22]**

Reproductive health education and relationship skills class-based format **[Eisen 1990][24]**

Health education, skills building, contraceptiveeducation, abstinence, ethnic/cultural values, family options, career counseling by peer counsellors**[Ferguson 1998][28]**

250 hours each of educational activities, community service and personal development during high school years (Quantum Opportunities Program) **[Hahn 1994][30]**

Peer and school-counsellor delivered personal development **[Handler 1987][32]**

Family/individual counseling on sex/contraception versus follow-up phone calls **[Herceg-Brown 1986][34]**

School-based sex education and skills building delivered by older peers**[Howard 1990][36]**

Peer counseling on oral contraceptives versus nurse-counseling **[Jay 1984][38]**

School-based activities for personal development, with sex education **[Kirby 1997][40]**

Postponing sexual involvement (ENABL)**[Kirby 1997a-d]** Peer, teacher, randomized schools, randomized individuals[42]

Extended school-based sex education including skills building **[Mitchell-DiCenso 1997][44]**

Community-centre educational and vocational support, sex education, medical care, sports, and arts, free STI testing and condoms (Children's Aid Society Carrera Program) **[Philliber 2001][47]**

All school-based postponing sexual involvement and relationship education –different states**[Trenholm 2007a-d][49]**

School-based sex education and skills building, primarily video (SHARE) **[Wight 2002][50]**

Community-centre and home-delivered (with parents) risk behavior education through activities **[Wu 2003][52, 53]**

Table 2.3.1: Interventions to prevent teenage pregnancy				
	Knowledge	**Attitudes**	**Behavior**	**Teenage pregnancy**
Community meetings, audiovisual displays at public events, peer educators, "adolescent-friendly" reproductive health services, school-based reproductive health education and counseling, condom demonstrations and printed material (Kenya Adolescent Reproductive Health Project) Cost of school-based approximately 3,000,000 Kenyan shillings more than community and health service intervention **[Askew 2004]**[55]	-Reproductive health: 52-75% for community and health services versus 47-74% for school-based versus 27-50% for control -Contraception: 5% increase for community and health services versus 1% decrease for school-based and control. Of these, significant increase in knowing of specific methods -STIs/HIV: By the end of the interventions there was almost universal awareness, however the proportion citing abstinence/fidelity/condom use for prevention increased 6-27% for community and health services, increased 4-11% for school-based (except fidelity which *decreased)* and increased 5-18% (except for fidelity which remained same or decreased) for control	-Approve use of contraception: increase 0-18% for community and health services, 0-11% for school-based (except for *decrease* among unmarried adolescents), 3-21% for control (except for *decrease* among unmarried adolescents) -Approve intimate partner violence: significant decrease among boys at all sites	-Discussing reproductive health with parents: 7% increase for community and health services versus 3% increase for control and 2% decrease for school-based -Penetrative sex: same or decreased for adolescents age 10-14 at all sites. Variable results for adolescents age 15-19 at intervention sites, but consistently less than control -Age at first intercourse: Significant increase of 0.5 yrs for both boys and girls for school-based intervention -Girls reporting persuaded or forced sex decreased from 39% to 11% for community and health services intervention -Use of contraception at first and last intercourse: School-based increase only for girls, community and health services increase slightly greater	Among unmarried girls: Decrease 16% for community and health services, 5% for school-based, 25% for control
Community youth activities, teacher-led peer-assisted sexual health education in years 5–7 of primary school, "adolescent-friendly" reproductive health services, and peer condom social marketing (MEMA kwaVijana) **[Ross 2007]**[56]	HIV transmission: aRR 1.44 for males, 1.41 for females STD transmission: aRR 1.28 for males, 1.41 for females Pregnancy prevention: aRR 1.66 for males, 1.58 for females	Attitudes to coerced sex, "sugar daddies" and intimate partner violence improved: aRR 1.77 (1.42-2.22) for males, 1.42 (1.11-1.81)	First sexual experience: aRR 0.84 for males, 1.03 for females Multiple partners: aRR 0.69 for males, 1.04 for females Began condom use: aRR 1.41 for males, 1.30 for females Condom use during last sex: aRR 1.47 for males, 1.12 for females Sought STI treatment at health facility: aRR	Pregnancy test-taking: aRR 1.09 (0.85-1.40) Pregnancy: aRR 1.03 (0.89-1.20)

			0.84 for males, 1.02 for females	
Conditional cash transfer to stay in school (Zomba Cash Transfer Program) **[Baird 2010]**[64]			Get married: 16.4% intervention versus 27.7% control (among initial dropouts) Onset of sexual activity: Reductions of 46.6% (-5.5%) among initial dropouts and 31.3% (-2.5%) among initial schoolgirls (p= 0.112, significant at the1% level) Number of partners: approximately 25% decrease for both No difference in condom use	Get pregnant: 11.1% intervention versus 16.2% control(among initial dropouts)
Media campaign promoting self-control and self-respect through posters, leaflets, newsletter, drama, launch events, radio. Also had peer educators, hotline and "adolescent-friendly" clinics. (Promotion of Youth Responsibility Project) **[Kim 2001]**[65]	Of contraceptive methods: OR 1.2-8.2 after intervention versus baseline and 0.9-5.3 without intervention versus baseline. Of reproductive health: OR 1.2, p<0.05 for correct answer to "Can family planning methods cause deformities" in intervention versus baseline. OR 1.9, p<0.001 for correct answer to "Can a health-looking person have HIV" in comparison versus baseline		Launch events most successful at changing behavior, and greater intensity of exposure increased odds of behavior change Discuss reproductive health with anyone (OR 5.6, p<0.001): Partner- OR 3.8 Parent- OR 4.3 Adopted safer sexual behavior (OR 2.9, p<0.001): Said no to sex- OR 2.5 Continued abstinence- OR 1.2 Avoided "sugar daddy"- OR 1.1 Sought reproductive health services- OR 7.6 Those with sexual experience: Stopped having sex- OR 2.1 Stuck to single partner- OR 26.1, p<0.001 Began condom use- OR 5.7, p<0.05 Asked partner to use condoms- OR 1.5	

Follow-up phone counseling on reproductive health – 2.7 calls per participant instead of the 9 planned (Project Reach) **[Kirby 2010]**[66]			Use of contraception at last sex: at 18 months, intervention 79% and control 78% No difference in use of emergency contraception, correct use of contraception, STDs or pregnancy	
pharmacy access, advance provision, or clinic access (control) to emergency contraception (Plan B) **[Harper 2005]**[54]			-Used emergency contraception: 29.8% pharmacy, 44.3% advance (p=0.001), 28.9% clinic -Unprotected intercourse: 39.5% pharmacy, 45.8% advance provision, 47.2% clinic -Consistent condom use: 17.2% pharmacy, 16.8% advance provision, 12.1% clinic -Pressure into sex: 2.4% pharmacy, 3.4% advance provision, 3.5% clinic -Multiple sexual partners: 24.5% pharmacy, 22.7% advance provision, 20.4% clinic -STIs: 14.2% pharmacy, 12.1% advance provision, 13.4% clinic	7.8% pharmacy, 12.4% advance provision, 9.9% clinic.
Frequent postpartum home visits for teen mothers focusing on contraceptive use and breastfeeding **[Quinlivan 2003]**[67]			Effective contraceptive use at 6 months: OR 3.24 (95% CI 1.35-7.79)	
Education and skills, daycare, parenting skills, referrals and nutrition (Women's centre of Jamaica Foundation) **[McNeil 1988]**				Over 15 years, 50.7% of program participants had only one child and birth spacing was 5.5 yrs. Jamaica's teen birth rate decreased from 31% to 23% over 20 years

Computer-assisted intervention versus home-visits versus usual care- focused on mother-child interaction and sexual relationships, contraception **[Barnet 2009]**[68]				Computer-assisted 13/80 (HR 0.4, 95% CI 0.16-0.98) repeat births, home visits only 15/87 (HR 0.19, 95% CI 0.05-0.69), usual care 17/68
Peer-led versus teacher-led sex education (RIPPLE) **[Ross/Stephenson 2008]**[46]				Self-reported abortions aOR 0.56, 95% CI 0.31-1.02 Registered abortion aOR 1.19, 95% CI 0.81-1.75 Self-reported pregnancy OR 0.62, 95% CI 0.42-0.91 Registered pregnancy OR 0.74, 95% CI 0.47-1.17
Peer education and media campaigns (Among Youth) **[IRESCO 2002]**[69]			Abstinence increased 12% at intervention site and decreased 4% at control site 7% decrease in youth having multiple partners at intervention site. Increase in condom use with regular partner: boys- 20%, girls 11% at intervention site (similar for control). Increase in condom use with occasional partners increased 35% for girls at intervention site	

Table 2.3.2: Summary impact estimates for teenage pregnancy			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
Birth intervals: 4.03 years for adolescents versus 4.82 years, p<0.01[Buvinic 1998 Rev][70] UTI: OR 1.0, 95% CI 0.7-1.3 [dos Santos 2009][71] OR 1.0, 95% CI 0.98-1.04 [Conde-Agudelo 2005][72] 16.6% versus 13% [Iloki 2004][73] OR 1.60, 95% CI 1.11-2.31 [Jolly 2000][74] Anaemia: 7.9% versus 8.2% [Al-Ramahi 2006][75] OR 0.9, 95% CI 0.6-1.5 [Ebeigbe 2007][76] OR 1.82, 95% CI 1.63-2.03 [Jolly 2000][74] 2.5% versus 2.1%, p<0.0001 [Aliyu 2010][77] OR 1.04, 95% CI 1.00-1.09 [Conde-Agudelo 2005][72]	Hypertensive disorders of pregnancy: 4.9% adolescents versus 5.2% [Al-Ramahi 2006 Obs- compares women age 25-30 yrs] [75] OR 1.1, 95% CI 0.2-5.0 [dos Santos 2009][71] OR 0.5, 95% CI 0.3-1.0 [Ebeigbe 2007] [76] 0.58% adolescents versus 0.81%, p<0.0001[Aliyu 2010 Obs- compares women age 20-24 yrs][77] OR 0.8, 95% CI 0.4-1.3 [Galvez-Myles 2005][83] OR 0.96, 95% CI 0.31-2.9 for women ages 17-19. OR 4.83, 95% CI 1.76-13, p< 0.001 [Goonewardene 2005 Coh- compares women age 20-24 yrs][78] 12% versus 9.2% [Hediger 1997][79] 0.2% versus 0.6% [Isaranurug 2006][80] 25/750 versus 29/750 [Kovavisarach 2010][82] GDM: 0% versus 1.2% [Al-Ramahi 2006] [75] OR 0.19, 95% CI 0.07- 0.50 [Jolly 2000][74] 0.26% versus 0.49%, p<0.0001 [Aliyu 2010][77] OR 0.39, 95% CI 0.37-0.42 [Conde-Agudelo 2005][72] 1.6% versus 6.7% [Hediger 1997][79] OR 0.13, 95% CI 0.02-0.60, p<0.002 [Kovavisarach 2010 Coh- compares women age 20-	Low birth weight: OR 2.9, 95%CI 1.5–5.6 [Kurth 2010 CS- compares <16 to >16 yrs][88] OR 1.47, 95% CI 1.13- 1.90 [dos Santos 2009] [71] OR 1.5, 95% CI 0.8-2.8 [Ebeigbe 2007][76] OR 0.95, 95% CI 0.82-1.09 [Jolly 2000][74] RR 1.24, 95% CI 1.20-1.27 [Chen 2007 Coh- compares women age 20-24 yrs][89] OR 1.25, 95% CI 1.22-1.28 [Conde-Agudelo 2005][72] RR 1.7, 95% CI 1.5–2.0 [Fraser 1995][90] OR 0.7, 95% CI 0.9-1.3 [Galvez-Myles 2005][83] OR 1.13, 95% CI 0.71-1.79 for women ages 17-19. OR 0.86, 95% CI 0.43-1.73 for women ages 13-16 [Goonewardene 2005][78] 8.5% versus 10% [Hediger	Breastfeeding: OR 0.24, 95% CI 0.22-0.26 [Jolly 2000][74]

Table 2.3.2: Summary impact estimates for teenage pregnancy			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
OR 2.35, 95% CI 1.52-3.64, p<0.001for ages 17-19. OR 2.13, 95% CI 1.09-4.15, p<0.01 for ages 13-16. [Goonewardene 2005][78] 44.8% versus 41% [Hediger 1997] [79] 3.2% versus 2.3% [Iloki 2004][73] 11.2% versus 9.4% [Isaranurug 2006][80] OR 2.8 (1.2-6.6) [Phupong 2007 CC-compares women age 20-29 yrs][81] <u>Maternal death:</u> OR 1.12, 95% CI 0.87-1.37 [Conde-Agudelo 2005][72] 10% versus 7.2%, p=0.053 [Kovavisarach 2010][82] <u>STD:</u> OR 1.4, 95% CI 0.8-2.4 [Galvez-Myles 2005][83]	34 yrs][82] <u>Placental (abruption/previa):</u> Abruption:1.9% versus 0.8% Previa: 0% versus 0.6% [Al-Ramahi 2006] [75] Abruption: 0.71, 95% CI 0.36-1.24 Previa: 0.48, 95% CI 0.15-1.52 [Jolly 2000][74] Abruption: 0.02% versus 0.04% Previa: 0.08% versus 0.14%, p<0.0001 [Aliyu 2010][77] OR 0.4, 95% CI 0.1-1.4 [dos Santos 2009][71] Abruption: 1.4% versus 0.4%. Previa: 1.1% versus 2.5% [Hediger 1997][79] Abruption: 0% versus 1% [Hidalgo 2005][84] Abruption: 1/750 versus 0/750. Previa: 0/750 versus 2/750 [Kovavisarach 2010][82] <u>Breech:</u> OR 0.75, 95% CI 0.48-1.18 [Jolly 2000][74] No difference [Kovavisarach 2010][82] <u>Multiple gestation:</u> 3.8% versus 2.2% [Al-Ramahi 2006] [75] OR 0.9, 95% CI 0.3-3.2 [Ebeigbe 2007] [76] No difference [Kovavisarach 2010][82] <u>Stillbirth:</u> OR 0.75, 95% CI 0.42-1.34 [Jolly 2000][74] RR 1.20, 95% CI 0.88-1.64 [van der Klis 2002][85] 1/76 women <18 yrs versus 6/371 [van Dillen 2008][86]	1997] [79] 19.9% versus 11.4% , p<0.05 [Hidalgo 2005][84] 22.1% versus 15.7%, p<0.05 [Iloki 2004][73] 15.1% versus 8.8%, p< 0.001 [Isaranurug 2006][80] RR 1.43, 95% CI 1.31-1.56 [van der Klis 2002][85] 12% among women <18 yrs versus 14% among women >19 yrs [van Dillen 2008][86] OR 1.71, 95% CI 1.15–2.50, p= 0.006 [Kongnyuy 2008][92] 132/750 versus 92/750, p=0.008 [Kovavisarach 2010][82] 87.2% women age <18 yrs, 31.6% women age 18-19 yrs, 32.3% women age 20-30 yrs, p<0.01 [Kumar 2007 CC][93] 54/533 versus 522/9347 ,	

Table 2.3.2: Summary impact estimates for teenage pregnancy			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
6/750 versus 5/750 [Kovavisarach 2010][82] Illicit drug use: OR 1.8, 95% CI 0.8-4.2 [Galvez-Myles 2005][83] Vaginal infections: 40.9% versus 19.4%, p< 0.05 [Hidalgo 2005] [84] 19.9% versus 12.6% [Iloki 2004][73] OR 1.29, 95% CI 0.89-1.88 [Jolly 2000][74] Unplanned pregnancy: OR 1.59, 95% CI 1.00-2.52, p=0.02 for ages 17-19. OR 6.1, 95% CI 3.5-10.61, p< 0.001 for ages 13-16. [Goonewardene 2005][78] 41.8% versus 31.1%, p< 0.001 [Isaranurug 2006][80] 39.6% versus 70% [Kovavisarach 2010][82] Smoking: Quit smoking before 1st antenatal visit: RR 1.8,	7/750 versus 0/750, p= 0.015 [Kovavisarach 2010][82] OR 2.0 (0.2-22.5) [Phupong 2007 CC- compares women age <15 yrs to women age 20-29][81] aOR 1.47 (0.71,3.03)for women <16 yrs [Robson 2006 Obs- compares women age 18-19 yrs][87] Preterm birth: OR 1.3, 95%CI 0.6–2.6 [Kurth 2010][88] OR=1.46, 95% CI 1.14-1.88 [dos Santos 2009 Obs- compares adolescents to women age 20-34] [71] OR 0.9, 95% CI 0.4-1.8 [Ebeigbe 2007][76] OR1.53, 95% CI 1.33-1.91 [Jolly 2000][74] 10.4% versus 8.9%, p<0.0001 [Aliyu 2010][77] RR 1.17, 95% CI 1.14-1.20 [Chen 2007][89] OR 1.22, 95% CI 1.19-1.25 [Conde-Agudelo 2005][72] RR 1.9, 95% CI 1.7–2.1 [Fraser 1995 Obs- compares <17 with women age 20-24 yrs][90] OR 1.4, 95% CI 0.7-2.5 [Galvez-Myles 2005 Obs- compares women age 25-24 yrs][83] OR 0.93, 95% CI 0.51-1.69 for women ages 17-19. OR 1.78, 95% CI 0.88-3.60, p=0.06 for women ages 13-16 [Goonewardene 2005][78] 13.4% versus 10% [Hediger 1997] [79] RR 1.28, 95% CI 1.18-1.40, p<0.05 for increasing maternal age [van der Klis 2002 Obs-	p<0.000 [Kuo 2010 Coh- compares women age 20-34 yrs][94] OR 1.72 (1.44-2.06) [Cooper 1995 Obs- compares women age 10-15 yrs to women age 20-24- abstract only][14] aOR 2.75 (2.16, 3.49)for women ages 12-15, 1.76 (1.56, 1.99)for women ages 16-17, 1.46 (1.32, 1.62)for women ages 18-19 [Sharma 2008 Coh- compares women age 20-24yrs][96] Macrosomia: OR 0.95, 95% CI 0.82-1.09 [Jolly 2000][74] Birth asphyxia: OR 1.1, 95% CI 0.4-3.3 [Ebeigbe 2007][76] 22.4% women age < 18 yrs, 6.1% women age 18-19 yrs, 1.9% women age 20-30 yrs, p<0.01[Kumar 2007 CC][93] NICU admission: 22.7% versus 13.5% , p<0.001[Al-Ramahi 2006]	

Table 2.3.2: Summary impact estimates for teenage pregnancy			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
95% CI 0 1.54-2.10 [van der Klis 2002][85]	compares women age >20 yrs][85] aOR 1.2, 95% CI 1.01-1.45 for women ages 14-17 yrs, aOR 1.10, 95% CI 0.95-1.28 for women ages 18-19. Increased for second births to teen mothers [Khashan 2010 Coh- compares women age 20-29 yrs][91] OR 1.77, 95% CI 1.24–2.52, p= 0.002 [Kongnyuy 2008][92] 158/750 versus 89/750, p<0.001 [Kovavisarach 2010][82] 87.2% women age <18 yrs, 33.6% women age 18-19 yrs, 17.5% women age 20-30 yrs, p<0.01 [Kumar 2007 CC][93] 79/533 versus 801/9347, p<0.000 [Kuo 2010 Coh][94] OR 3.59 (1.5-8.1) [Phupong 2007 CC- compares women age 20-29 yrs][81] OR 0.97 (0.69-1.36) [Ekwo 2000 Obs- compares women age <15 to women age 20-24 yrs][95] aOR 1.62 (1.25, 2.10)for women ages 12-15, 1.47 (1.29, 1.68)for women ages 16-17, 1.27 (1.14, 1.43)for women ages 18-19 [Sharma 2008 Coh- compares women age 20-24yrs][96] <u>Preterm labour:</u> 14.6% versus 8% [Al-Ramahi 2006] [75] 18.6% versus 12.6% [Hediger 1997 Coh- compares < 16 to women age 18-29][79] 6.8% versus 2.3%, p<0.05 [Iloki 2004][73] OR 1.81, 95% CI 1.27-2.59, p=0.001 [Kovavisarach 2010][82] <u>Preeclampsia:</u>	[75] OR 0.88, 95% CI 0.75-1.03 [Jolly 2000] [74] OR 0.5, 95% CI 0.3-0.9, p< 0.021 [Galvez-Myles 2005][83] RR 1.24, 95% CI 1.06-1.46, p<0.05 for increasing maternal age [van der Klis 2002][85] 55/750 versus 28/750, p= 0.003 [Kovavisarach 2010][82] <u>Congenital anomalies:</u> 1.4% versus 0.8% [Al-Ramahi 2006] [75] OR 1.3, 95% CI 0.7-2.4 [dos Santos 2009][71] RR 1.01, 95% CI 0.84-1.20 [van der Klis 2002][85] 11/750 versus 8/750 [Kovavisarach 2010][82] 0.8% women age < 18 yrs, 0.4% women age 18-19 yrs, 0.4% women age 20-30 yrs [Kumar 2007 CC][93]	

Table 2.3.2: Summary impact estimates for teenage pregnancy			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
	OR 0.2, 95% CI 0.2-0.4 [dos Santos 2009][71] OR 1.30, 95% CI 0.94-1.82 [Jolly 2000][74] 5.4% versus 4.6%, p<0.0001 [Aliyu 2010][77] OR 1.01, 95% CI 0.97-1.06 [Conde-Agudelo 2005 Obs- compares women age 20-24 yrs][72] OR 2.1, 95% CI 0.7-6.1 [Galvez-Myles 2005][83] OR 0.73, 95% CI 0.08-5.4 for ages 17-19. OR 5, 95% CI 1.01-27, p=0.03 for ages 13-16 [Goonewardene 2005][78] 6.1% versus 8.3%, p<0.05 [Iloki 2004][73] OR 1.99, 95% CI 1.24–3.15, p=0.004 [Kongnyuy 2008][92] OR 5.4 (1.2-25) [Phupong 2007 CC- compares women age 20-29 yrs][81] <u>Eclampsia:</u> 0.23% versus 0.17%, p< 0.0001 [Aliyu 2010][77] OR 1.20, 95% CI 0.97-1.44 [Conde-Agudelo 2005][72] 2.5% versus 0% , p<0.05 [Hidalgo 2005] [84] 3.2% versus 0.7%, p<0.05 [Iloki 2004][73] OR 3.18, 95% CI 1.21–8.32 [Kongnyuy 2008][92] 1/750 versus 0/750 [Kovavisarach 2010][82] <u>PROM:</u> OR 0.99, 95% CI 0.97-1.01 [Conde-Agudelo 2005][72]	<u>SGA:</u> RR 1.23, 95% CI 1.21-1.26 [Chen 2007][89] OR 1.35, 95% CI 1.32-1.38 [Conde-Agudelo 2005][72] RR 1.3, 95% CI 1.2–1.4 [Fraser 1995][90] 15.4% versus 13% [Hidalgo 2005] [84] RR 1.43, 95% CI 1.33-1.54 [van der Klis 2002][85] aOR 0.89, 95% CI 0.74-1.07 for women ages 14-17, aOR 1.13, 95% CI 0.99-1.28 for women ages 18-19 yrs. For second births to teen mothers age 14-17 yrs, aOR 1.23, 95% CI 0.88-1.71 and for second birth to teen mothers age 18-19 aOR 1.25, 95% CI 1.05-1.48 [Khashan 2010 Coh][91] OR 4.8 (1.2-22.6) [Phupong 2007 CC- compares women age 20-29 yrs] [81] aOR 2.15 (1.65, 2.82)for	

Table 2.3.2: Summary impact estimates for teenage pregnancy			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
	OR 0.4, 95% CI 0.1-1.0 [dos Santos 2009][71] OR 0.8, 95% CI 0.3-2.1 [Galvez-Myles 2005][83] 7.1% versus 8% [Hediger 1997][79] OR 1.17, 95% CI 0.57–2.28 [Kongnyuy 2008][92] OR 0.5 (0.1-1.7) [Phupong 2007 CC- compares women age 20-29 yrs][81] <u>Caesarean section:</u> 7.1% versus 16.8% , p<0.001 [Al-Ramahi 2006] [75] OR 0.68, 95% CI 0.6-0.7 [dos Santos 2009][71] OR 0.83, 95% CI 0.81-0.85 [Conde-Agudelo 2005][72] OR 2.5, 95% CI 1.6-3.9 [Ebeigbe 2007][76] OR 0.3, 95% CI 0.2-0.5, p< 0.001 [Galvez-Myles 2005][83] OR 0.65, 95% CI 0.26-1.61 for ages 17-19. OR 1.59, 95% CI 0.60-4.17 [Goonewardene 2005][78] 13.4% versus 20.5% [Hediger 1997] [79] 24.3% versus 20.4% [Hidalgo 2005][84] 10.8% versus 8% [Iloki 2004][73] 3.9% among women <18 yrs versus 7.3% among women >19 yrs [van Dillen 2008 Obs][86] OR 1.29, 95% CI 0.80–2.04 [Kongnyuy 2008][92]	women ages 12-15, 1.62 (1.44, 1.83)for women ages 16-17, 1.25 (1.14, 1.38)for women ages 18-19 [Sharma 2008 Coh- compares women age 20-24yrs][96] aOR 0.84 (0.67,1.05) for women <16 yrs [Robson 2006 Obs- compares women age 18-19 yrs][87] <u>Neonatal death:</u> RR 1.32, 95% CI 1.18-1.48 [Chen 2007][89] Early: OR 1.02, 95% CI 0.95-1.09 [Conde-Agudelo 2005][72] RR 1.77, 95% CI 1.18-2.64 [van der Klis 2002][85] Early: 0/76 women <18 yrs versus 4/371 women >19 yrs[van Dillen 2008][86] Early: 2.18, 95% CI 1.04–4.48 [Kongnyuy 2008][92] 8% women age <18 yrs, 1.6% women age 18-19 yrs, 0.5% women age 20-30 yrs [Kumar 2007 CC][93]	

Table 2.3.2: Summary impact estimates for teenage pregnancy			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
	140/750 versus 100/750, p= 0.005 [Kovavisarach 2010][82] 88/533 versus 2823/9347, p<0.000 [Kuo 2010 Coh][94] OR 0.2 (0.1-0.4) [Phupong 2007 CC- compares women age 20-29 yrs][81] <u>Induction of labor:</u> 5.6% versus 10% [Al-Ramahi 2006] [75] OR 1.1, 95% CI 0.6-1.9 [Ebeigbe 2007] [76] OR 0.83, 95% CI 0.75-0.92 [Jolly 2000][74] 59.8% versus 59.4% [Hidalgo 2005] [84] RR 0.99, 95% CI 0.94-1.04 [van der Klis 2002][85] 49/750 versus 74/750 [Kovavisarach 2010][82] <u>Instrumental delivery:</u> 9% versus 3.8% [Al-Ramahi 2006] [75] OR 0.8, 95% CI 0.4-1.7 [Ebeigbe 2007] [76] OR 1.24, 95% CI 1.20-1.28 [Conde-Agudelo 2005] [72] OR 1.1, 95% CI 0.31-3.91 for ages 17-19. OR 1.46, 95% CI 0.28-6.74 [Goonewardene 2005][78] 1.4% versus 1.6%, p<0.05 [Iloki 2004][73] OR 0.46, 95% CI 0.41-0.56 [Jolly 2000][74] OR 0.51, 95% CI 0.15–1.39 [Kongnyuy 2008][92]	aOR 2.24 (1.40, 3.59) for women ages 12-15, 1.61 (1.22, 2.12) for women ages 16-17, 1.25 (0.97, 1.59) for women ages 18-19 [Sharma 2008 Coh-compares women age 20-24yrs][96] aOR 2.7 (1.5-4.8) for women age 13-15 yrs, 1.4 (1.1-1.8) for women age 16-17 yrs, 1.1 (0.97-1.3) for women age 18-19 yrs [Olausson 1999 Obs-compares women age 20-24 yrs][97] <u>Low APGARs at 5 minutes:</u> < 7: OR 1.66, 95% CI 0.9-2.8 [dos Santos 2009][71] < 7: RR 1.15, 95% CI 1.09-1.22 [Chen 2007][89] OR 1.00, 95% CI 0.95-1.05 [Conde-Agudelo 2005][72] < 7: OR 0.7, 95% CI 0.3-1.7 [Galvez-Myles 2005][83] < 7: 4% versus 2.5% [Hidalgo 2005] [84]	

Table 2.3.2: Summary impact estimates for teenage pregnancy			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
	40/750 versus 53/750 [Kovavisarach 2010][82] OR 1.3 (0.7-2.8) [Phupong 2007 CC- compares women age 20-29 yrs][81] <u>PPH:</u> 1.5% versus 1% [Al-Ramahi 2006] [75] OR 0.83 0.72-0.95 [Jolly 2000][74] OR 1.23, 95% CI 1.19-1.27 [Conde-Agudelo 2005] [72] 2.5% versus 2% [Hidalgo 2005] [84] 3% versus 1.8% [Isaranurug 2006 Coh- compares women age >20 yrs][80] 22/750 versus 26/750 [Kovavisarach 2010][82] OR 4.1 (0.5-37.3) [Phupong 2007 CC- compares women age 20-29 yrs][81] <u>Malaria:</u> OR 5.9, 95%CI 1.7–19.9 [Kurth 2010][88] 14.1% versus 7.3%, p<0.05 [Iloki 2004Coh- compares < 18 to > 18 yrs][73] <u>Malposition:</u> OR 0.6, 95% CI 0.3-1.2 [dos Santos 2009][71] <u>Fetal distress:</u> OR 0.8, 95% 0.4-1.6 [dos Santos 2009][71] 3.5% versus 4.5% [Hidalgo 2005] [84] 9/750 versus 6/750 [Kovavisarach 2010][82]	< 7: OR 1.72, 95% CI 1.03–2.81 [Kongnyuy 2008][92] <7: 19/750 versus 8/750 OR 2.05, 95% CI 1.17-3.60 [Kovavisarach 2010][82] OR 1 (0.1-16.2) [Phupong 2007 CC- compares women age 20-29 yrs][81] <u>Perinatal mortality:</u> 53% versus 14%, p<0.05 [Iloki 2004][73] RR 1.37, 95% CI 1.07-1.75 [van der Klis 2002][85] <u>Neonatal sepsis:</u> 2.4% women age <18 yrs, 1.6% women age 18-19 yrs, 1.2% women age 20-30 yrs [Kumar 2007 CC][93] <u>Infant mortality:</u> aOR 2.6 (0.97-7.0)for women age 13-15 yrs, 2.0 (1.5-2.8) for women age 16-17 yrs, 1.4 (1.1-1.7)for women age 18-19 yrs [Olausson 1999 Obs- compares women age 20-24 yrs][97]	

Table 2.3.2: Summary impact estimates for teenage pregnancy			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
	OR 3.1 (0.3-29.8) [Phupong 2007 CC- compares women age 20-29 yrs][81] <u>Antenatal care:</u> None: OR 2.8, 95%CI 1.2–6.5 [Kurth 2010][88] Late: OR 3.35, 95% CI 3.05-3.69 [Jolly 2000 Obs- compares adolescents to women age 18-34][74] None: OR 2.6, 95% CI 1.7-3.9 Late (in 3rd trimester) OR 4.6, 95% CI 2.6-8.1, p< 0.0001 [Ebeigbe 2007 Obs- compared to women age 20-29][76] Late: OR1.86, 95% CI 1.43-2.43 and fewer visits: OR 2.03, 95% CI 1.5-2.6 [dos Santos 2009][71] Booking in 1st trimester: OR 0.6, 95% CI 0.36-1.02, p< 0.02 for adolescents age 17-19. > 5 visits: OR 2.32, 95% CI 0.77-6.84, p=0.08 [Goonewardene 2005][78] Booked: 21% versus 54.6%, p<0.001 [Al-Ramahi 2006][75] Adequate: 25.4% versus 32% , p<0.0001 [Aliyu 2010][77] Late: 79% versus 73.3% and > 5 visits: 41.2% versus 45.2% [Conde-Agudelo 2005][72] Adequate: 52% versus 76% [Fraser 1995][90] Adequate: 37.3% versus 94.5%, p<0.05 [Hidalgo 2005 CC- compares < 15 with women age 20-30 yrs][84] Seldom: 2.9% versus 4% [Isaranurug 2006][80] Booking in 1st trimester: 11.8% women <18 yrs versus 10.2% women >19 yrs. < 3 visits: 22.4% versus 15.4% [van Dillen 2008][86]		

Table 2.3.2: Summary impact estimates for teenage pregnancy			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
	> 4 visits: 72.8% versus 89.4%, p<0.001 [Kongnyuy 2008][92] None: OR 0.31, 95% CI 1.96-3.50 Adequate: 18.4% women <18 yrs, 70.5% women age 18-19 yrs, 68.7% women age 20-30 yrs [Kumar 2007 CC][93] Booking in 1st trimester: 275/533 versus 6508/9347, p<0.000 [Kuo 2010 Coh][94] <u>Abortion:</u> OR=2.34, 95% CI 1.38-3.98 [dos Santos 2009][71] <u>Use bed nets:</u> OR 2.8, 95%CI 1.2–6.5 [Kurth 2010][88] <u>IPTP:</u> OR 0.8, 95%CI 0.5–1.5 [Kurth 2010][88] <u>Third-trimester bleeding:</u> OR 0.66, 95% CI 0.62-0.71 [Conde-Agudelo 2005][72] <u>Episiotomy:</u> OR 2.09, 95% CI 2.06-2.12 [Conde-Agudelo 2005][72] OR 1.2, 95% CI 0.7-1.9 [Ebeigbe 2007][76] 82.9% versus 87.5% [Hidalgo 2005][84] OR 1.82, 95% CI 1.20–2.73, p=0.005 [Kongnyuy 2008][92] <u>Puerperal endometritis:</u> OR 2.00, 95% CI 1.95-2.05 [Conde-Agudelo 2005][72] <u>Fetal death:</u> OR 0.99, 95% CI 0.95-1.04 [Conde-Agudelo 2005][72]		

Table 2.3.2: Summary impact estimates for teenage pregnancy			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
	4.3% versus 0.3%, p<0.05 [Iloki 2004][73] OR 0.42, 95% CI 0.12–1.12 [Kongnyuy 2008 CS- compares women age 20-29 yrs][92] 1 (0.1-16.2) [Phupong 2007 CC- compares women age 20-29 yrs[81] aOR 1.4 (0.6-3.1)for women age 13-15 yrs, 1.2 (0.9-1.5)for women age 16-17 yrs, 1.0 (0.9-1.2)for women age 18-19 yrs [Olausson 1999 Obs- compares women age 20-24 yrs][97] <u>Cephalopelvic disproportion:</u> OR 0.7, 95% CI 0.5-0.9 [dos Santos 2009][71] 41/750 versus 37/750 [Kovavisarach 2010][82] OR 0.3 (0.1-1.0) [Phupong 2007 CC- compares women age 20-29 yrs][81] <u>Prolonged gestation:</u> OR 1.0, 95% CI 0.2-4.2 [dos Santos 2009][71] OR 0.66, 95% CI 0.24-1.76 [Jolly 2000][74] 3/750 versus 2/750 [Kovavisarach 2010][82] <u>Polyhydramnios:</u> 1% versus 0.3% [Iloki 2004][73] 1/750 versus 2/750 [Kovavisarach 2010][82]		

Key messages

- Adolescent pregnancy can have serious consequences for the young mother and her child, including obstructed and prolonged labor, high risk of development of vesico-vaginal fistulae, infectious morbidity, stillbirths and neonatal deaths, as well as preterm birth, low birth weight and asphyxia.
- There are social causes and consequences of adolescent pregnancy- lack of education for girls and poverty, for example, are perpetuated since adolescent mothers are often without social support, and unable to finish their own schooling.
- Promising interventions to prevent teenage pregnancy are multifaceted and include communities, schools, health services, and the promotion and distribution of contraceptives; as well as programs that facilitate personal and social development; conditional cash transfers for girls' education must be further explored (risk reductions of 41-57%).
- For adolescents who are already mothers, parental skills training and encouraging them to complete their education, while providing them with medical care, prevents repeat pregnancy during adolescence (risk reductions of 59-89%).

3.2. Advance Maternal Age

Background

Couples' decisions regarding childbearing are strongly influenced by socio-cultural and economic factors. In many developing countries, girls are traditionally married at a very young age, and therefore much emphasis has been placed on the attendant risks of pregnancy during adolescence (see chapter on Teenage/Adolescent health). Across the world, however, there is a growing trend towards delayed childbearing as more young people pursue higher education and desire financial independence before they start a family. Higher divorce rates and the lack of a strong support system also play a role in the decision to become a parent during later reproductive years.[98] There is a general understanding that as fertility declines, couples may have more difficulty conceiving at a later age, and that the risk of triploid disorders is increased. Multiple studies have shown that that there is also an increased risk of maternal complications,[99] a greater need for obstetric intervention,[100] and a higher frequency of adverse perinatal outcomes,[99] of which women are largely unaware. More recent evidence suggests that advanced paternal age also contributes to the higher risk of genetic abnormalities[101-103] and early pregnancy loss with delayed childbearing; and that later parenthood might have long-term consequences for parents and children, [104-106] including increased risk of mental health disorders.[107-110]

Scope of Intervention

Pregnancy risks show a rising trend with increasing maternal age above 30 years; however the accepted definition of "advanced" maternal age is >35 years. We were unable to find any trials where an intervention was carried out to educate women so that they would not delay childbearing. We therefore compared MNCH outcomes for women any age over 35, with women any age between 20 and 35 from **risk-aversion** studies. Studies that only reported outcomes for women of "advanced" maternal age without a comparison group were only presented in the table of impact estimates. Where authors had presented disaggregated data, we used numbers for naturally conceived pregnancies and multiparas. Since the association of advanced maternal age and chromosomal aberrations is already well established, this data was not used.

Preconception care for women- advanced maternal age at conception
• Couples who might delay childbearing should be made aware that they are at increased risk for genetic abnormalities, early pregnancy loss, Caesarean delivery, stillbirths, perinatal death, preterm births and low birth weight babies. • All women of reproductive age, and couples, should be encouraged to have a reproductive life plan that includes age at first conception, number and spacing between children, and family planning method

Impact estimates

This review found a significantly increased risk of Caesarean delivery with advanced maternal age (RR 1.72, 95% CI 1.59-1.85) (**Figure 3.1.1**). However, since this estimate includes elective C-sections, the risk might simply be attributable to obstetricians, and women themselves, exercising more caution at later reproductive age. We also found a significantly higher (62%) risk of stillbirths with delayed childbearing. This effect estimate was derived from a total of 40 cohort and case-control studies (**Figure 3.1.2**).

Although fewer studies were included in the meta-analyses for advanced maternal age and the risk of perinatal death (increased risk by 44%) (**Figure 3.1.3**), preterm birth (increased risk by 29%) (**Figure 3.1.4**) and low birth weight (increased risk by 61%) (**Figure 3.1.5**), the analysis yielded significant effects for maternal age >35 years on each of these outcomes.

Previous reviews have suggested that with advanced maternal age, the presence of co-morbidities -especially diabetes and hypertension- increases (Katwijk), and this might largely be responsible for the pregnancy outcomes in women who delay childbearing. Although hypertension was defined differently in various studies, the risk of hypertension during pregnancy increased 3 times for women of advanced maternal age (**Figure 3.1.6**). We also found an elevated, but insignificant, risk of pre-eclampsia (0R 2.06, reduced to 1.60 when a study with very wide confidence intervals was removed from the analysis) (**Figure 3.1.7**), which was taken to be a more sensitive indicator than hypertension overall. The risk for antepartum hemorrhage, specifically which is due to placenta previa, was significant, being approximately 3 times higher in women of advanced maternal age (**Figure 3.1.8**). The risk for maternal diabetes (gestational) was also significantly 3 times higher, whereas the risk for pregestational diabetes was increased six-fold (OR 6.4 and 6.88 in 2 studies) (**Figure 3.1.9**). Schoen (2009)[111] also reported significantly increased risks of maternal complications in women who delayed pregnancy till their later reproductive years.

While there was a significant impact of delaying childbearing on selected MNCH outcomes, these estimates must be interpreted with caution since included studies considered different age cut-offs as “advanced” and comparison groups, and studies did not separate conceptions through assisted reproduction. There are a myriad number of methodological limitations in the literature addressing this risk factor (Newburn-Cook)[112], and perhaps as this population grows in number, larger prospective studies that control for confounders will substantiate whether advanced maternal age really is an independent risk factor for poor MNCH outcomes.

Conclusion

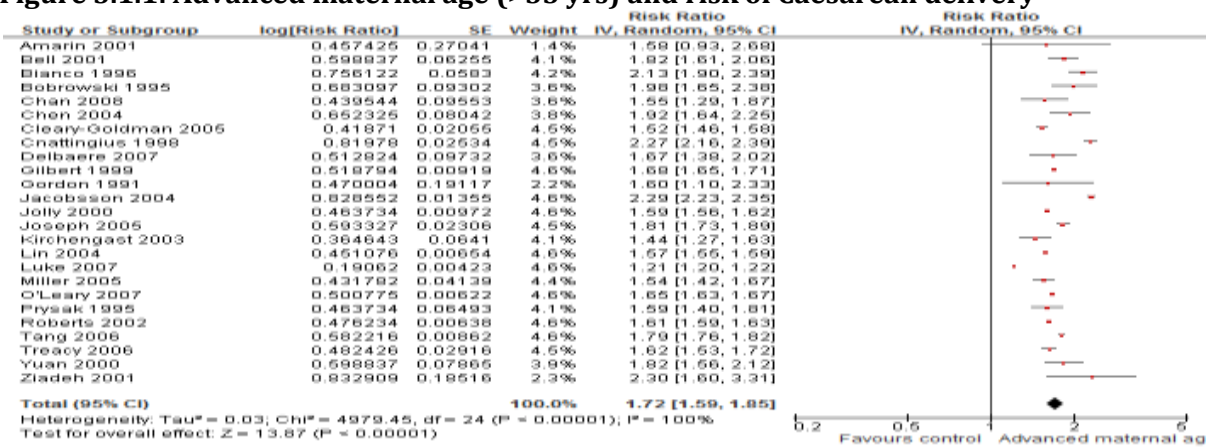
Although the evidence shows an inherently greater risk of adverse maternal and child outcomes- including stillbirths and Caesarean delivery- at advanced maternal age, the

social stimulus behind this trend might prove difficult to change, especially with the advent of assisted reproductive technology. Couples' reproductive plans are very personal, and therefore it is necessary that they understand the risks of later parenthood, so that they can make an informed decision. (O'Reilly-Green 1993)[113] The intention to have children, age at first conception, and intervals between pregnancies should all be considered, so that counselling can be provided at an appropriate stage. Counselling is especially important for women with pre-existing medical conditions, such as diabetes and hypertension, since these contribute to excess morbidity during gestation. Research might provide further insight into the mechanisms of risk including possible confounders such as parity and method of conception, and possible interventions such as preimplantation genetic diagnosis might become more accessible. At present, public health interventions can increase awareness regarding advanced parental age, allowing couples to weigh the risks and benefits of delaying childbearing.

Key messages

- There are many social and personal reasons that couples may choose to delay childbearing. Women of "advanced" maternal age (currently defined as those over age 35 years) are therefore, an increasing obstetric population
- Women who delay childbearing are at a 72% increased risk of Caesarean delivery, and face a higher risk of stillbirths (62% greater), perinatal death (44%), preterm births (29%) and low birth weight babies (61%).
- It is unclear, however, whether this increased risk is solely due to advanced maternal age, or whether other factors, such as parity, mode of conception and pre-existing maternal medical conditions might play a significant role. Further, the literature in this area is quite heterogeneous when defining both the exposure ("advanced" maternal age) and the outcomes (preterm birth, stillbirths)
- Until stronger evidence is available, women who plan to delay childbearing should be counselled regarding increased risks of adverse MNCH outcomes, and quality antenatal care should be provided to those women who do become pregnant during their later reproductive years since appropriate screening and management could ensure better outcomes for them are their newborns.

Figure 3.1.1: Advanced maternal age (>35 yrs) and risk of Caesarean delivery

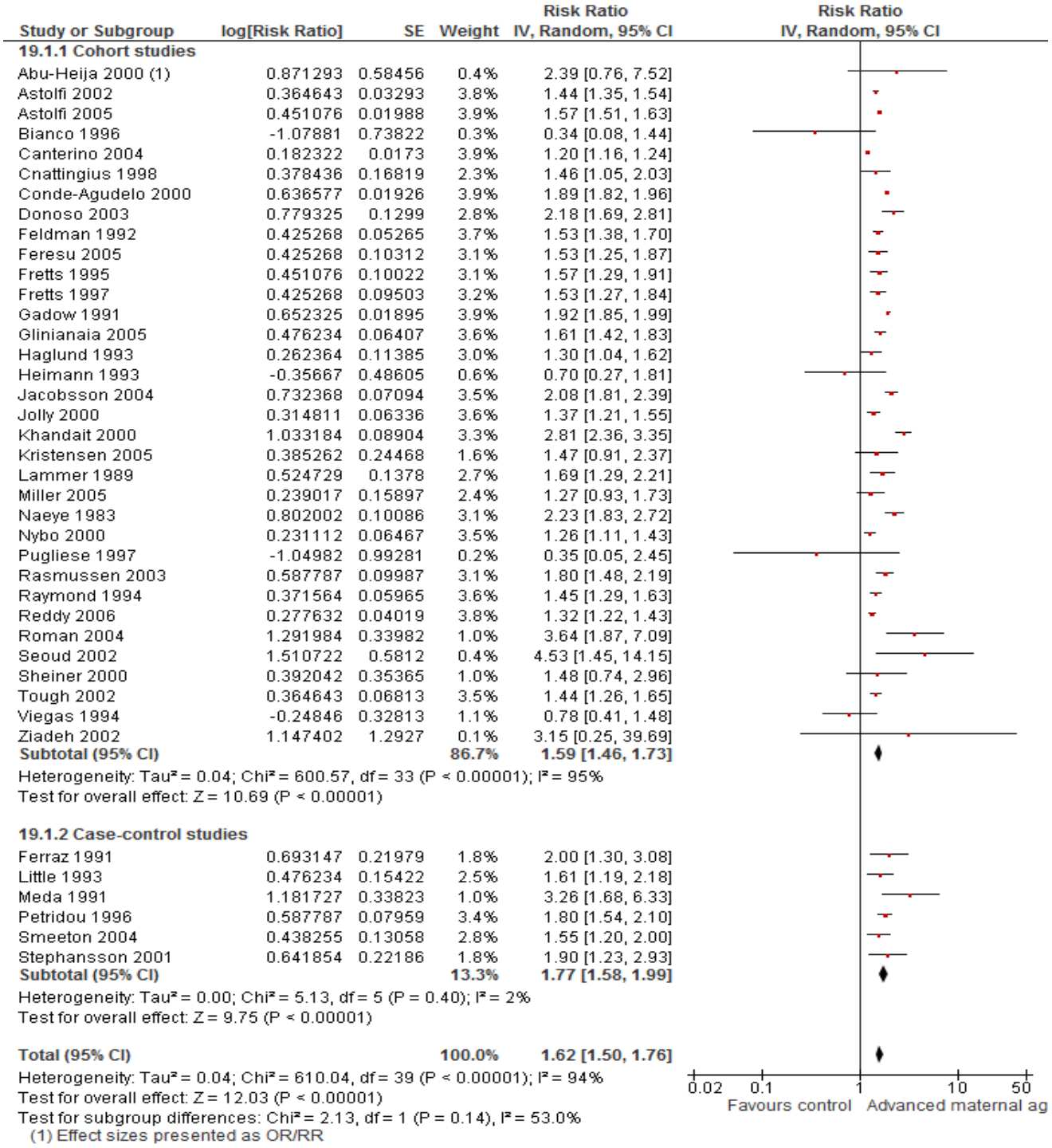


NOTE: No distinction was made between elective and emergency Caesarean deliveries.

Citations to the included studies:

Amarin 2001[114], Bell 2001[115], Bianco 1996[116], Bobrowski 1995[117], Chan 2008[118], Chen 2004[119], Cleary-goldman 2005[120],Cnattingius 1998[121], Delbaere 2007[122], Gilbert 1999[123], Gordon 1991[124], Jacobsson 2004[125], Jolly 2000[126], Joseph 2005[127], Kirchengast 2003[128], lin 2004[129], Luke 2007[130], Miller 2005[131], O'leary 2007[132], Prysak 1995[133], Roberts 2002[134], Tang 2006[135], Treacy 2006[136], Yuan 2000[137], Ziadeh 2001[138].

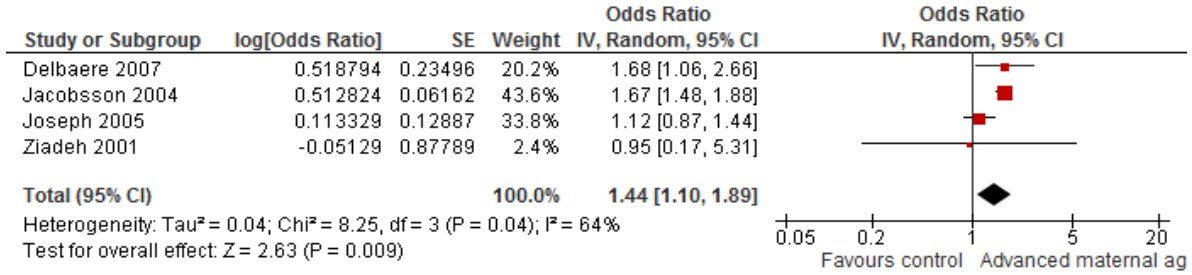
Figure 3.1.2: Advanced maternal age and the risk of stillbirths



Citations to the included studies

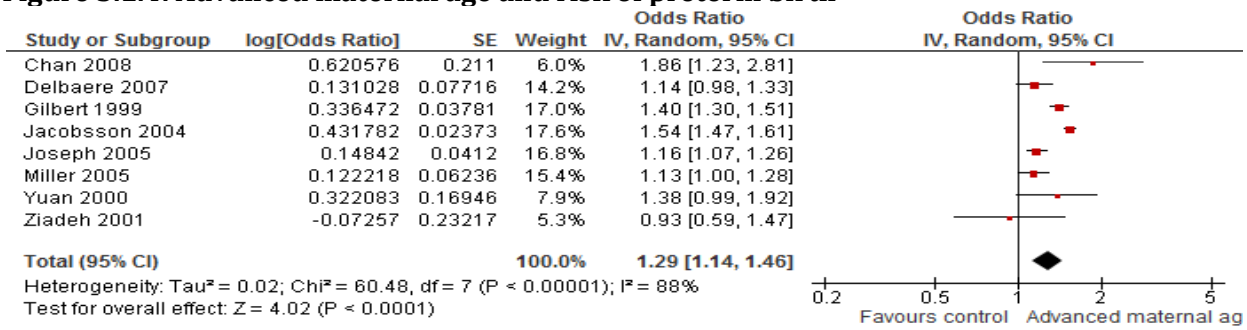
Abu-heija 2000[139], Astolfi 2002[140], Astolfi 2005[141], Bianco 1996[116], Canterino 2004[142], Cnattingius 1998[121], Conde-Agudelo 2000[143], Donoso 2003[144], Feldman 1992[145], Feresu 2005[146], frets 1995[147], Frets 1997[148], Gadow 1991[149], Gliniania 2005[150], Haglund 1993[151], Heimann 1993[152], Jacobsson 2004[125], Jolly 2000[126], Khandait 2000[153], Kristensen 2005[154], Lammer 1989[155], Miller 2005[131], Naeye 1983[156], Nybo 2000[157], Pugliese 1997[158], Rasmussen 2003[159], Raymond 1994[160], Reddy 2006[161], Roman 2004[162], Seoud 2002[163], Sheiner 2000[164], Tough 2002[165], Viegas 1994[166], Ziadeh 2002[167], Ferraz 1991[168], Little 1993[169], meda 1991[170], Petridou 1996[171], Smeeton 2004[172], Stephansson 2001[173].

Figure 3.1.3: Advanced maternal age and risk of perinatal death



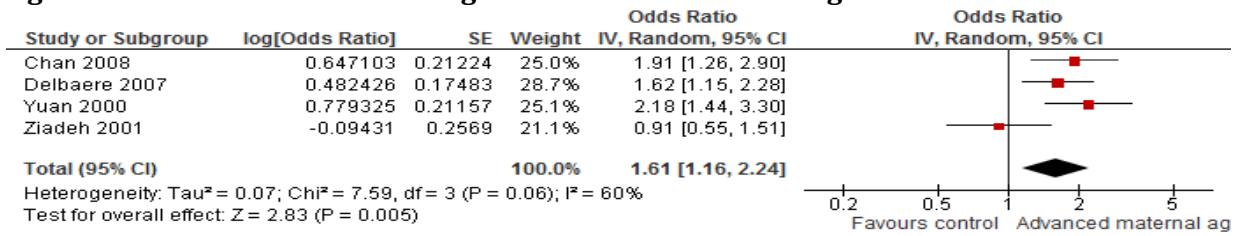
Citations to the included studies:
Delbaere 2007[122], Jacobsson 2004[125], joseph 2005[127], Ziadeh 2001[138].

Figure 3.1.4: Advanced maternal age and risk of preterm birth



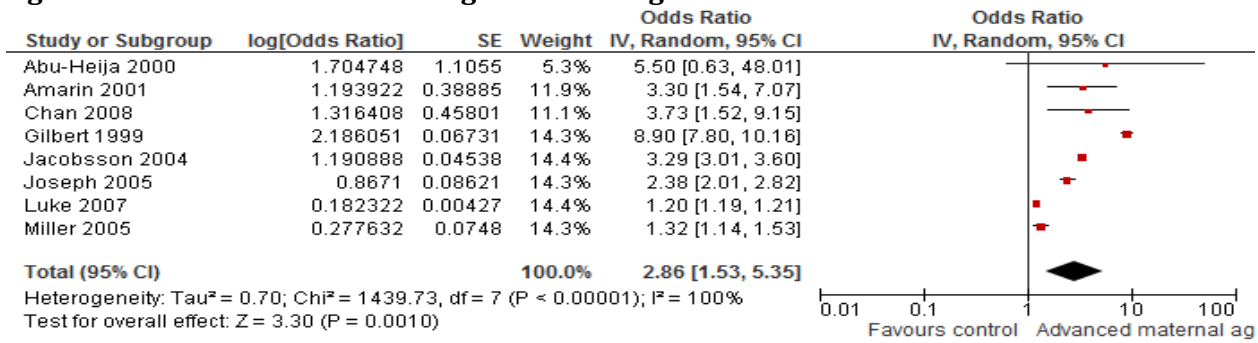
Citations to the included studies:
Chan 2008[118], Delbaere 2007[122], Gilbert 1999[123], Jacobsson 2004[125], joseph 2005[127], Miller 2005[131], Yuan 2000[137], Ziadeh 2001[138].

Figure 3.1.5: Advanced maternal age and risk of low birth weight



Citations to the included studies:
Chan 2008[118], Delbaere 2007[122], Yuan 2000[137], Ziadeh 2001[138].

Figure 3.1.6: Advanced maternal age and risk of gestational HTN

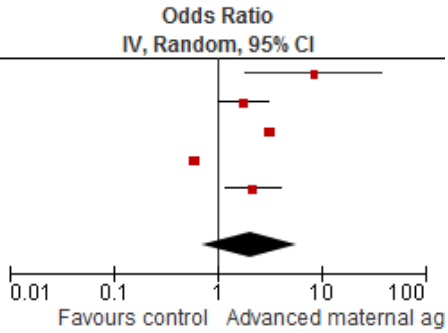


Citations to the included studies
Abu-heija 2000[139], Amarin 2001[114], Chan 2008[118],Gilbert 1999[123], Jacobsson 2004[125], joseph 2005[127], Luke 2007[130], Miller 2005[131]

Figure 3.1.7: Advanced maternal age and risk of preeclampsia

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Abu-Heija 2000	2.119863	0.76769	15.1%	8.33 [1.85, 37.51]
Chan 2008	0.565314	0.28843	20.6%	1.76 [1.00, 3.10]
Gilbert 1999	1.131402	0.05193	21.9%	3.10 [2.80, 3.43]
Jacobsson 2004	-0.54473	0.046	21.9%	0.58 [0.53, 0.63]
Ziadeh 2001	0.765468	0.31482	20.4%	2.15 [1.16, 3.98]
Total (95% CI)			**100.0%**	**2.06 [0.72, 5.89]**

Heterogeneity: Tau² = 1.31; Chi² = 594.83, df = 4 (P < 0.00001); I² = 99%
Test for overall effect: Z = 1.35 (P = 0.18)

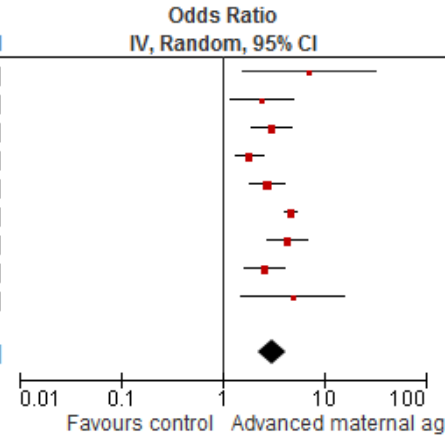


Citations to the included studies
Abu-heija 2000[139], Chan 2008[118],Gilbert 1999[123], Jacobsson 2004[125], Ziadeh 2001[138].

Figure 3.1.8: Advanced maternal age and risk of antepartum hemorrhage

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Abu-Heija 2000	1.94591	0.77584	3.4%	7.00 [1.53, 32.03]
Amarin 2001	0.8671	0.36229	9.1%	2.38 [1.17, 4.84]
Chan 2008	1.085189	0.22888	12.7%	2.96 [1.89, 4.64]
Cleary-Goldman 2005	0.587787	0.16603	14.5%	1.80 [1.30, 2.49]
Gilbert 1999	0.993252	0.20687	13.3%	2.70 [1.80, 4.05]
Jacobsson 2004	1.528228	0.07114	16.6%	4.61 [4.01, 5.30]
Joseph 2005	1.453953	0.23129	12.6%	4.28 [2.72, 6.73]
Miller 2005	0.928219	0.2306	12.6%	2.53 [1.61, 3.98]
Ziadeh 2001	1.576915	0.59429	5.1%	4.84 [1.51, 15.51]
Total (95% CI)			**100.0%**	**3.11 [2.28, 4.25]**

Heterogeneity: Tau² = 0.15; Chi² = 37.14, df = 8 (P < 0.0001); I² = 78%
Test for overall effect: Z = 7.12 (P < 0.00001)

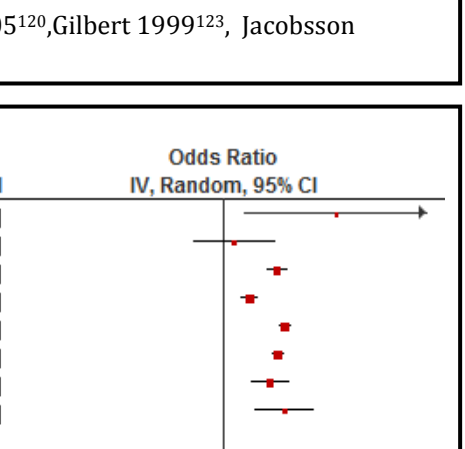


Citations to the included studies
Abu-heija 2000[139], Amarin 2001[114], Chan 2008[118], Cleary-goldman 2005[120],Gilbert 1999[123], Jacobsson 2004[125], joseph 2005[127], Miller 2005[131], Ziadeh 2001[138].

Figure 3.1.9: Advanced maternal age and risk of GDM

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Abu-Heija 2000	2.551006	1.05226	1.5%	12.82 [1.63, 100.83]
Amarin 2001	0.24686	0.46949	5.6%	1.28 [0.51, 3.21]
Chan 2008	1.205971	0.10853	17.0%	3.34 [2.70, 4.13]
Cleary-Goldman 2005	0.587787	0.09302	17.5%	1.80 [1.50, 2.16]
Gilbert 1999	1.386294	0.05376	18.6%	4.00 [3.60, 4.44]
Jacobsson 2004	1.23256	0.06158	18.4%	3.43 [3.04, 3.87]
Joseph 2005	1.054312	0.21313	12.8%	2.87 [1.89, 4.36]
Ziadeh 2001	1.386294	0.33364	8.7%	4.00 [2.08, 7.69]
Total (95% CI)			**100.0%**	**3.00 [2.31, 3.89]**

Heterogeneity: Tau² = 0.09; Chi² = 62.15, df = 7 (P < 0.00001); I² = 89%
Test for overall effect: Z = 8.27 (P < 0.00001)



Citations to the included studies
Abu-heija 2000[139], Amarin 2001[114], Chan 2008[118], Cleary-goldman 2005[120],Gilbert 1999[123], Jacobsson 2004[125], joseph 2005[127], Ziadeh 2001[138].

Table . .: Summary impact estimates of advanced maternal age

Maternal Outcomes	Pregnancy/Fetal Outcomes	Newborn Outcomes	Infant/Child Outcomes
Caesarean delivery: (as quoted in Bayrampour 2010 SR >35 yrs)[174] 1.59 [1.40, 1.80]Prysak 1995[133] 1.98 [1.65, 2.38]Bobrowski 1995[117] 2.13 [1.90, 2.39]Bianco 1996[116] 2.27 [2.16, 2.39] Cnattingius 1998[121] 1.82 [1.56, 2.12] Yuan 2000[137] 1.82 [1.61, 2.05] Bell 2001[115] 1.44 [1.27, 1.64] Kirchengast 2003[128] 1.92 [1.64, 2.25] Chen 2004[119] 1.81 [1.73, 1.89] Joseph 2005[127] 1.79 [1.76, 1.81] Tang 2006[135] 1.67 [1.38, 2.02]Delbaere 2007[122] 1.62 [1.53, 1.73]Treacy 2006[136] 1.59 [1.56, 1.62] Jolly 2000[126] 1.61 [1.59, 1.64] Roberts 2002[134] 1.57 [1.55, 1.58] Lin 2004[129] 1.52 [1.46, 1.58] Cleary-Goldman 2005[120] 1.65 [1.63, 1.68] O'Leary 2007[132] 40-44 yrs 2.66 (2.58–2.73) [Jacobsson 2004][125] >35 yrs RR 1.6 (1.1-2.4) multiparas; RR 2.5 (1.8-3.5) primiparas versus 20-29 yrs [Gordon 1991][124] 14/73 versus 57/471 [Amarin 2001][114] 44.6%, as opposed to 23% in the 20–29 year age group (p<0.001) [Callaway 2005 Coh][175] >40 yrs multiparas OR 1.73 (1.36–2.19). OR 2.93 in primiparas[Chan 2008][118] >40 yrs 7945/24032 versus 126538/642525 20-29 yrs [Gilbert 1999	Stillbirths: [Huang 2008][177] 9/114 versus 4/121 [Abu-Heija 2000][139] 0 in >45 yrs [Callaway 2005][175] >35 yrs RR 1.27 (0.93-1.75) versus <35 yrs [Miller 2005 Coh][131] RR 1.32 (1.22-1.43) for women 35- 39 yrs and 1.88 (1.64-2.16) for women >40 yrs at 37 to 41 weeks versus women <35 yrs, irrespective of parity, ethnicity or pre-existing medical condition [Reddy 2006 Obs][161] Preeclampsia: >45 yrs 14/114 versus 20-29 yrs 2/121 [Abu-Heija 2000 Obs][139] >35 yrs 17% versus 10.8% in control group [Tan 1994][178] Rate nearly 3 times higher than in women >35 yrs, however largely due to pre-existing hypertension [Barton 1997][179] >40 yrs multiparas OR 1.76 (1.00–3.09). OR 2.68 in primiparas[Chan 2008][118] >40 yrs 3.1 (2.8, 3.4) in multiparas. OR 1.8 in primiparas[Gilbert 1999][123] Severe preeclampsia 40-44 yrs 1.40 (1.26–1.56). Mild preeclampsia 0.58 (0.53–0.64) [Jacobsson 2004][125] >40 yrs 22/418 versus 20/794 for 20-29 yrs [Ziadeh 2001 CC][138] Antepartum haemorrhage: 12/114 versus 2/121 [Abu-Heija 2000][139] >35 yrs 12/73 versus 20-25 yrs 36/471 [Amarin 2001 Obs][114] Placental abruption increased by 23% for women age 35-49, especially with twin pregnancies [Ananth 2001][180] >40 yrs primiparas OR 2.96 (1.89–4.62) [Chan 2008][118] Placenta previa: 35-39 yrs 1.8 (1.3–2.6) [Cleary-Goldman 2005][120] Placenta previa: >40 yrs 2.7 (1.8, 3.6) in multiparas [Gilbert 1999][123] Placenta previa: 40-44 yrs 4.61 (4.01–5.30) [Jacobsson 2004][125]	NICU admission: 3% of infants born to women >40 yrs, but account for 5% NICU admissions [Battin 2007 Obs][181] >35 yrs 1.34 (1.22–1.48) [Delbaere 2007][122] >40 yrs 32/794 versus 15/418 for 20-29 yrs [Ziadeh 2001 CC][138] Macrosomia; 16/73 versus 39/471 [Amarin 2001][114] 35-39 yrs 1.4 (1.1–1.8) [Cleary-Goldman 2005][120] Perinatal death: >35 yrs 1.68 (1.06–2.65) [Delbaere 2007][122] 40-44 yrs 1.67 (1.48–1.88) [Jacobsson 2004][125] 35-39 yrs 1.63 (1.03–2.58) [Joseph 2005][127] >40 yrs 2/418 versus 4/794 for 20-29 yrs [Ziadeh 2001 CC][138] Neonatal death: >40 yrs 1.7 (1.3, 1.9) [Gilbert 1999][123] >40 yrs 1/794 versus	Infant death: >40 yrs 1.5 (1.3, 1.8) [Gilbert 1999][123] 35-39 yrs 0.98 (0.96– 1.01)for multiparas and 1.05 (1.00–1.10) for primiparas versus 30-34 yrs [Luke 2007 Coh][130]

Table . .: Summary impact estimates of advanced maternal age			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
Obs][123] >35 yrs 631/2304 versus 2336/13098 [Miller 2005][131] >40 yrs 58/418 versus 48/794 for 20-29 yrs [Ziadeh 2001 CC][138] 35-39 yrs 1.23 (1.22–1.24) versus 30-34 yrs for multiparas and 1.41 (1.40–1.42) for primiparas [Luke 2007][130] <u>Maternal mortality:</u> >35 yrs 2.20 (0.23-21.25) [Delbaere 2007][122] <u>Interpregnancy interval:</u> Mothers aged >35 at first pregnancy had increased odds for a second pregnancy following short IPI <6 months; (35-39 OR = 1.26 95% CI 1.11–1.44; 40–50 OR = 1.91 95% CI 1.13–3.24). [Nabukera 2009][176]	Placental abruption 1.64 (1.24–2.16), previa: 4.25 (2.71–6.66) [Joseph 2005][127] Placenta previa: >35 yrs 27/2304 versus 61/13098 [Miller 2005][131] >40 yrs 10/418 versus 4/794 for 20-29 yrs [Ziadeh 2001 CC][138] <u>Diabetes:</u> 11/114 versus 1/121 [Abu-Heija 2000][139] 9/73 versus 12/471 [Amarin 2001][114] >35 yrs 16.2% versus 2.8% in control group [Tan 1994][178] >40 yrs OR 6.88 (2.11–22.45) in multiparas pre-gestational; 3.34 (2.70–4.14) GDM. Slightly higher in primiparas [Chan 2008 Coh-versus <40 yrs][118] GDM: 35-39 yrs 1.8 (1.5–2.1) [Cleary-Goldman 2005][120] >40 yrs 6.4 (5.8, 7.1) pre-gestational and OR 3.3 in primiparas; 4.0 (3.6, 4.5) GDM, same in primiparas [Gilbert 1999][123] GDM: 40-44 yrs 3.43 (3.04–3.86) versus 20-29 [Jacobsson 2004 Coh][125] 35-39 yrs 2.85 (1.89–4.28) [Joseph 2005][127] GDM: >40 yrs 28/418 versus 14/794 for 20-29 yrs [Ziadeh 2001 CC][138] <u>Hypertension:</u> 5/114 versus 1/121 [Abu-Heija 2000][139] 11/73 versus 24/471 [Amarin 2001][114] >45 yrs 11% compared to 10% in the 20–29 year age group (P = 0.45) [Callaway 2005][175] >40 yrs multiparas OR 3.73 (1.52–9.14). Risk doubled in primiparas[Chan 2008][118] >40 yrs 8.9 (7.8, 10.2) in multiparas. OR 4.7 in primiparas [Gilbert 1999][123] 40-44 yrs 3.29 (3.01–3.59) [Jacobsson 2004][125] 35-39 yrs Rate ratio 2.32 (1.97–2.72) versus 20-24 yrs [Joseph 2005 Coh][127] >35 yrs 249/2304 versus 1101/13098 [Miller 2005][131]	1/418 for 20-29 yrs [Ziadeh 2001 CC][138] <u>Non-chromosomal fetal malformations:</u> 187/4189 versus 20-24 yrs 2600/71018. Cardiac malformations increased from an OR of 1.3 among women age 25-29 to 3.95 among women >40 yrs compared to those 20-24 years of age [Hollier 2000][182] <u>Down's Syndrome:</u> Women age >35 yrs now account for more than half of all Down's Syndrome pregnancies. However, the use of maternal age as a screening tool has poorer sensitivity and specificity than combined serum and sonographic antenatal testing in the first or second trimester, and would result in 1/7 pregnant women undergoing amniocentesis. [Resta 2005][183]	

Table . .: Summary impact estimates of advanced maternal age			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
	35-39 yrs 1.20 (1.19–1.21) for multiparas, 1.13 (1.11–1.14) for primiparas versus 30-34 yrs [Luke 2007 Coh][130] <u>Twins:</u> 6/73 versus 10/471 [Amarin 2001][114] <u>Preterm birth:</u> >40 yrs1.86 (1.23–2.82) [Chan 2008][118] >35 yrs 1.14 (0.98–1.33) [Delbaere 2007][122] >40 yrs 1.4 (1.3, 1.5) in multiparas, OR 1.7 in primiparas[Gilbert 1999][123] 40-44 yrs 1.54 (1.47–1.60) [Jacobsson 2004][125] 35-39 yrs 1.61 (1.42–1.82) [Joseph 2005][127] >35 yrs 272/2304 versus 1363/13098 [Miller 2005][131] >40 yrs 25/418 versus 51/794 for 20-29 yrs [Ziadeh 2001 CC][138] >35 yrs 1.38 (0.99-1.93) versus 20-29 yrs [Yuan 2000 Coh][137] <u>Low birth weight:</u> >40 yrs 1.91 (1.26–2.91) [Chan 2008][118] >35 yrs 1.62 (1.15–2.28) versus 25-29 yrs [Delbaere 2007 Coh][122] >40 yrs 21/418 versus 44/794 for 20-29 yrs [Ziadeh 2001 CC][138] >35 yrs 2.18 (1.44-3.29) versus 20-29 yrs [Yuan 2000 Coh][137] <u>Miscarriage:</u> 35-39 yrs 2.0 (1.5–2.6) [Cleary-Goldman 2005 Coh- versus <35 yrs][120]		

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Section IV

Reproductive planning

4.1 Birth Spacing

Background

Half a million women die from causes related to pregnancy and childbirth each year.[1] Over a tenth of these maternal deaths are due to unsafe abortion. The incidence of abortion is similar in developing and developed countries, with 26-29 abortions per 1000 women of reproductive age. Of the 205 million pregnancies occurring worldwide each year, one third are unintended and 20% end in abortion. Many women have abortions because they do not have recourse to family planning services, and thus are unable to plan when or how many children they have. Despite some progress towards achieving Millennium Development Goal 5 to reduce the maternal mortality ratio, a large unmet need for family planning still exists with over 100 million unmarried women in developing countries not using contraception.[2]

Scope of Intervention

Family planning allows women and couples to anticipate and attain their desired number of children and spacing between births, and to select the means by which this may be achieved. A woman's ability to space and limit her pregnancies has a direct impact on her health and well-being as well as on the outcome of each pregnancy. This review summarizes the effects of long and short inter-pregnancy intervals on MNCH outcomes, in the attempt to establish and define the ideal interval that can be used to counsel new mothers and mothers-to-be. For this review the exposure *inter-pregnancy interval* was largely used, to accommodate those intervals where the preceding pregnancy may not have ended in a birth, and short (<6 months) and long (>60 months) intervals were compared to the "ideal" interval (which was usually 12-23 months).

The content of preconception care

- Women, and couples, should be encouraged to have a reproductive life plan
- Counseling should help women understand the possible risks to themselves and their children of very short (stillbirths, uterine rupture with VBAC) and very long (neonatal deaths, preeclampsia) inter-pregnancy intervals. (Risks with both include maternal mortality, preterm births, low birth weight, small-for-gestational age babies)
- Counseling should help women understand the possible risks of having an unintended pregnancy, including the dangers of unsafe abortion
- Women should be advised to wait 18-24 months after pregnancies ending in live birth, and at least 6 months after an abortion, to conceive again. They should not wait longer than 5 years.
- Women should be encouraged to exclusively breastfeed their newborns for the first 6 months of life, and counseled when and how to start using contraception after giving birth
- Women should receive an effective contraceptive method with clearly demonstrated understanding of its proper use and possible side-effects. Whenever possible, contraceptive counseling should be provided to couples together. Advance provision of emergency contraception should also be considered.

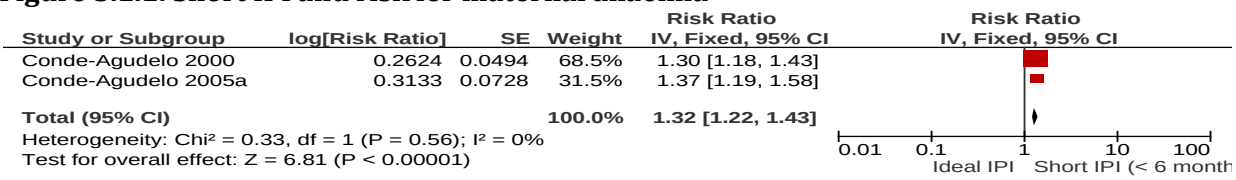
Impact estimates

Studies have long shown that inter-pregnancy intervals <12 months or >60 months have an adverse effect on maternal and perinatal outcomes.[3] Two recent reviews

undertaken by Conde-Agudelo (2006, 2007)[4, 5] to examine the impact of the inter-pregnancy interval on MNCH outcomes found a J-shaped dose-response relationship for perinatal outcomes, but were unable to pool the results for maternal outcomes. This review includes **risk-aversion** studies which assess maternal and child outcomes in relation to short and long inter-pregnancy intervals.

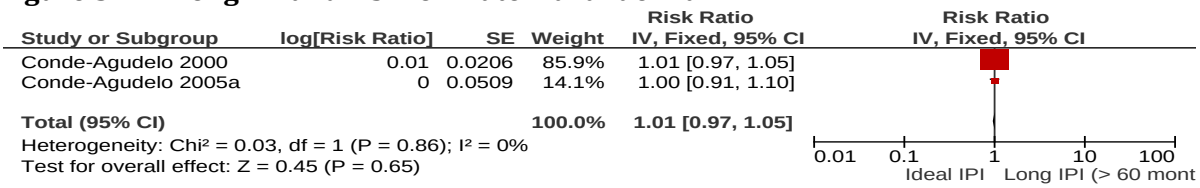
This review found a 32% increase in maternal anemia for short intervals (**Figure 5.1.1**), but no effect for long intervals (**Figure 5.1.2**). The apparent increased risk with short intervals is not consistent with previous work because it pooled only two studies, one of which included only women whose preceding pregnancy ended in an abortion.[6] For the same reason, the evidence presented for the effect of long intervals on eclampsia (**Figure 5.1.3**), third-trimester bleeding (**Figure 5.1.4**), and fetal death (**Figure 5.1.5**), and the effect of short intervals on puerperal endometritis (**Figure 5.1.6**) (**Figure 5.1.7**), must be treated with caution- other systematic reviews have not found consistent evidence on these outcomes either.

Figure 5.1.1: Short IPI and risk for maternal anaemia



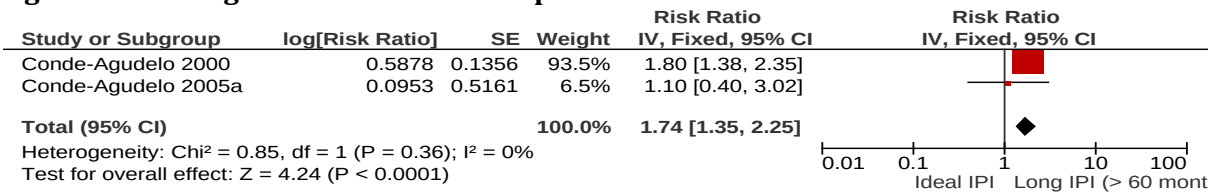
Citations to the included studies:
Conde-Agudelo 2000[7], Conde-Agudelo 2005a[6]

Figure 5.1.2: Long IPI and risk for maternal anaemia



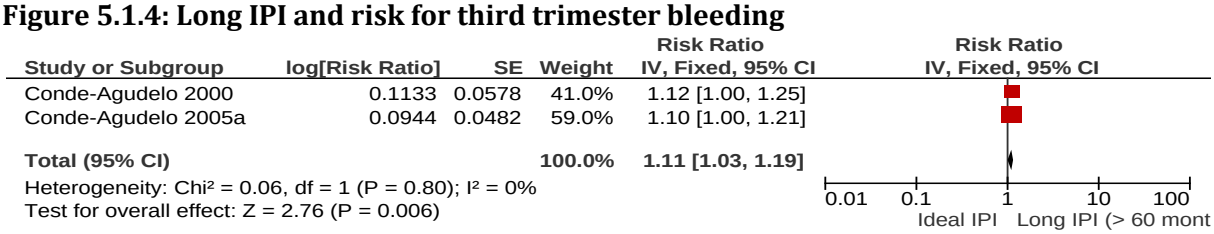
Citations to the included studies:
Conde-Agudelo 2000[7], Conde-Agudelo 2005a[6]

Figure 5.1.3: Long IPI and risk for eclampsia



Citations to the included studies:
Conde-Agudelo 2000[7], Conde-Agudelo 2005a[6]

Figure 5.1.4: Long IPI and risk for third trimester bleeding

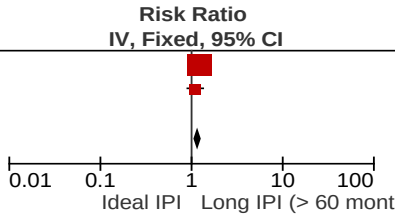


Citations to the included studies:
Conde-Agudelo 2000[7], Conde-Agudelo 2005a[6]

Figure 5.1.5: Long IPI and risk for fetal death

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
Conde-Agudelo 2000	0.1906	0.0627	72.1%	1.21 [1.07, 1.37]
Conde-Agudelo 2005a	0.0935	0.1009	27.9%	1.10 [0.90, 1.34]
Total (95% CI)			**100.0%**	**1.18 [1.06, 1.31]**

Heterogeneity: Chi² = 0.67, df = 1 (P = 0.41); I² = 0%
Test for overall effect: Z = 3.07 (P = 0.002)

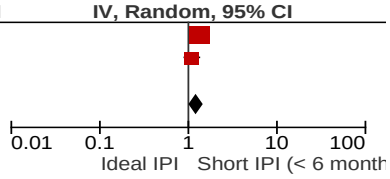


Citations to the included studies:
Conde-Agudelo 2000[7], Conde-Agudelo 2005a[6]

Figure 5.1.6: Short IPI and risk for puerperal endometritis

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Conde-Agudelo 2000	0.2852	0.044	60.3%	1.33 [1.22, 1.45]
Conde-Agudelo 2005a	0.0917	0.0983	39.7%	1.10 [0.90, 1.33]
Total (95% CI)			**100.0%**	**1.23 [1.02, 1.48]**

Heterogeneity: Tau² = 0.01; Chi² = 3.23, df = 1 (P = 0.07); I² = 69%
Test for overall effect: Z = 2.20 (P = 0.03)

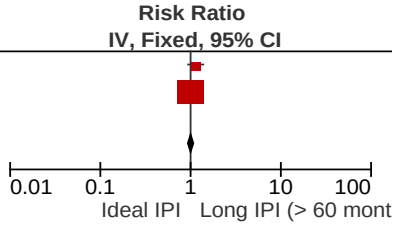


Citations to the included studies:
Conde-Agudelo 2000[7], Conde-Agudelo 2005a[6]

Figure 5.1.7: Long IPI and risk for puerperal endometritis

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
Conde-Agudelo 2000	0.131	0.0984	21.5%	1.14 [0.94, 1.38]
Conde-Agudelo 2005a	0	0.0515	78.5%	1.00 [0.90, 1.11]
Total (95% CI)			**100.0%**	**1.03 [0.94, 1.12]**

Heterogeneity: Chi² = 1.39, df = 1 (P = 0.24); I² = 28%
Test for overall effect: Z = 0.62 (P = 0.54)



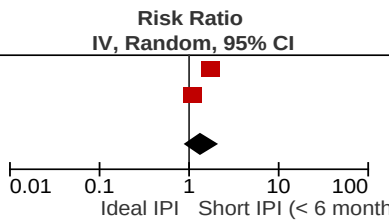
Citations to the included studies:
Conde-Agudelo 2000[7], Conde-Agudelo 2005a[6]

No significant effects were found for short intervals on third trimester bleeding (**Figure 5.1.8**), postpartum haemorrhage (**Figure 5.1.9**), gestational diabetes mellitus (**Figure 5.1.10**), fetal deaths (**Figure 5.1.11**), preeclampsia (**Figure 5.1.12**) or eclampsia (**Figure 5.1.13**). However, risk of uterine rupture after short intervals was higher (**Figure 5.1.14**). The results for the association of long intervals with postpartum haemorrhage (**Figure 5.1.15**), premature rupture of membranes (**Figure 5.1.16**) and gestational diabetes were also not significant (**Figure 5.1.17**).

Figure 5.1.8: Short IPI and risk for third trimester bleeding

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Conde-Agudelo 2000	0.5481	0.1007	50.0%	1.73 [1.42, 2.11]
Conde-Agudelo 2005a	0.0944	0.1014	50.0%	1.10 [0.90, 1.34]
Total (95% CI)			**100.0%**	**1.38 [0.88, 2.15]**

Heterogeneity: Tau² = 0.09; Chi² = 10.08, df = 1 (P = 0.001); I² = 90%
Test for overall effect: Z = 1.42 (P = 0.16)

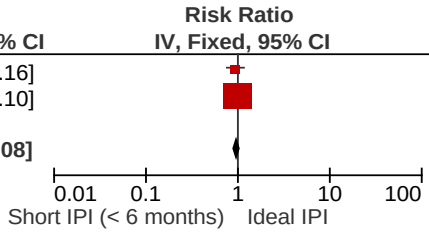


Citations to the included studies:
Conde-Agudelo 2000[7], Conde-Agudelo 2005a[6]

Figure 5.1.9: Short IPI and risk for post-partum haemorrhage

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
Conde-Agudelo 2000	-0.0619	0.1084	18.1%	0.94 [0.76, 1.16]
Conde-Agudelo 2005a	0	0.0509	81.9%	1.00 [0.91, 1.10]
Total (95% CI)			**100.0%**	**0.99 [0.90, 1.08]**

Heterogeneity: Chi² = 0.27, df = 1 (P = 0.61); I² = 0%
Test for overall effect: Z = 0.24 (P = 0.81)

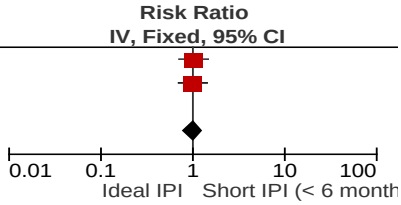


Citations to the included studies:
Conde-Agudelo 2000[7], Conde-Agudelo 2005a[6]

Figure 5.1.10: Short IPI and risk for GDM

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
Conde-Agudelo 2000	0.0198	0.1848	48.8%	1.02 [0.71, 1.47]
Conde-Agudelo 2005a	0	0.1805	51.2%	1.00 [0.70, 1.42]
Total (95% CI)			**100.0%**	**1.01 [0.78, 1.30]**

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.94); I² = 0%
Test for overall effect: Z = 0.07 (P = 0.94)

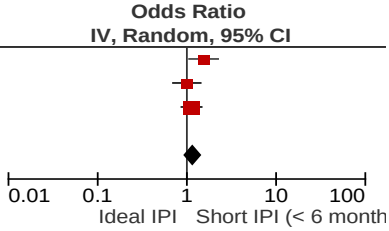


Citations to the included studies:
Conde-Agudelo 2000[7], Conde-Agudelo 2005a[6]

Figure 5.1.11: Short IPI and risk for fetal death

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Conde-Agudelo 2005	0.4318	0.1906	27.1%	1.54 [1.06, 2.24]
Conde-Agudelo 2005a	0	0.182	29.0%	1.00 [0.70, 1.43]
Nabukera 2008	0.1222	0.1334	43.8%	1.13 [0.87, 1.47]
Total (95% CI)			**100.0%**	**1.19 [0.95, 1.49]**

Heterogeneity: Tau² = 0.01; Chi² = 2.88, df = 2 (P = 0.24); I² = 31%
Test for overall effect: Z = 1.49 (P = 0.14)

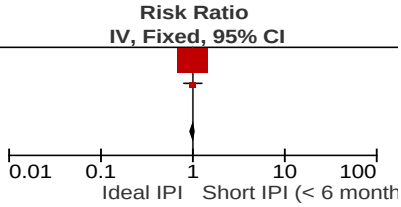


Citations to the included studies:
Conde-Agudelo 2005[8], Conde-Agudelo 2005a[6], Nabukera 2008[9]

Figure 5.1.12: Short IPI and risk for preeclampsia

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
Conde-Agudelo 2000	0	0.037	90.0%	1.00 [0.93, 1.08]
Conde-Agudelo 2005a	0	0.1107	10.0%	1.00 [0.80, 1.24]
Total (95% CI)			**100.0%**	**1.00 [0.93, 1.07]**

Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)

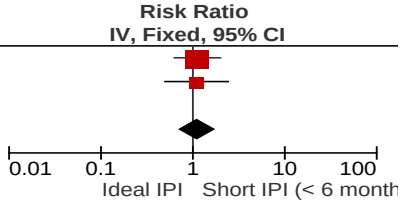


Citations to the included studies:
Conde-Agudelo 2000[7], Conde-Agudelo 2005a[6]

Figure 5.1.13: Short IPI and risk for eclampsia

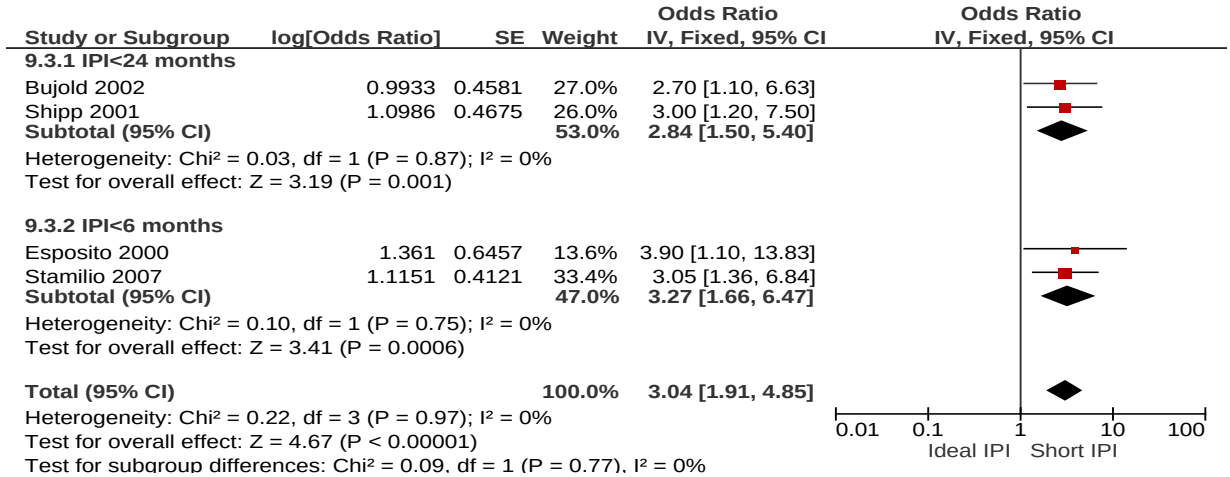
Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
Conde-Agudelo 2000	0.1133	0.2936	65.2%	1.12 [0.63, 1.99]
Conde-Agudelo 2005a	0.0953	0.4023	34.8%	1.10 [0.50, 2.42]
Total (95% CI)			**100.0%**	**1.11 [0.70, 1.77]**

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.97); I² = 0%
Test for overall effect: Z = 0.45 (P = 0.65)



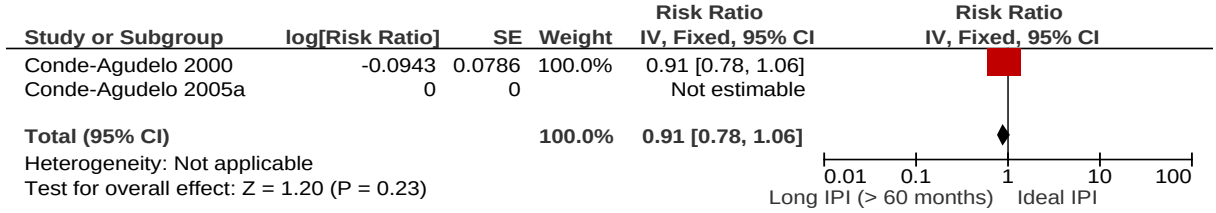
Citations to the included studies:
Conde-Agudelo 2000[7], Conde-Agudelo 2005a[6]

Figure 5.1.14: Short IPI and risk for uterine rupture during vaginal birth after Caesarean delivery



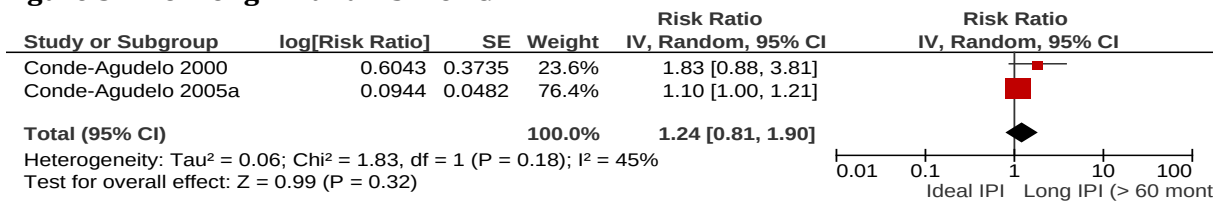
Citations to the included studies:
Bujold 2002[10], Shipp 2001[11], Esposito 2000[12], Stamilio 2007[13]

Figure 5.1.15: Long IPI and risk for post-partum haemorrhage



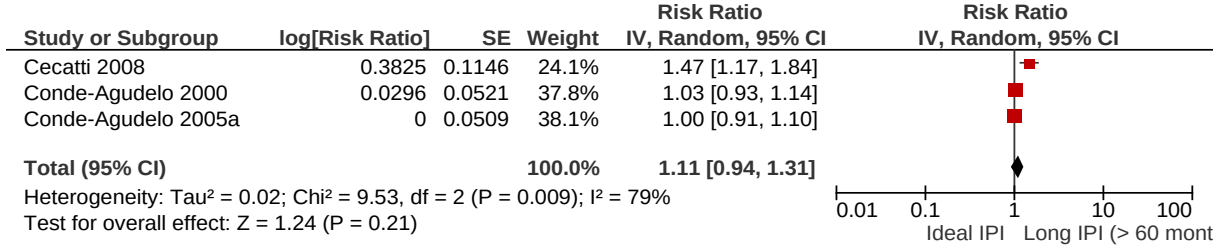
Citations to the included studies:
Conde-Agudelo 2000[7], Conde-Agudelo 2005a[6]

Figure 5.1.16: Long IPI and risk for GDM



Citations to the included studies:
Conde-Agudelo 2000[7], Conde-Agudelo 2005a[6]

Figure 5.1.17: Long IPI and risk for PROM



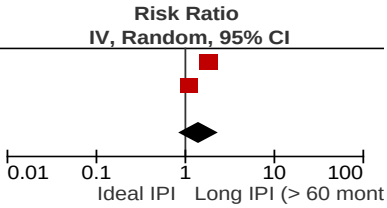
Citations to the included studies:
Conde-Agudelo 2000[7], Conde-Agudelo 2005a[6]

We were unable to pool more than two studies for the effect of long intervals on preeclampsia, however, the current evidence suggests an increased risk of 60-80% for intervals >60 months (**Figure 5.1.18**).

Figure 5.1.18: Long IPI and risk for preeclampsia

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Conde-Agudelo 2000	0.6043	0.0316	51.7%	1.83 [1.72, 1.95]
Conde-Agudelo 2005a	0.0917	0.0988	48.3%	1.10 [0.90, 1.33]
Total (95% CI)			**100.0%**	**1.43 [0.86, 2.36]**

Heterogeneity: Tau² = 0.13; Chi² = 24.42, df = 1 (P < 0.00001); I² = 96%
Test for overall effect: Z = 1.39 (P = 0.16)



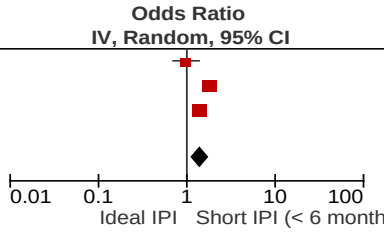
Citations to the included studies:
Conde-Agudelo 2000[7], Conde-Agudelo 2005a[6]

Pooling results from four studies showed that women undergoing a trial of labor after a short interval were 3 times more likely to suffer uterine rupture (OR 3.04, 95% CI 1.91-4.85) (**Figure 5.1.19**). Further, short intervals (*<12 months*) increased the risk of maternal deaths by an alarming 66% (OR 1.66, 95% CI 1.19-2.33) (**Figure 5.1.20).**

Figure 5.1.19: Short IPI and risk for PROM

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Cecatti 2008	-0.0202	0.1717	22.9%	0.98 [0.70, 1.37]
Conde-Agudelo 2000	0.5861	0.0657	37.1%	1.80 [1.58, 2.04]
Conde-Agudelo 2005a	0.3365	0.0378	40.0%	1.40 [1.30, 1.51]
Total (95% CI)			**100.0%**	**1.42 [1.11, 1.80]**

Heterogeneity: Tau² = 0.04; Chi² = 16.58, df = 2 (P = 0.0003); I² = 88%
Test for overall effect: Z = 2.83 (P = 0.005)

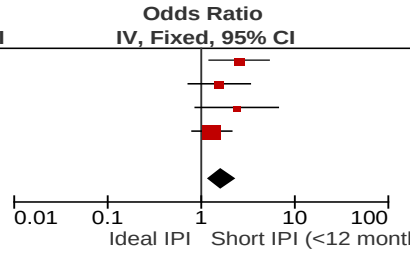


Citations to the included studies:
Cecatti 2008[14], Conde-Agudelo 2000[7], Conde-Agudelo 2005a[6]

Figure 5.1.20: Short IPI and risk of maternal death

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Conde-Agudelo 2000	0.9322	0.3741	21.1%	2.54 [1.22, 5.29]
Da Vanzo 2005	0.4447	0.3874	19.7%	1.56 [0.73, 3.33]
Fortney 1998	0.8755	0.5192	11.0%	2.40 [0.87, 6.64]
Ronsmans 1998	0.2624	0.2477	48.2%	1.30 [0.80, 2.11]
Total (95% CI)			**100.0%**	**1.66 [1.19, 2.33]**

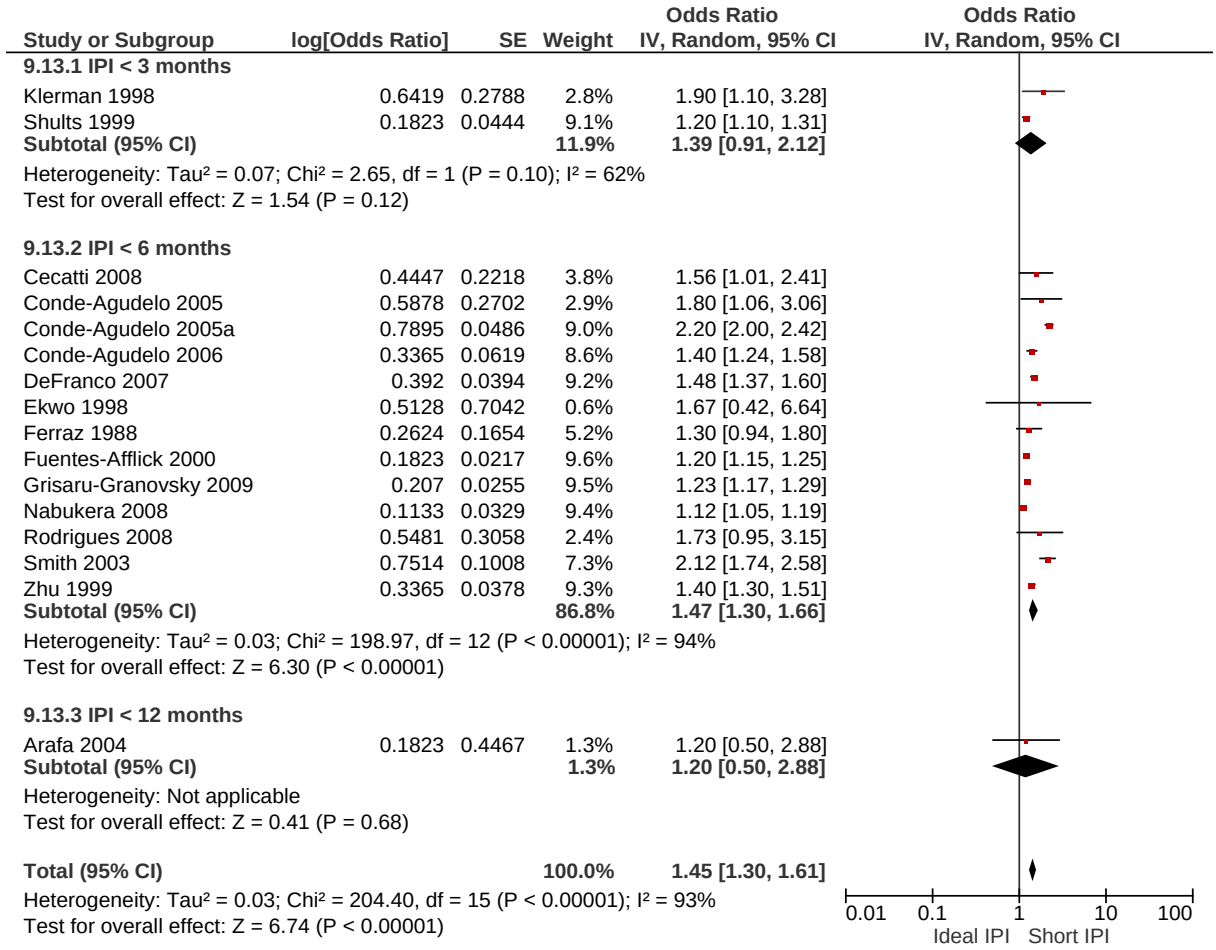
Heterogeneity: Chi² = 2.80, df = 3 (P = 0.42); I² = 0%
Test for overall effect: Z = 2.95 (P = 0.003)



Citations to the included studies:
Conde-Agudelo 2000[7], DaVanzo 2007[15]

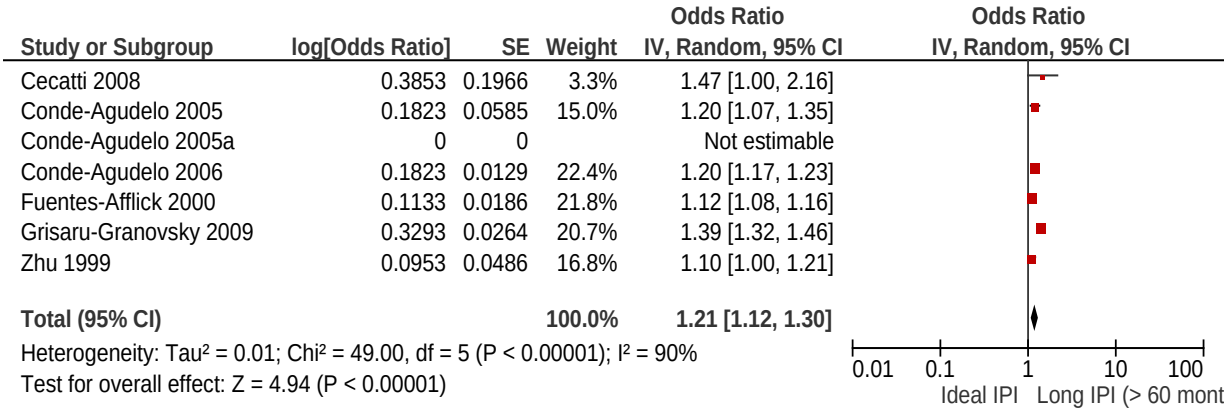
Among adverse perinatal outcomes, the increased risk of short and long inter-pregnancy intervals on preterm birth (OR 1.4 and 1.2 respectively), low birth weight (OR 1.61 and 1.43 respectively) and small-for-gestational age (OR 1.26 and 1.29 respectively) have been assessed in an earlier review (Conde-Agudelo 2006). This review also found a significantly increased risk with short and long intervals of preterm birth (OR 1.45 and 1.21 respectively) (**Figure 5.1.21**) (**Figure 5.2.22**), low birth weight (OR 1.65 and 1.37 respectively) (**Figure 5.1.23**) (**Figure 5.1.24**), and a slightly increased risk of small-for-gestational age (OR 1.17 and 1.18 respectively) (**Figure 5.1.25**) (**Figure 5.1.26**). A plausible explanation for the adverse perinatal outcomes associated with short inter-pregnancy intervals is that women who have closely-spaced pregnancies have not yet restored their body's reserves and are unable to provide their fetuses with adequate nutrition.[16, 17]

Figure 5.1.21: Short IPI and risk for preterm birth



Citations to the included studies:
Klerman 1998[18], Shults 1999[19], Cecatti 2008[14], Conde-Agudelo 2005[8], Conde-Agudelo 2005a[6], Conde-Agudelo 2006[4], DeFranco 2007[20], Ekwo 1998[21], Ferraz 1988[22], Fuentes-Afflick 2000[23], Grisaru-Granovsky 2009[24], Nabukera 2008[9], Rodrigues 2008[25], Smith 2003[26], Zhu 1999[27], Arafa 2004[28]

Figure 5.1.22: Long IPI and risk for preterm birth

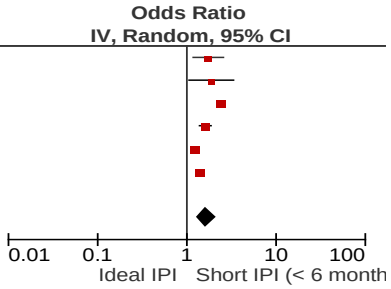


Citations to the included studies:
Cecatti 2008[14], Conde-Agudelo 2005[8], Conde-Agudelo 2005a[6], Conde-Agudelo 2006[4], Fuentes-Afflick 2000[23], Grisaru-Granovsky 2009[24], Zhu 1999[27]

Figure 5.1.23: Short IPI and risk for low birth weight

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Cecatti 2008	0.5539	0.1981	13.7%	1.74 [1.18, 2.57]
Conde-Agudelo 2005	0.6313	0.2923	10.2%	1.88 [1.06, 3.33]
Conde-Agudelo 2005a	0.8755	0.0444	19.2%	2.40 [2.20, 2.62]
Conde-Agudelo 2006	0.4762	0.075	18.5%	1.61 [1.39, 1.86]
Nabukera 2008	0.1989	0.0436	19.2%	1.22 [1.12, 1.33]
Zhu 1999	0.3365	0.0378	19.3%	1.40 [1.30, 1.51]
Total (95% CI)			**100.0%**	**1.65 [1.27, 2.14]**

Heterogeneity: Tau² = 0.09; Chi² = 134.71, df = 5 (P < 0.00001); I² = 96%
Test for overall effect: Z = 3.71 (P = 0.0002)

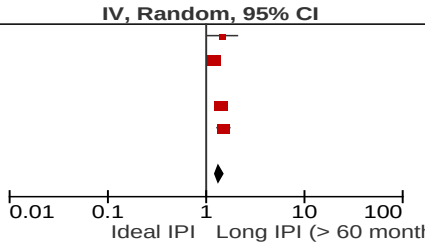


Citations to the included studies:
Cecatti 2008[14], Conde-Agudelo 2005[8], Conde-Agudelo 2005a[6], Conde-Agudelo 2006[4], Nabukera 2008[9], Zhu 1999[27]

Figure 5.1.24: Long IPI and risk for low birth weight

Study or Subgroup	log[]	SE	Weight	IV, Random, 95% CI
Cecatti 2008	0.3784	0.178	10.0%	1.46 [1.03, 2.07]
Conde-Agudelo 2005	0.174	0.0542	32.3%	1.19 [1.07, 1.32]
Conde-Agudelo 2005a	0	0		Not estimable
Conde-Agudelo 2006	0.3577	0.0605	30.5%	1.43 [1.27, 1.61]
Zhu 1999	0.4055	0.073	27.2%	1.50 [1.30, 1.73]
Total (95% CI)			**100.0%**	**1.37 [1.21, 1.55]**

Heterogeneity: Tau² = 0.01; Chi² = 8.57, df = 3 (P = 0.04); I² = 65%
Test for overall effect: Z = 4.87 (P < 0.00001)

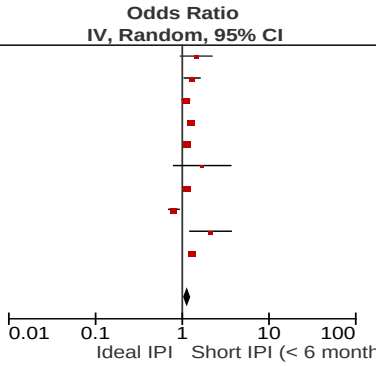


Citations to the included studies:
Cecatti 2008[14], Conde-Agudelo 2005[8], Conde-Agudelo 2005a[6], Conde-Agudelo 2006[4], Zhu 1999[27]

Figure 5.1.25: Short IPI and risk for SGA

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Cecatti 2008	0.3716	0.2104	3.4%	1.45 [0.96, 2.19]
Conde-Agudelo 2005	0.2624	0.1041	8.5%	1.30 [1.06, 1.59]
Conde-Agudelo 2005a	0.0953	0.0486	13.6%	1.10 [1.00, 1.21]
Conde-Agudelo 2006	0.2311	0.0335	14.9%	1.26 [1.18, 1.35]
Grisaru-Granovsky 2009	0.131	0.0229	15.6%	1.14 [1.09, 1.19]
Lieberman 1989	0.5306	0.3846	1.2%	1.70 [0.80, 3.61]
Nabukera 2008	0.131	0.0371	14.6%	1.14 [1.06, 1.23]
Smith 2003	-0.2231	0.0681	11.7%	0.80 [0.70, 0.91]
van Eijsden 2008	0.7514	0.2778	2.2%	2.12 [1.23, 3.65]
Zhu 1999	0.2624	0.0408	14.3%	1.30 [1.20, 1.41]
Total (95% CI)			**100.0%**	**1.17 [1.07, 1.27]**

Heterogeneity: Tau² = 0.01; Chi² = 53.60, df = 9 (P < 0.00001); I² = 83%
Test for overall effect: Z = 3.55 (P = 0.0004)

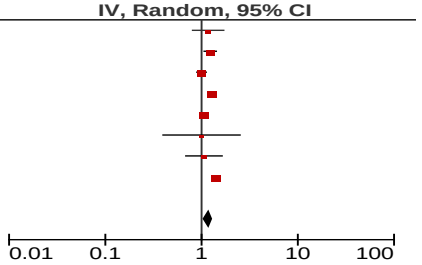


Citations to the included studies:
Cecatti 2008[14], Conde-Agudelo 2005[8], Conde-Agudelo 2005a[6], Conde-Agudelo 2006[4], Grisaru-Granovsky 2009[24], Lieberman 1989[29], Nabukera 2008[9], Smith 2003[26],Van Eijsden 2008[30], Zhu 1999[27]

Figure 5.1.26: Long IPI and risk for SGA

Study or Subgroup	log[]	SE	Weight	IV, Random, 95% CI
Cecatti 2008	0.157	0.1876	6.5%	1.17 [0.81, 1.69]
Conde-Agudelo 2005	0.207	0.0711	15.1%	1.23 [1.07, 1.41]
Conde-Agudelo 2005a	0	0.0538	16.7%	1.00 [0.90, 1.11]
Conde-Agudelo 2006	0.2546	0.0369	18.0%	1.29 [1.20, 1.39]
Grisaru-Granovsky 2009	0.0677	0.0194	19.0%	1.07 [1.03, 1.11]
Lieberman 1989	0	0.4675	1.4%	1.00 [0.40, 2.50]
van Eijsden 2008	0.0583	0.219	5.2%	1.06 [0.69, 1.63]
Zhu 1999	0.3365	0.0378	18.0%	1.40 [1.30, 1.51]
Total (95% CI)			**100.0%**	**1.18 [1.05, 1.32]**

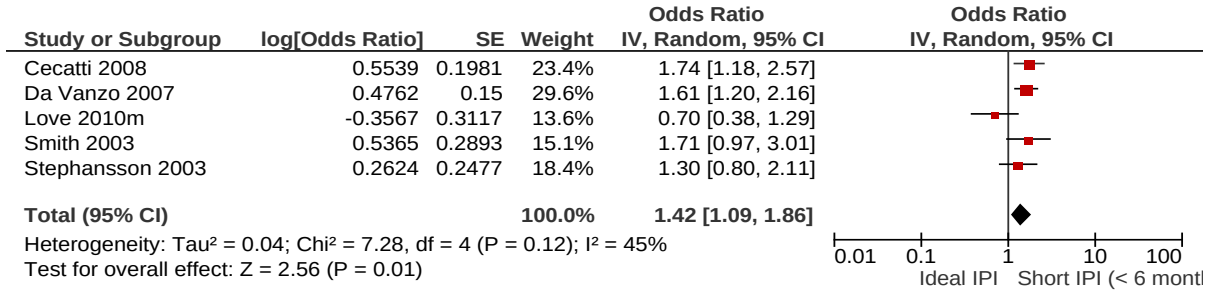
Heterogeneity: Tau² = 0.02; Chi² = 58.44, df = 7 (P < 0.00001); I² = 88%
Test for overall effect: Z = 2.80 (P = 0.005)



Citations to the included studies:
Cecatti 2008[14], Conde-Agudelo 2005[8], Conde-Agudelo 2005a[6], Conde-Agudelo 2006[4], Grisaru-Granovsky 2009[24], Lieberman 1989[29], Van Eijsden 2008[30], Zhu 1999[27]

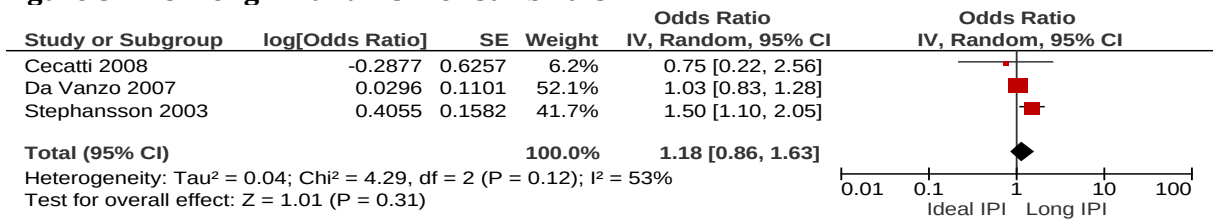
Conde-Agudelo et al did not pool the estimates for stillbirth and neonatal death; however our results show an increase in stillbirths for short intervals (OR 1.42, 95% CI 1.09-1.86) (**Figure 5.1.27**) and no significant effect for long intervals (**Figure 5.1.28**). Conversely, there was an increased risk of neonatal deaths with long (OR 1.15, 95% CI 1.06-1.25) (**Figure 5.1.29**), but not short intervals (**Figure 5.1.30**). Whereas there was no significant impact on miscarriages with short intervals (**Figure 5.1.31**).

Figure 5.1.27: Short IPI and risk for stillbirths



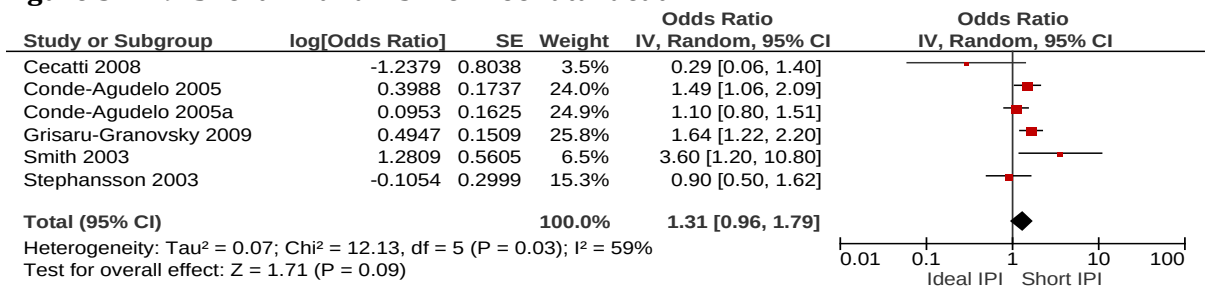
Citations to the included studies:
Cecatti 2008[14], DaVanzo 2007[15], Love 2010m[31], Smith 2003[26], Stephansson 2003[32]

Figure 5.1.28: Long IPI and risk for stillbirths



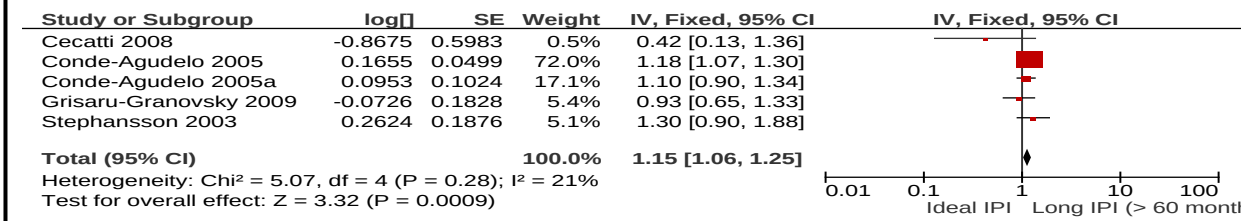
Citations to the included studies:
Cecatti 2008[14], DaVanzo 2007[15], Stephansson 2003[32]

Figure 5.1.29: Short IPI and risk for neonatal death



Citations to the included studies:
Cecatti 2008[14], Conde-Agudelo 2005[8], Conde-Agudelo 2005a[6], Grisaru-Granovsky 2009[24], Smith 2003[26], Stephansson 2003[32]

Figure 5.1.30: Long IPI and risk for neonatal death



Citations to the included studies:
Cecatti 2008[14], Conde-Agudelo 2005[8], Conde-Agudelo 2005a[6], Grisaru-Granovsky 2009[24], Stephansson 2003[32]

Table 5.1.1: Summary impact estimates of birth spacing			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
Maternal death: Short IPI (<6 months) adj. RR = 2.54 (9.5/10 000 women in cohort with singleton deliveries). Long IPI (> = 60 months) adj. RR = 1.07 (5.5/10 000) [Conde-Agudelo 2000 Obs-referent 18-23 months][7] Short IPI (< 12 months) OR= 1.5, 95% CI 0.7-3.2 [Da Vanzo 2005[33], quoted in Conde-Agudelo 2007 SR][5] Short BI (< 24 months) RR = 2.5, 95% CI 1.5-4.3 [Anandalakshmy 1993[34], quoted in	Ectopic pregnancy: Short IPI (< 6 months) aOR= 0.48, 95% CI 0.34-0.69 (p< 0.05). Long IPI (> 24 months) aOR=1.97, 95% CI 1.42-2.72 (p<0.05) [Love 2010 Coh- referent 6-12 months][31] Miscarriage: Short IPI (< 6 months) aOR= 0.66, 95% CI 0.57-0.77 (p<0.05). Long IPI (> 24 months) aOR= 0.99, 95% CI 0.84-1.18 (p< 0.05) [Love 2010 after miscarriage Coh- referent 6-12 months][31] Short IPI (<6 months) aOR= 3.30 95% CI 2.77–3.90. Long IPI (51-74 months) aOR= 1.00, 95% CI 0.86–1.17 [DaVanzo 2007 Obs-referent 27-50 months][15] Fetal death: Short IPI (<6 months) aOR=1.54, 95% CI 1.06-1.96 (4.91% of infants). Long IPI (> = 60 months) aOR= 1.21, 95% CI 1.07-1.31 (1.83% of infants) [Conde-Agudelo 2005 Obs- referent 18-23 months][8] Short IPI (< 6 months) aOR= 1.13, 95% CI 0.87–1.47 [Nabukera 2008 Coh- referent 18-23 months][9] Short IPI (3-5 months) aOR= 1.0, 95% CI 0.7-1.4. Long IPI (> 60 months) aOR= 1.1, 95% CI 0.9-1.2 [Conde-Agudelo 2005 Obs-referent 18-23 months][6] Third trimester bleeding: Short IPI (<6 months) adj. RR = 1.73, 95% CI 1.42-2.24 (1.9% of women in cohort with singleton deliveries). Long IPI (> = 60 months) adj. RR = 1.12 95% CI 1.00-1.24 (1.5%) [Conde-Agudelo 2000 Obs- referent 18-23 months][7] Short IPI (3-5 months) aOR= 1.1, 95% CI 0.9-1.4. Long IPI (> 60	Neonatal death: Short IPI (0-3 months) aOR= 0.9, 95% CI 0.5-1.6. Long IPI (> = 72 months) aOR= 1.3, 95% CI 0.9-2.1 [Stephansson 2003 Coh- referent 12-35 months][32] Short IPI (<6 months) aOR= 1.49, 95% CI 1.06-1.96 (3.1% of infants). Long IPI (> = 60 months) aOR= 1.18, 95% CI 1.07-1.31 (0.86% of infants) [Conde-Agudelo 2005 Obs-referent 18-23 months][8] Short IPI (< 6 months) 71/494 OR= 1.64, 95% CI 1.22-2.19, p<0.05. Long IPI (> = 60 months) 44/494 OR= 0.93, 95% CI 0.65-1.33 [Grisaru-Granovsky 2009 Coh-referent 12-23 months][24] Short IPI (< 6 months) aOR=0.29, 95% CI 0.06-1.48. Long IPI (>59 months) aOR= 0.42, 95% CI 0.13-1.32 [Cecatti 2008 Obs- referent 18-23 months][14] Short IPI (3-5 months) aOR= 1.1, 95% CI 0.8-1.5. Long IPI (> 60 months) aOR= 1.1, 95% CI 0.9-1.2 [Conde-Agudelo 2005 Obs-referent 18-23 months][6] Short IPI (< 6 months) aOR= 3.6,	(Rutstein 2005): Child mortality : The longer the birth interval, the lower the risk, even for intervals of 48 months or more. (Greenspan 1993): Mortality<5yrs was higher in children with birth order of 5 or more and who were conceived within 15mo of last birth and lowest among children with birth order 2-4 an who were conceived after 15mo of previous birth. Children whose mother gave birth within 24 months were 3 times more likely to be malnourished

Table 5.1.1: Summary impact estimates of birth spacing			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
	months) aOR= 1.1, 95% CI 1.0-1.3 [Conde-Agudelo 2005 Obs- referent 18-23 months][6]	95% CI 1.2-10.7 [Smith 2003 Coh- referent 18-23 months][26] <u>LBW:</u> Short IPI (< 6 months) aOR= 1.61, 95% CI 1.39 – 1.86. Risk increase/month for intervals < 18 months= 3.25.	even at 3yrs of age. <u>Vaccinations:</u> OR 3.07 (95% CI 2.98-3.17) for mothers with unwanted pregnancies to not complete the course of vaccinations for their children [Marston 2003 CS][35]
Conde-Agudelo 2007 SR][5] Short IPI (< 9 months) OR= 1.3, 95% CI 0.8-2.1 [Ronsmans 1998[36], quoted in Conde-Agudelo 2007 SR][5] Short BI (< 12 months) OR= 2.4, 95% CI 0.9-6.3 [Fortney1998[37] , quoted in Conde-Agudelo 2007 SR][5] <u>Anaemia:</u> Short IPI (< 6 months) adj. RR = 1.30, 95% CI 1.18-1.43 (7.9% women in cohort with singleton deliveries). Long IPI (> = 60 months) adj. RR = 1.01, 95% CI 0.97-1.05 (6.2%) [Conde-Agudelo 2000 Obs- referent 18-23 months][7] Short IPI (3-5 months) aOR= 1.4,	<u>Peripartum haemorrhage:</u> Short IPI (< 6 months) aOR= 1.01, 95% CI 0.48-2.14. Long IPI (>59 months) aOR= 1.29, 95% CI 0.72-2.29 [Cecatti 2008 Obs- referent 18-23 months][14] <u>PPH:</u> Short IPI (<6 months) adj. RR = 0.94, 95% CI 0.76-1.13 (5.1% of women in cohort with singleton deliveries). Long IPI (> = 60 months) adj. RR = 0.91 95% CI 0.78-1.04 (5.3%) [Conde-Agudelo 2000 Obs- referent 18-23 months][7] Short IPI (3-5 months) aOR= 1.0, 95% CI 0.9-1.1. Long IPI (> 60 months) aOR= 1.0, 95% CI 1.0-1.1 [Conde-Agudelo 2005 Obs- referent 18-23 months][6] <u>GDM:</u> Short IPI (<6 months) adj. RR = 1.02, 95% CI 0.71-1.35 (3.4% of women in cohort with singleton deliveries). Long IPI (> = 60 months) adj. RR = 1.83, 95% CI 0.88-1.63 (6.6%) [Conde-Agudelo	Long IPI (> = 60 months) aOR = 1.43, 95% CI 1.27 – 1.62. Risk increase/month for intervals > 59 months= 0.91 [Conde-Agudelo 2006 MA- referent 18-23 months][4] Short IPI (<6 months) aOR= 1.88, 95% CI 1.06-1.96 (15.3% of infants). Long IPI (> = 60 months) aOR= 1.19, 95% CI 1.07-1.31 (8.4% of infants) [Conde-Agudelo 2005 Obs- referent 18-23 months][8] Short IPI (< 6 months) aOR= 1.22, 95% CI 1.12–1.32 [Nabukera 2008 Coh- referent 18-23 months][9] Short IPI (< 6 months) aOR= 1.74, 95% CI 1.18-2.55. Long IPI (>59	<u>Stunting:</u> OR 2.71 (95% CI 2.63-2.79) for children whose mothers termed pregnancy as unwanted [Marston 2003 CS][35] Reduction in stunting associated with a previous birth interval >36 months ranged from approximately 10% to 50%

Table 5.1.1: Summary impact estimates of birth spacing			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
95% CI 1.2-1.6. Long IPI (> 60 months) aOR= 1.0, 95% CI 0.9-1.1 [Conde-Agudelo 2005 Obs- referent 18-23 months][6] <u>Uterine rupture after VBAC:</u> Short BI (<19 months) OR= 3.0, 95% CI 1.2-7.2 [Shipp 2001[11], as quoted in Conde-Agudelo 2007 SR][5] Short BI (< = 24 months) OR= 2.7, 95% CI 1.1-5.5 [Bujold 2002[10], as quoted in Conde-Agudelo 2007 SR][5] Short IPI (< 6 months) OR= 3.9, 95% CI 1.1-14.3 [Esposito 2000[12], as quoted in Conde-Agudelo 2007 SR][5] Short IPI (< 6 months) aOR= 3.05, 95% CI 1.36–6.87. Long IPI (>60 months) aOR= 1.08, 95% CI 0.66–1.77 [Stamilio 2007 Coh- referent 18-59 months][13] <u>Mean Arterial Pressure:</u> Short IPI (6 months) MAP was 1.10 mmHg lower in second pregnancy (95 % CI -1.650to -0.45), decreased linearly with increasing IPI and was not apparent after 24 months [Mikolajczyk 2008 Obs][38] <u>Antenatal care:</u> OR 2.96 (95% CI 2.88-3.05) for	2000 Obs- referent 18-23 months][7] Short IPI (3-5 months) aOR= 1.0, 95% CI 0.7-1.2. Long IPI (> 60 months) aOR= 1.1, 95% CI 1.0-1.3 [Conde-Agudelo 2005 Obs- referent 18-23 months][6] <u>Maternal hypertensive disorders:</u> Short IPI (< 6 months) aOR= 1.36, 95% CI 0.91-2.04. Long IPI (>59 months) aOR= 1.24, 95% CI 0.89-1.72 [Cecatti 2008 Obs- referent 18-23 months][14] <u>Pre-eclampsia:</u> Short IPI (<6 months) adj. Relative Risk= 1.00, 95% CI 0.93-1.07 (3.4% of women in cohort with singleton deliveries). Long IPI (> = 60 months) adj. Relative Risk= 1.83, 95% CI 1.72-1.94 (6.6%) [Conde-Agudelo 2000 Obs- referent 18-23 months][7] Long IPI (> = 60 months) OR= 1.6 [Basso 2001[39], as quoted in Conde-Agudelo 2007 SR][5] Long BI (> = 60 months) OR= 1.6 [Trogstad 2001[40], as quoted in Conde-Agudelo 2007 SR][5] OR for each 1-yr increase in BI= 1.12 [Skjærven 2002[41], as quoted in Conde-Agudelo 2007 SR][5] Short IPI (< 6 months) OR= 2.19. Long IPI (> = 75 months) OR= 2.44 [Razzaque 2005[42], as quoted in Conde-Agudelo 2007 SR][5] Each 1-yr increase in IPI conferred a 10% increased risk [Mostello 2002[43], as quoted in Conde-Agudelo 2007 SR][5] Short IPI (3-5 months) aOR= 1.0, 95% CI 0.8-1.2. Long IPI (> 60 months) aOR= 1.1, 95% CI 0.9-1.2 [Conde-Agudelo 2005 Obs- referent 18-23 months][6]	months) aOR= 1.46, 95% CI 1.03-2.06 [Cecatti 2008 Obs- referent 18-23 months][14] Short IPI (3-5 months) aOR= 2.4, 95% CI 2.2-2.7. Long IPI (> 60 months) aOR= 1.0, 95% CI 1.0-1.1 [Conde-Agudelo 2005 Obs- referent 18-23 months][6] Short IPI (< 6 months) aOR= 1.4, 95% CI 1.3-1.6. Long IPI (60-120 months) aOR= 1.5, 95% CI 1.3-1.6 [Zhu 1999 Obs- referent 18-23 months][27] Long IPI (> 24 months) aOR= 1.06, 95% CI 0.74-1.54 [Klebanoff 1988 Coh- referent < 3 months][46] <u>SGA:</u> Short IPI (<6 months) aOR = 1.26, 95% CI 1.18 – 1.33. Risk increase/month for intervals <18 months= 1.52. Long IPI (> = 60 months) aOR = 1.29, 95% CI 1.20 – 1.39. Risk increase/month for intervals > 59 months= 0.76 [Conde-Agudelo 2006 MA- referent 18-23 months][4] Short IPI (<6 months) aOR= 1.30, 95% CI 1.06-1.96 (16.9% of	[Dewey 2007 SR- referent 24-35 months][56] Second-born children conceived after an IPI of <12 months had more than threefold increased odds of autism relative to those with IPIs of >36 months [Cheslack-Postava 2011 Obs][57] Children born with inadequate birth intervals (less than 24 months) are more likely to fail the Cognitive Skills Assessment Battery for school readiness [Hayes 2006 Obs][58]

Table 5.1.1: Summary impact estimates of birth spacing			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
women with unwanted pregnancies to receive no antenatal care [Marston 2003 CS][35]	<u>Eclampsia:</u> Short IPI (<6 months) adj. RR = 1.12, 95% CI 0.63-2.29 (0.12% of women in cohort with singleton deliveries). Long IPI (> = 60 months) adj. RR = 1.80, 95% CI 1.38-2.32 (0.20%) [Conde-Agudelo 2000 Obs- referent 18-23 months][7] Short IPI (3-5 months) aOR= 1.1, 95% CI 0.5-2.3. Long IPI (> 60 months) aOR= 1.1, 95% CI 0.4-3.2 [Conde-Agudelo 2005 Obs- referent 18-23 months][6] <u>PROM:</u> Short IPI (<6 months) adj. RR = 1.72, 95% CI 1.53-1.93 (9.8% of women in cohort with singleton deliveries). Long IPI (> = 60 months) adj. RR 1.03, 95% CI 0.93-1.14 (6.5%) [Conde-Agudelo 2000 Obs- referent 18-23 months][7] Short IPI (< 6 months) aOR= 0.98, 95% CI 0.70-1.37. Long IPI (>59 months) aOR= 1.57, 95% CI 1.20-2.06 [Cecatti 2008 Obs- referent 18-23 months][14] Short IPI (< 6 months) OR = 4.3, 95% CI: 1.8–10.0 [Rodrigues 2008 CC][25] Short IPI (3-5 months) aOR= 1.4, 95% CI 1.3-1.6. Long IPI (> 60 months) aOR= 1.0, 95% CI 0.9-1.1 [Conde-Agudelo 2005 Obs- referent 18-23 months][6] <u>Maternal infection:</u> Short IPI (< 6 months) aOR= 1.39, 95% CI 0.89-2.17. Long IPI (>59 months) aOR= 1.00, 95% CI 0.68-1.46 [Cecatti 2008 Obs- referent 18-23 months][14] <u>Puerperal endometritis:</u> Short IPI (<6 months) adj. RR = 1.33, 95% CI 1.22-1.45 (1.4% of women in cohort with singleton deliveries). Long IPI (> = 60	infants). Long IPI (> = 60 months) aOR= 1.23, 95% CI 1.07-1.31 (16.0% of infants) [Conde-Agudelo 2005 Obs- referent 18-23 months][8] Short IPI (< 6 months) 3364/35311 OR= 1.14, 95% CI 1.09-1.19, p<0.0001. Long IPI (> = 60 months) 3659/35311 OR= 1.07, 95% CI 1.03-1.12, p<0.05 [Grisaru-Granovsky 2009 Coh- referent 12-23 months][24] Short IPI (< 6 months) aOR= 1.14, 95% CI 1.06–1.22 [Nabukera 2008 Coh- interaction with maternal age referent 18-23 months][9] Short IPI (<6 months) aOR= 2.12, 95% CI 1.23-3.65. Long IPI (> 60 months) aOR= 1.06, 95% CI 0.69-1.63 [van Eijsden 2008 Coh- referent 18-23 months][30] Short IPI (<12 months) 7.4% of infants were SGA, versus Long IPI (>36 months) 8.2% of infants [Auger 2008 Coh- referent 12-36 months][49] Short IPI (< 6 months) aOR= 1.45, 95% CI 0.96-2.46. Long IPI (>59 months) aOR= 1.17, 95% CI 0.81-1.70 [Cecatti 2008 Obs- referent	

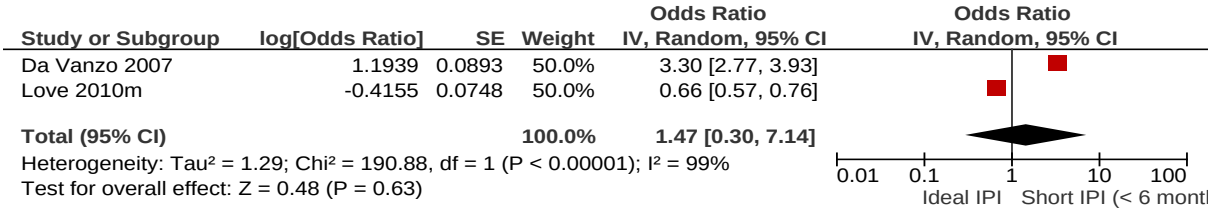
Table 5.1.1: Summary impact estimates of birth spacing			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
	months) adj. RR = 1.14, 95% CI 0.94-1.15 (2.4%) [Conde-Agudelo 2000 Obs- referent 18-23 months][7] Short IPI (3-5 months) aOR= 1.1, 95% CI 0.9-1.2. Long IPI (> 60 months) aOR= 1.0, 95% CI 0.9-1.1 [Conde-Agudelo 2005 Obs- post-abortion referent 18-23 months][6] <u>Preterm birth:</u> Short IPI (<6 months) aOR = 1.40, 95% CI 1.24 – 1.58. Risk increase/month for intervals < 18 months= 1.92. Long IPI (> = 60 months) aOR = 1.20, 95% CI 1.17 – 1.24. Risk increase/month for intervals > 59 months= 0.55[Conde-Agudelo 2006 MA- referent 18-23 months][4] Short IPI (<6 months) aOR= 1.80, 95% CI 1.06-1.96 (18.9% of infants). Long IPI (> = 60 months) aOR= 1.20, 95% CI 1.07-1.31 (10.2% of infants) [Conde-Agudelo 2005 Obs- referent 18-23 months][8] Short IPI (< 6 months) 2141/22135 OR= 1.23, 95% CI 1.17-1.29, p<0.0001. Long IPI (> = 60 months) 2889/22135 OR= 1.39, 95% CI 1.32-1.46, p<0.0001 [Grisaru-Granovsky 2009 Coh- referent 12-23 months][24] Short IPI (< 6 months) aOR= 1.12, 95% CI 1.05–1.20 [Nabukera 2008 Coh- referent 18-23 months][9] Short IPI (<6 months) aOR= 1.48, 95% CI 1.37-1.61 [DeFranco 2007 Coh- referent >18 months][20] Short IPI (< 6 months) aOR= 1.56, 95% CI 1.01-2.46. Long IPI (>59 months) aOR= 1.47, 95% CI 1.00-2.19 [Cecatti 2008 Obs- referent 18-23 months][14]	18-23 months][14] Short IPI (3-5 months) aOR= 1.1, 95% CI 1.0-1.2. Long IPI (> 60 months) aOR= 1.0, 95% CI 0.9-1.1 [Conde-Agudelo 2005 Obs- referent 18-23 months][6] Short IPI (< 6 months) aOR= 1.3, 95% CI 1.2-1.4. Long IPI (60-120 months) aOR= 1.4, 95% CI 1.3-1.5 [Zhu 1999 Obs- referent 18-23 months][27] Short IPI (< 6 months) aOR= 0.8, 95% CI 0.7-1.1 [Smith 2003 Coh- referent 18-23 months][26] Short IPI (< 3 months) aOR= 1.6, 95% CI 1.4-1.8 [Shults 1999 Obs- referent 13-24 months][19] Short IPI (<6 months) aOR= 1.7, 95% CI 0.8-3.6. Long IPI (> 60 months) aOR= 1.0, 95% CI 0.4-2.6 [Lieberman 1989 Coh- referent 24-36 months][29] <u>LGA:</u> Short IPI (< 6 months) 3177/49534, OR= 0.83, 95% CI 0.80–0.87, p<0.0001. Long IPI (> = 60 months) 5373/49534 OR= 1.04, 95% CI 1.00-1.08, p<0.05 [Grisaru-	

Table 5.1.1: Summary impact estimates of birth spacing			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
	Short IPI (< 6 months) aOR= 3.60, 95% CI 1.41-8.98 for early preterm, but no association with late preterm birth (OR= 0.80, 95% CI 0.32-1.83) [Rodrigues 2008 CC][25] Short IPI (<6 months) OR= 2.8 [Dedecker 2006- referent 18-23 months][44] Short IPI (3-5 months) aOR= 2.2, 95% CI 2.0-2.4. Long IPI (> 60 months) aOR=1.0 , 95% CI 1.0-1.1[Conde-Agudelo 2005 Obs- referent 18-23 months][6] Short IPI (< 6 months) aOR= 1.4, 95% CI 1.3-1.5. Long IPI (60-120 months) aOR= 1.1, 95% CI 1.0-1.2 [Zhu 1999 Obs- referent 18-23 months][27] Results were similar when further studies in 2001 and 2003 were stratified by race and birth order Short IPI (< 6 months) aOR= 1.6 (33-36 weeks) to 2.2 (24-32 weeks) [Smith 2003 Coh- referent 18-23 months][26] Short IPI (lowest quartile 2.8-8.9 months) aOR= 8.2, 95%CI 3.5-19.2 [Al-Jasmi 2002 CC- referent 3rd quartile 16.0-22.9 months][45] Short IPI (< 6 months) aOR= 1.20, 95% CI 1.15-1.26. Long IPI (>59 months) aOR= 1.12, 95% CI 1.08-1.15 [Fuentes-Afflick 2000 Obs- referent 18-59 months][23] Short IPI (<3 months) aOR= 1.2, 95% CI 1.1-1.3 [Shults 1999 Obs- referent 13-24 months][19] Short IPI (< 6 months) aOR= 1.67, 95% CI 0.42-2.91 [Ekwo 1998 Obs][21] Short intervals (< = 3 months) 22.6% versus 24 month IPI rate of preterm= 13.0% [Klerman 1998 Obs- referent > 6.5 months][18] Short IPI (< 12 months) aOR= 1.2, 95% CI 0.5-3.1 [Arafa 2004	Granovsky 2009 Coh- referent 12-23 months][24] <u>Major Congenital Malformation:</u> Short IPI (< 6 months) 726/7966 OR= 1.14, 95% CI 1.04-1.24 p<0.05. Long IPI (> = 60 months) 832/7966 OR= 1.05, 95% CI 0.96-1.14 [Grisaru-Granovsky 2009 Coh- referent 12-23 months][24] <u>NTDs:</u> Short IPI (< 6 months) aOR= 1.2, 95% CI 0.67-2.20 [Todoroff 2000 CC- referent 12-24 months][50] <u>Cleft palate:</u> Prevalence increased from 0.27/1000 live births to 0.85/1000 with IPI from <12 to > = 48 months for isolated cleft palate, p for trend 0.0003 (aOR= 2.84 with long IPI, p= 0.002) [Villamor 2008 Coh- referent < 12 months][51] Long IPI (>48 months) OR= 0.53 [Martelli 2010 CC- referent <24 months][52] <u>Other:</u> Ideal IPI was 18-23 months; there was a significant increase in fetal death, low birth weight, preterm birth and SGA at < 6 months and >	

Table 5.1.1: Summary impact estimates of birth spacing			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
	Obs- referent >60 months][28] Short IPI (< 6 months) OR= 1.30, 95% CI 0.94-1.79 [Ferraz 1988 CC- referent >= 13 months][22] <u>IUGR:</u> Short intervals (< = 3months) 8.5% versus 24 month IPI rate of 5.8% [Klerman 1998 Obs][18] Short IPI (< 6 months) aOR= 1.25, 95% CI 0.91-1.72 [Ferraz 1988 CC- referent >= 13 months][22] Long IPI (>24 months) aOR= 0.92, 95% CI 0.64-1.33 [Klebanoff 1988 Coh- referent < 3 months][46] <u>Labour dystocia:</u> Long IPI (48-60 months) aOR= 1.15, greater association with functional dystocia [Zhu 2006 Obs- referent < 24 months][47] <u>C-section rate:</u> Short IPI (< 6 months) aOR= 0.99, 95% CI 0.78-1.25. Long IPI (>59 months) aOR= 0.69, 95% CI 0.56-0.82 [Cecatti 2008 Obs- referent 18-23 months][14] <u>Stillbirth:</u> Short IPI (0- 3 months) aOR= 1.3, 95% CI 0.8-2.1. Long IPI (> = 72 months) aOR= 1.5, 95% CI 1.1-2.1 [Stephansson 2003 Coh- referent 12-35 months][32] Short IPI (< 6 months) aOR= 0.70 95% CI 0.38-1.29. Long IPI (> 24 months) aOR= 1.07, 95% CI 0.54-2.15 [Love 2010 Coh- referent 6-12 months][31] Short IPI (<6 months) aOR= 1.61, 95% CI 1.20–2.18. Long IPI (51-74 months) aOR= 1.03, 95% CI 0.83–1.27 [DaVanzo 2007 Obs-	60 months. For mothers aged >35, however the ideal IPI was 12-17 months [Nabukera 2008 Coh][9] As compared to IPI of <18months an IPI of 18-23 months was associated with a decreased risk of Perinatal mortality: AOR= 0.45 95%CI 0.20-0.98 Post neonatal mortality decreased as IPI increased compared to IPI<18 months 36-47 months: AOR= 0.27 95%CI 0.09-0.82 [Huttly 1992][53] Short and long IPI increases the risk of IUGR, fetal loss and low birth weight [Kallan 1992 Obs][54] Long IPI (>6 years) does not adversely impact maternal or perinatal outcomes versus average spacing of 2-5 years [Orji 2004 CC][55] The risk of low birth weight or preterm birth among women with early or closely spaced pregnancies in the United States is at least 50% greater than that of adult women with a inter-pregnancy interval of 18–23 mo. Infants conceived at less than 6 months compared to 18 to 23 months after a live birth	

Table 5.1.1: Summary impact estimates of birth spacing			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
	referent 27-50 months][15] Short IPI (< 6 months) aOR= 1.74, 95% CI 1.18-2.55. Long IPI (>59 months) aOR= 0.75, 95% CI 0.22-2.57 [Cecatti 2008 Obs- referent 18-23 months][14] Short IPI (< 6 months) aOR= 1.2- 2.3 depending on cause [Smith 2003 Coh- referent 18-23 months][26] <u>Maternal hospital stay:</u> Short IPI (< 6 months) aOR= 0.78, 95% CI 0.22-2.77. Long IPI (>59 months) aOR= 1.16, 95% CI 0.47-2.90 [Cecatti 2008 Obs- referent 18-23 months][14] <u>Postpartum depression:</u> Women with a higher score on the Beck Depression Inventory were more likely to have short IPI (<24 months) 25% versus controls 17% [Gürel 2000 Obs][48]	preterm birth : OR 1.4 (95% CI 1.3 to 1.5 SGA: OR 1.3 95% CI, 1.2 to 1.4. (Zhu P 1999)[27]	

Figure 5.1.31: Short IPI and risk for miscarriage



Citations to the included studies:
DaVanzo 2007[15], Love 2010[31]

A WHO technical consultation[59] was held in 2005 to decide, based on the research evidence, what constitutes the ideal inter-pregnancy interval. Noting the effects of short intervals (<12 months) and long intervals (>60 months) on maternal and perinatal outcomes, including mortality, the experts recommend a space of at least 18-24 months after a live birth. They also recommend that women wait at least 6 months after an abortion to become pregnant again, however, this recommendation is based on a single study and thus further research is necessary to support this view.

Conclusion

In spite of increased contraceptive coverage, many women continue to become pregnant when they do not intend to. Women may not use contraception or may not use it effectively; rates of teenage pregnancy continue to be high across the world; simultaneously many women are choosing to delay initiation of childbearing; women also continue to suffer the consequences of coerced sex and intimate partner violence- these are just a few of the complex factors that lead to unintended pregnancy, and deleterious inter-pregnancy intervals. Many women who have unintended pregnancies undergo unsafe abortions. Women who have unplanned pregnancies are also less likely to seek prenatal care, are more likely to engage in risky behaviour such as alcohol use and smoking, and are more likely to become depressed. When women carry these pregnancies to term, they are less likely to breastfeed or continue breastfeeding, and their children are more likely to be neglected and undernourished.[60, 61]

It seems logical that a substantial proportion of these adverse outcomes could be averted by the use of contraception to prevent unwanted pregnancies.[62-65] The interaction between contraceptive use and pregnancy intention is complex,[66, 67] yet recent reviews have found a trend (results could not be pooled since majority of studies were retrospective examination of survey data and heterogeneous) toward increasing intervals and fewer unplanned pregnancies with the use of family planning.[68-70] Other reviews also examine the effect of advance provision of emergency contraception and pericoital contracapetion, however these show mixed results.[71, 72] Another simple way to prevent closely-spaced pregnancies is exclusive breastfeeding,[73] which continues to be underused despite overwhelming evidence of its positive effect on maternal and newborn health. Meanwhile, women should be educated regarding contraceptive use in the postpartum period.[74] Preconception care must therefore include family planning, so that pregnancies are intended, and women are able to receive counselling before the next time they want to conceive.[75]

Key messages

- One third of all pregnancies are unintended and a fifth end in abortion- there is a

sizable unmet need for family planning that could prevent the poor maternal and child outcomes resulting from such pregnancies and unsafe abortions.

- Adverse outcomes associated with short intervals include uterine rupture during trial of labor (OR 3.04), stillbirths (OR 1.42), and maternal death (OR 1.66).
- There is an increased risk of neonatal deaths following long intervals (OR 1.15).
- This review also found a significantly increased risk with short and long intervals of preterm birth (OR 1.45 and 1.21 respectively), low birth weight (OR 1.65 and 1.37 respectively), and a slightly increased risk of small-for-gestational age (OR 1.17 and 1.18 respectively).
- After a live birth, women should space their pregnancies with at least 18-24 months before the next conception. Women should not wait longer than 5 years between pregnancies as this may increase the risk of preeclampsia, and maternal and neonatal mortality.
- Preconception care should encourage all women to have a reproductive life plan, and to use exclusive breastfeeding and modern contraception so that pregnancies are intended, and women are physically and emotionally healthy before they conceive.

4.2. Post-abortion care

Background

Many women resort to unsafe or clandestine abortions as a means of family planning. Lack of access to services and the illegality or social unacceptability of abortion in many countries means that women often resort to crude and dangerous means to end a pregnancy.[76] Post-abortion care includes emergency treatment of abortion complications, family planning counseling and services, and provision of (or referral to) other reproductive health services[77]regardless of whether the abortion was spontaneous or induced.

Scope of Intervention

Complications of unsafe abortion include incomplete abortion, hemorrhage, sepsis, uterine perforation, intra-abdominal injury, psychological trauma, infertility, reproductive tract infections, and maternal death. Safe abortion care has the potential to save the lives of 70,000 women and prevent 5 million disabilities annually.[78] Unsafe abortion has been clearly linked to maternal morbidity (especially poor mental health, but not preeclampsia[79] and mortality after the event, however, risk-aversion studies also show increased odds of preterm birth, low birth weight,[80-83] post-term delivery[84] and early vaginal bleeding[85] in the subsequent pregnancy. Post-abortion care, therefore, is necessary for healthy future pregnancies, and is a form of interconception care. Even with access to contraceptives and low fertility rates, unintended pregnancies will continue to occur, and thus the need for post-abortion care will remain.[76]

The content of preconception care for women undergoing an abortion (Tabutt-Henry 2003)[86]

- Provide emergency post-abortion care, for example if the woman has severe hemorrhage or signs of infection.
- Healthcare providers should first explore the woman's needs and feelings regarding the abortion. Providers may need to provide extra sensitive counseling for adolescents (Dragoman 2008).[87]
- Next, counsel about any clinical or laboratory findings. Explain the procedure with the aims of making the woman as comfortable as possible and having the least possible complications. The use of manual vacuum

aspiration or medications, along with prophylactic antibiotics have proven safe and effective.

- After the woman has recovered from the procedure, discuss any concerns she might have.
- Give verbal and written instructions of how she should care for herself and possible risks and warning signs for which she should seek immediate medical attention.
- Explain that in order to prevent the chances of an unintended pregnancy, and repeat abortion, she should use effective family planning methods. Detailed counseling (explicitly telling her that she could become pregnancy before her next menstrual period), and if possible free provision of contraception, is necessary to increase contraceptive use among women who have had an abortion. Whenever possible, women should be counseled with their partners about contraception.
- Discuss reproductive tract infections including sexually transmitted infections, and provide screening and management as needed (including for partner).
- Schedule a convenient follow-up for the woman and take steps to ensure that a follow-up visit occurs, since this allows reinforcement of contraceptive counseling and provision of further interconception care.

Impact estimates

The included studies were all **interventional.** Studies focused on whether there was an increase in the use of manual vacuum aspiration, if women received post-abortion contraceptive counseling, receipt of a contraceptive method before leaving the health facility, and use of contraception at follow-up. Very few studies reported a decrease in prevalence of abortions, or decrease in repeat abortions. Most studies were pre-post design. The methods of improving post-abortion care included introducing manual vacuum aspiration, training healthcare providers, providing equipment and contraceptive methods, counseling partners, service reorganization and collaboration, improved follow up, emergency treatment of complications, linkage with other reproductive health services, and rarely, increasing community awareness.

One study[88] demonstrated the improvements in maternal outcomes with the use of MVA, with a significant reduction in blood loss and hospital stay. Another study[89] demonstrated that training and support of providers resulted in significantly increased availability of emergency uterine evacuation from 57 to 79% and MVA from 21 to 83%.

The greatest improvement in the number of women receiving/accepting a contraceptive method post-abortion was seen with 2 interventions: **a)** provision of emergency post-abortion treatment, contraceptive counseling, and community-service provider partnerships[90] from 2 to 86.6% in three years **b)** training of providers, counseling, free contraception and follow-up 96% at intervention site versus 5% at control site. The second intervention also showed that women receiving post-abortion care were 3.38 times less likely to have an unplanned pregnancy, and a decrease of 8% in the women undergoing repeat abortion postintervention versus controls.

The least improvement (14%) was seen in one study[91] with free contraceptive provision. This should be interpreted with caution because repeat abortions among women receiving the intervention decreased to half the rate in the general population.

An intervention in Russia to strengthen post-abortion family planning showed that women using modern contraception increased from 50 to 58% and abortions decreased from 49 to 43/1000 women. Another intervention showed no effect, however, and attributed this to the number of women undergoing repeat abortions.[92]

Counseling women post-abortion also creates opportunities to involve their partners[93] - husbands who are counseled are 1.6 times more likely to support their wives and

women who receive support from their partners are nearly 6 times more likely to use family planning methods.[94]

Table 6.1.1: Interventions for post-abortion care

Intervention	Outcome
Training of staff in manual vacuum aspiration (MVA) and post-abortion family planning; provision of equipment; and service reorganization [Solo J 1999][93]	Received family planning counseling: Increased from 7 to 68% Decided to use family planning after counseling: Increased from 22 to 69% Received a method of contraception: 3 to 70% Staff enthusiasm resulted in higher rates (95% receiving a method) at one intervention site. The most acceptable, feasible and effective intervention model was counseling provided in the ward by the same staff who had managed the patient's procedure (versus staff from the family planning clinic at the same hospital coming to the ward, or patients going to the clinic), however the most patients received information on contraceptive side effects if they went to the clinic (71%). Further counseling in the ward allowed staff to access women's partners- 72% of women said they would like to be counseled with their partner, and 15% of the men interviewed and 20% of women said they would like to receive separate counseling.
Counseling of husbands by primary physician before discharge [Abdel-Tawab 1999][94]	aOR that husbands who were counseled would -provide instrumental support to their wives 1.5 -provide emotional support to their wives 1.3 -provide family planning support 1.6 aOR that wives would have -good physical recovery 1.3 -good emotional recovery 1.0 aOR for intention or use of family planning -if supported by husband 5.9 -if husband counseled 0.6
Training, improvement of facilities and women given post-abortion follow-up at 1 and 6 months after discharge [Diaz 1999][94]	Women receiving post-abortion contraceptive counseling increased from between 2.8-12.2% to 73.2-100%. Women not accepting contraception dropped from 85.7-89.7% to 11.9-53.1%. Women attending follow-up increased from 2.0-3.6% to 14-48.8%
Training and changing staff attitudes, decreasing wait time for patients, printed material for staff and patients, replacing D&C with MVA and expanding contraceptive options available [Langer, Brambila 1999][94]	Patients receiving counseling increased from 3-19.1% to 15-54.4%, and those receiving family planning counseling increased from 42.4 to 85.5%, $p<0.05$. Women accepting a contraceptive method increased from 29.5 to 59.7%, $p<0.05$ and women receiving contraception from 29.5 to 56%, $p<0.05$ Cost per patient decreased from US$ 264.47 to $180.22 (-32%)
Training for healthcare providers, printed material for participating facilities, and national media campaign[David 2007][92]	Women counseled about post-abortion contraception before discharge increased from 41.1 to 91.5%, $p<0.001$ and those receiving printed information on pregnancy prevention increased from 5.9 to 60.9%, $p<0.001$. Women who knew that fertility could return as early as 2 weeks increased from 61.6 to 76.5%. However the total mean number of abortions stayed the same 2.3 to 2.2 per woman largely attributed to similar number of women having a repeat abortion 76.2 to 74.6%.
Post-abortion visit at 1-2 weeks with counseling about contraception and free contraceptive method of woman's choice [Ferreira 2010][95]	Although knowledge of contraceptives was very high, 68.6% of women were using no protection at the time of conception. 150/186 women attended the counseling session, and of these 97.4% accepted at least one contraceptive method (mainly injectable and oral contraceptives)
18-month scaling up of post-abortion care at 22/33 district maternity hospitals- training and contraceptive counseling, development of post-abortion care	Family planning counseling increased from 31 to 78%, $p<0.0001$ and women using an effective method increased from 20 to 49%. Women with severe post-abortion complications decreased from 5.95 to 5.16%, $p=0.445$

Table 6.1.1: Interventions for post-abortion care	
Intervention	**Outcome**
team and provision of MVA cart, additionally printed material for staff and in-service facilitation for 1 week. Development of quantitative indicators and collaboration between facilities and Ministry of Public Health [Kestler 2006][96]	
10 weeks free provision of long-acting reversible contraception, printed material for display and for staff. Follow-up phone call for women using the LNG-IUS at 6 weeks and 6 months [Rose 2010][97]	Use of long-acting reversible contraception (LARC) increased from 44.5 to 60.8%, p< 0.05. At 6 weeks, 89.1% were still using LARC and at 6 months, 77.6%.
Establishment of a MVA unit at national maternity hospital [Thapa 2004][88]	MVA versus D&C in operating room: Blood loss: 17.54 versus 26.30 mL (P<0.001) Duration of hospital stay: 19.75 versus 33.42 hrs (p<0.001) Contraception counseling: 95.6 versus 6.4% (p<0.001) Contraception dispensed: 50.7 versus 0% At 6 week follow-up, continuous use of contraception since discharge: 75.5 versus 0% Desire for next pregnancy within 15 months: 79.8 versus 64.1% (p<0.001) however women in the MVA group had fewer children on average before the index abortion.
Emergency treatment for post-abortion complications; family planning counseling and service provision; STI evaluation and treatment; HIV counseling and/or referral for testing; and community empowerment through community awareness and mobilization[Curtis 2007][77]	Bolivia: use of contraception at last sexual intercourse from 46% to 54% Kenya: increase in knowledge regarding vaginal bleeding as a danger sign of pregnancy from 66% to 90.5%; the causes of maternal death (vaginal bleeding from 41% to 64%; violence against women 24% in posttest); and delays in seeking care (96% posttest). Condoms were cited by 77% of respondents as having dual protection against HIV and pregnancy. Peru: 100% of post-abortion women being counseled on family planning and 30% of clients accepting a method before leaving the facility Egypt: trained male religious leaders about problems related to unintended pregnancy and abortion, and held 246 community awareness sessions *After decentralizing post-abortion care*, the number of women accepting a contraceptive method post-abortion was 91% in Nepal Senegal: women receiving post-abortion contraceptive counseling increased from 36 to 78% and women accepting contraception was 51% Tanzania: women receiving contraception increased from 89 to 97% at intervention sites (versus 14-41% at control sites)
Post-abortion family planning-training for staff, ward-based counseling and free provision of contraception, reminders at 3-month intervals, those who returned for follow-up given Z$50 for transport/lunch, attempts to visit those who did not return at their homes [Johnson 2002][98]	Women choosing highly-effective contraception were 96% at the intervention sites compared to 5% at control sites (p<0.0001) Over 1-year follow-up, 42 unplanned pregnancies at intervention site versus 96 at control site (aOR 3.38, 95% CI 2.16-5.29) 2.5% of 276 women at intervention site versus 5.3% of 281 women at control site underwent repeat abortion.
Emergency post-abortion treatment, contraceptive counseling, community-service provider partnerships [Billings 2005][90]	Women receiving a contraceptive method at discharge increased Peru: from 2 to 58.8%, p<0.05 and increased to 86.6% three years later. Honduras: 13 to 54%, p<0.05 Mexico: 36.5% who received minimal counseling versus 63.3% who received in-depth counseling, p<0.05 Average length of patient's stay decreased 6.4-17.4 hours, and average cost per patient decreased 31.9-72%

Table 6.1.1: Interventions for post-abortion care	
Intervention	**Outcome**
Contraceptive and HIV counseling, and ward-based contraceptive service [Rasch 2008][99]	89% accepted counseling and received contraceptive method of their choice. At 1-year follow-up, women using oral or injectable contraception increased from 14-18% to 77-84% (p<0.000). There was no change in the number of women using condoms during the last year, however among single women there was an increase from 10 to 23% (p<0.05) of condom use in more than half their total sexual encounters in the past month.
Training of healthcare providers, supplies and technical support [Fetters 2008][89]	Increase in availability of emergency uterine evacuation 57 to 79%, p=0.005 and in availability of MVA 21 to 83%, p<0.001. Provision of post-abortion contraceptives increased from 50 to 57%, p<0.001 (dropped at control site from 58 to 17%)
In-service training of staff especially in post-abortion contraceptive counseling, printed material for staff, monitoring [Kestler 2009][100]	Women receiving post-abortion counseling increased from 31 to 96% after 3.5 years (p<0.0001) and women receiving an effective contraceptive method increased from 20 to 64% (p<0.0001)
1 day training course for nurses in post-abortion contraception counseling [Rasch 2005][101]	93% of women with *unwanted pregnancies* in urban centers and 71% in rural received contraception.
Training physicians in use of vacuum aspiration and improved counseling for complications and contraception, referral for provision of contraception, nurse training and development of new protocol for care [Huntington 1995][102]	Women receiving counseling about what to if complications arose post-abortion increased from 1% to 49% and women receiving contraceptive counseling increased from 10 to 49%. Nurses providing contraceptive counseling increased from 36 to 100%. Women accepting use of contraception increased 30% - 93% of women were referred to family planning center to obtain contraception and 4% were told to follow-up.
Intervention groups received refresher course for providers in either D&C or MVA with post-abortion counseling, versus control- D&C and standard care [Billings 2003][103]	Women in the D&C+ post-abortion counseling received counseling on post-abortion complications, care at home and contraception method with counseling, than women in either of the other groups (p<0.01) Women in both intervention groups with counseling were given information about the side-effects of contraception. 80.2% of women with D&C+ counseling versus 43.4% with MVA+ counseling received their preferred contraception
[Curtis 2010][104]	Turkey: provided contraception after abortion- women receiving a method increased from 65 to 90% at public facilities over 8 years, and from 37 to 72% in private facilities over 3 years. Russia: strengthened post-abortion family planning- women using modern contraception increased from 50 to 58% and abortions decreased from 49 to 43/1000 women Cambodia: Family planning counseling and provision at same site- contraceptive uptake increased from 51 to 90% and from 7 to 30% at another site Cost estimated at $2.90 versus $35-180 for another unplanned pregnancy and repeat abortion. *Community mobilization*: Bolivia- women's awareness of contraception increased from 83 to 92%. In Kenya- emergency transport, funds, training and equipment increased initial contraceptive visits >50% and follow-up by 60%. In Senegal- increase in contraceptive practice from 27 to 62% and a10% reduction in the perception that family planning is only a concern for women
Training and printed material for staff and patients on post-abortion contraception counseling, training of management of post-abortion complications and linking of post-abortion care with other	Women having repeat abortion 10% at study sites versus 20% in general population 67% continued using modern contraception after 1year, versus 53% of women who did not receive free contraception. Women who received free contraception more often wanted a modern method and wanted to begin using contraception immediately.

Table 6.1.1: Interventions for post-abortion care	
Intervention	**Outcome**
reproductive healthcare Training, printed material and free provision of contraception [Savalieva 2003][91, 105]	
Training, equipment, printed material and post-abortion counseling and provision of contraception, and training of providers at nearby centers to increase referrals to study site, quarterly meetings to increase collaboration [Medina 2001][105]	Women receiving contraception information increased from 17 to 85%; offering of methods increased in the same proportion; acceptance of methods increased from 13 to 54%. *Similar improvements were found in postpartum contraception counseling and delivery*
Refresher training, introduction of MVA, post-abortion contraception counseling and provision of contraception, switch from necessary hospitalization to outpatient ward-based care [Benson 2002][106]	*Sustainability (from end of study in 1998 to four years later):* Women receiving contraception counseling increased from 77.5 to 89.1% ($p<0.05$) Women receiving contraceptive method increased from 58.8 to 86.6% ($p<0.05$) Providers less often told women about side-effects of injectable and oral contraception. However, counseling regarding post-abortion complications and resumption of fertility/sexual intercourse increased ($p<0.05$) Patient's expenses decreased from $37.40 to $ 32.75 and costs to the hospital also decreased, while hospital stay was approximately the same.

Conclusion

Approximately twenty two (21.6) million women are estimated to undergo unsafe abortions, and 47,000 to lose their lives as a result, a tragedy that could be avoided through access to family planning services, and safe abortion care.[107] Pre-post study designs with various interventions show that vacuum aspiration reduces the risk of maternal complications, as does training and technical support for healthcare providers along with improved partnerships and service organization.[108] They also demonstrate that post-abortion care successfully increases contraceptive uptake among approximately 90% of women who receive it, however more evidence is needed to state that this translates to fewer unintended pregnancies and fewer abortions. Post-abortion counselling also improves partner participation in and support for family planning.

Key messages

- Many women resort to risky abortion practices because they lack access to family planning services, or because of legal issues with induced abortion.
- Safe abortion care can prevent half a million maternal deaths, disability, reduce health costs that accrue from the treatment of complications of unsafe abortion, reduce repeat abortions, and possibly lower the prevalence of preterm birth and low birth weight babies.
- This review found evidence to support the increased use of contraception in women receiving post-abortion counselling (upto 90%), however better study designs and longer follow-up is necessary to evaluate if this translates to fewer unintended pregnancies, reduces repeat abortions or decreases maternal morbidity and mortality that result from unsafe abortion.

4.3 Genetic counselling

Background

Genetic counselling involves diagnosis, information provision/explanations, and discussion of possible options. The most common reason for genetic counselling among the prenatal patients was advanced maternal age (42.0%) followed by an abnormal triple test in the second trimester; the most common indications for postnatal patients were recurrent miscarriages (28.2%) and infertility (19.7%).[109]

The acceptance rate for prenatal screening for Fragile X was 85% (1477/1738).[110]One of the hurdles to effective utilization of genetic screening and counseling services is the apprehension among the people. Individuals identified by population screening as carriers of a gene for a serious recessive disease may have undesirable emotional responses.[111] In a Tay Sachs screening program nearly half the carriers and their spouses expressed some degree of shock, anger, anxiety, or sense of imperfection.[112]

There may be debate about what method may work best and what time may be appropriate for such an intervention to have the maximum effects. Rowley et al.[113] reported that a patient-structured counselling method, designed to minimize negative psychological effects via discussion of feelings, was equivalent to conventional and programmed methods in terms of learning or attitude change.

Scope of intervention

We set to look for studies talking about the importance of genetic counseling given to couples planning a pregnancy. We also looked for literature addressing the issue of genetic screening for multiple disorders in the preconception period. In doing so we wanted to analyze the effect such an intervention, if provided before pregnancy, would have on maternal as well as fetal outcomes. The content of preconception care for genetic counseling is summarized in table **4.1.1**.

4.1.1. Content of preconception care: genetic counseling

- Screen couples for genetic disorders, congenital malformations, developmental delay by taking a thorough family medical history
- Those with a family history of a genetic disease should be encouraged to undergo screening along with their partner to quantify the risk of the fetus being affected.
- Those at a high risk of ethnicity-based genetic diseases should be counseled about the importance of genetic screening tests.
- All couples should be informed about the availability of carrier screening for cystic fibrosis
- Those with identified genetic disease, or with a partner with an identified genetic disease, should be counseled about the risks to the fetus and informed about available options
- All women should be advised to start taking a multivitamin with at least 400 ug of folate daily, at least 1 month before conception.

Impact estimate

Despite an extensive search we did not find studies relevant to the outcome of interest. We only came across literature related to the attitudes and perception of couples regarding the provision of these services and the general attitude of physicians towards genetic counseling and screening in the preconception period. Our search yielded data only pertaining to a handful of genetic disorders: cystic fibrosis, fragile X, Tay Sachs and thalassemia.

Cystic fibrosis studies generally addressed the attitudes and perceptions of couples regarding the possibility of preconception screening. In a study where couples were asked if they would participate in a preconception screening for CF, majority replied in the affirmative.[114] However another study[115] reported a 74% acceptance rate of free preconception screening for common genetic disorders which only translated into a 2% submission rate of their blood samples. It was reported that a majority perceived no impact of carrier testing on their relationship status with their partner; this could generally be taken as a healthy sign for the woman's own health. Another study reported that carriers who had undergone had a poorer perception of their health 3 yrs post-testing, as compared to non-carriers.[116,117] Attitudes of health professionals regarding preconception CF carrier screening varied considerably. Greatest support to the notion was given by General Practitioners;[118, 119, 120] however this attitude was not translated into practice.[121] Among the mode of delivery of information for population based screening, studies showed that the uptake rates were higher if the written information was given[115], if screening was offered in person by a health professional[122, 123] and if immediate testing was offered.[123, 124]

A recent review for screening for Fragile X, found no trials to show whether offering the test to everyone is worthwhile. However studies have identified a positive attitude towards preconception screening amongst women planning a pregnancy as well as those in the general community[125] and amongst physicians.[126]

Studies for premarital screening for those with hemoglobinopathies showed varying results with most reporting couples still proceeding with their marriage plans despite the counseling;[127-130] some still showed a positive effect of such programs with couples paying heed to the advice.[131, 132] In the event of an 'inter-carriers' union, many of those who had received genetic counseling, whether in school[133-135] or elsewhere,[136] sought prenatal diagnosis.

With regards to an actual effect on the disease prevalence post screening interventions, data is only available from national screening programs for thalessemia. While the genetic screening program for Thailand may not have worked too well, that of Iran deserves to be applauded. This integrated premarital screening program led to a 70% reduction in thalassemia birth rate. At risk couples were henceforth referred for counseling and were subsequently followed. The program in Thailand suffered at the hands of ignorant administrators, unorganized team work, lack of education and a shortage of resources. Such national thalassaemia prevention programs and obligatory premarital screening programs have drastically reduced thalassaemia rates in these areas.[131, 137-139]

Conclusion

Genetic diseases comprise an important set of diseases affecting children. We found limited evidence[137] identifying the effectiveness of any genetic screening and counseling, provided in the preconception period, in dealing with outcomes in affected pregnancies. We found that couples are generallyreceptive to such services. This fact, and the example provided by Iran's screening programme for thalesemmia,needs to be utilized by health policy makers in devising comprehensive genetic counseling to all couples planning a pregnancy and genetic screening services to women, keeping in mind the regional prevalence of genetic disorders.

Table 4.1.2: Summary of impact estimates for genetic counseling					
intervention	**Maternal /Paternal**	**Pregnancy**	**Newborn**	**Infant**	**Others**
Genetic counseling					**<u>Physicians attitude:</u>** <u>Web survey (clinical vignette + picture of patient)</u> Factors influencing respondents' decisions to offer preconception genetic screening/ testing: Age- 259/294 (88.1%) Race- overall 191/294 (64.97%); saw black patient 131/172 (76%); saw white patient 60/122 (49.2%) (p<0.0001). Specific preconception screening/testing offers from physicians offering screening/testing by patient seen: Cystic fibrosis- Black 26.16 (45) vs White 48.78 (60) (p<0.0001) Sickle cell disease- Black 78.49 (135) vs White 7.32 (9) (p <0.0001). Differences were not significant for thalassaemias. [Bonham 2009][140]

Table 4.1.2: Summary of impact estimates for genetic counseling					
intervention	**Maternal /Paternal**	**Pregnancy**	**Newborn**	**Infant**	**Others**
Genetic counseling CF screening	**<u>Attitude:</u>** Most couples (94%) chose to be fully informed about the test results, including a +/– result. [henneman 2002][116] Out of a total of 450 pregnant women who were asked which screening method they preferred, if screening were available, 62% preferred stepwise screening with full disclosure of the test results, 26% preferred couple screening with non-disclosure, and 12% had no preference. [Miedzybrodzka 1995][141] 16% of 280 identified carriers remained worried after 3 years of follow-up (Axworthy *et al*., 1996)[117]. Seven out of 17 carriers felt less healthy due to their test results, despite being informed, both verbally and by letter, that their carrier status would have no effect on their health status. [Henneman 2002a][142] After 3 years of follow-up, CF carriers were reported to have a poorer perception of their current health than no carriers (Axworthy				**<u>Physicians attitude:</u>** Pediatrics: Would refer a pregnant CF carrier couple for genetic counseling OR 2.0 (0.7–5.6 [Baars 2004][119] 16 % GPs favored routinely offering CF carrier screening to all couples who were planning to have children, [Baars 2004][119] Those GPs and GYNs, who considered the test sensitivity less important, were more likely to be in favor of routinely offering the CF carrier test. [Baars 2004][119] none of the family medicine physicians, and only 19% of the obstetricians and 13% of the pediatricians, stated that they had ever ordered a CF carrier test or referred a patient for that reason (Mountcastle-Shah and

Table 4.1.2: Summary of impact estimates for genetic counseling					
intervention	**Maternal /Paternal**	**Pregnancy**	**Newborn**	**Infant**	**Others**
	et al., 1996)[117]. Overall, satisfaction was high: 88% would recommend testing to others, and 95% would decide to have the test if they had to decide again. [Henneman 2002a][142] majority of participants (98%) perceived no impact of carrier testing on the relationship with their partner [Henneman 2002a][142] Seventy-three percent of the respondents (fully) agreed that a CF carrier test should routinely be offered to couples planning a pregnancy, 11% were unsure, and 16% (fully) disagreed. [Poppelaars 2004a][118] If the currently available CF carrier test was routinely offered to couples planning a pregnancy, would you participate? the percentage of couples who answered Ô(probably) yes was 56%, 27% were unsure, and 17% answered that they would (probably) not participate [Poppelaars 2004a][118] <u>Population screening:</u> More than 90% of people thought				Holtzman, 2000)[121] More support among the physicians if couples who are planning to have children request a test (Faden *et al*., 1994[120]; Poppelaars *et al*., 2004a)[118]. primary care physicians, psychiatrists, medical geneticists, and genetic counselors in the United States, 92% of whom thought a couple should be tested if they so wished and 43.9% favored routinely offering preconceptional CF carrier screening (Faden et al., 1994)[120] Fifty-five percent of the GPs and 73% of the CHS workers favored routinely offering a CF carrier test to couples planning a pregnancy, whereas 18% of the GPs and 13% of the CHS workers were unsure [Poppelaars 2004][114]

Table 4.1.2: Summary of impact estimates for genetic counseling					
intervention	**Maternal /Paternal**	**Pregnancy**	**Newborn**	**Infant**	**Others**
	that genetic testing should at least be available. Views of their partners and physicians were important in their decision making but more than two-thirds indicated that such factors as insurability, being "at risk," what they would need to learn, abortion, and religious beliefs were important in their decision making. One-third (39%) feared that carriers would lose their health insurance. [Clayton 1996][115] Of the 216 respondents, 156 (74%) opined that the best time to have this test was prior to pregnancy, whereas 26 (12%) indicated that the test was best done when choosing a partner; only 2 (1%) thought that it was best to have CF carrier screening during pregnancy. [Clayton 1996][115] Two-thirds (411/616) of the respondents said that they would accept an offer of free carrier screening for a common genetic disorder. 192 of these 411 participants were offered free CF carrier screening; only 62/192 (32%) expressed interest; and only 4/192 (2%) of those offered CF carrier screening actually				

Table 4.1.2: Summary of impact estimates for genetic counseling					
intervention	**Maternal /Paternal**	**Pregnancy**	**Newborn**	**Infant**	**Others**
	submitted blood samples. [Clayton 1996][115] **<u>Effect of mode of distribution of information on uptake rate of the test:</u>** <u>Population screening:</u> Those who were randomized to receive written information were far more likely to submit blood samples than were those who viewed the videotape (50/71 [70%] of those who received written information, vs. 26/58 [45%] of those who viewed videotape; P < .01). [Clayton 1996][115] Acceptance rates high when screening was offered in person. Acceptance rates were 66% in general practices and 87% in family planning clinics; invitation by letter signed by the physician and enclosing a leaflet explaining CF resulted in an acceptance rate of only 10%. [Watson 1991][122] Having a health professional explain the test personally to patients attending the practice and offering immediate testing had the highest acceptance rate (70%). Requiring a return appointment,				

Table 4.1.2: Summary of impact estimates for genetic counseling					
intervention	**Maternal /Paternal**	**Pregnancy**	**Newborn**	**Infant**	**Others**
	having the receptionist hand patients a leaflet explaining the test, or inviting by personal letter with or without a leaflet resulted in an acceptance rate of 25% or below. [Bekker 1993][123] Uptake was considerably higher when (approach 2) testing could be obtained without making an additional visit (23.5%) than when (approach 1) attendance at an educational session was required as a prerequisite for having the test (3.7%); six times higher in approach 2 (23.5%) than in approach 1. [Tambor 1994][124] Factors (%) Associated with Having the CF Carrier Test, in Respondents Planning to Have Children: Approach 1: tested vs not tested- low fear of stigma: 79.1% of 86 vs 58.6% of 184; high fear of stigma: 20.9% vs 41.4% (p<0.01); high tolerance for test ambiguity: 60.5% vs 42.4% (p<0.01); High tolerance for test uncertainty: 69% vs 36.3% (p<0.01). Approach 2: tested vs not tested- low fear of stigma: 68.8% of 82 vs 45% 0f 40;				

Table 4.1.2: Summary of impact estimates for genetic counseling					
intervention	**Maternal /Paternal**	**Pregnancy**	**Newborn**	**Infant**	**Others**
	high fear of stigma: 31.3% vs 55% ($p<0.05$); high tolerance for test ambiguity: 54.9% vs 42.5%; high tolerance for test uncertainty: 55% vs 25% ($p<0.01$). [Tambor 1994][124]				
Fragile X screening	**<u>Prenatal/preconception screening:</u>** Screening for fragile X syndrome in the population without a known family history of the disorder can achieve a high rate of carrier identification and termination of affected pregnancies. Screening for fragile X syndrome in Israel suggests that it should be routinely offered to all pregnant women and when requested, it should be available to those who are planning to become pregnant. [Berkenstadt 2007][143] <u>Detection rates (Cascade testing):</u>				**<u>Attitudes of health professionals:</u>** Although the majority of our respondents (genetic health professionals) support both prenatal and neonatal screening, the single most favored approaches to Fragile X screening were targeted preconception screening of women with a family history of Intellectual Disability (ID) (43%) followed by universal

Table 4.1.2: Summary of impact estimates for genetic counseling					
intervention	**Maternal /Paternal**	**Pregnancy**	**Newborn**	**Infant**	**Others**
	In the start-up phase of the testing programme, 18% of couples who will have a fragile X syndrome child are detected. After this phase the (stabilised) cascade testing programme detects 7% of undetected couples who would have a fragile X syndrome child if only first degree relatives were tested, 12% if first to third degree relatives were tested, and 15% if first to fifth degree relatives were tested. To detect 90% of all premutation and full mutation carriers at least eight consecutive generations need to be tested. The results of our analysis show that cascade testing is not very effective in detecting carriers. [Wildhagen 1999][144] **Attitude**: Population-screening: Tested women had a more positive attitudes toward screening (Q1 [pretest]: $P < 0.001$; Q2[post-test]: $P < 0.001$) compared with untested. 217/253 (not tested) vs 56/65 (tested) said carrier testing for FXS should be available to all women in the general community. 144/253 (not tested) vs 35/65 (tested) had no concerns about genetic testing for the general community. Pretest 107/253 (not tested) vs 48/65 (tested) had a positive attitude to having genetic carrier testing for				preconception screening (29%) [Acharaya 2009][126]

Table 4.1.2: Summary of impact estimates for genetic counseling					
intervention	**Maternal /Paternal**	**Pregnancy**	**Newborn**	**Infant**	**Others**
	themselves; post-test, 47/59 (84%) had a positive attitude to having genetic carrier testing for themselves. [Metcalfe 2008][23] **Anxiety**: Mean anxiety scores of tested compared with untested women were not statistically significant in pretest [37.0 +/- 0.8 vs 35.9 +/- 1.3] (*P*=0.5) or post-test [36.1 _ 1.1 32.7 _ 1.6] (*P*=0.1). Reduction in mean anxiety score over time for tested women (*P* = 0.02). [Metcalfe 2008][125]				
Screening for Hemoglobinopathies	**Attitudes towards screening/counseling (pre or post):** Total of 30 couples (60 individuals) were referred for genetic counseling, 17 couples (56.7%) got married in spite of counseling, which is considered high.[Almutawa 2009]*[127] 51% of couples at-risk in the Mazandaran province, Iran, who received genetic counseling, decided not to marry. [Khorasani 2008][132] Among the 2,375 high-risk couples contacted by telephone, 89.6% married each other, despite the			**Thalassaemia birth rate:** Iran's National Thalassaemia prevention program - Preliminary data from the developing national thalassaemia register suggests that the affected birth rate had fallen to 30% of expectation by the year 2000 [Samavat 2004]#[137] Iran: 1995- Patients per 1000 birth 2.53. 2004- Patients per 1000 birth 0.82. [Karimi 2007]*#[138]	**Physician practices:** During the intervention year intervention practices made 292 more requests (requests in study year= 587; 99% increase) and control practices made 74 fewer requests (requests in study year= 254; 23% decrease; P = 0.001 for difference in median change). The number of requests from intervention practices, adjusted for baseline requests, was 3.2 times higher than control practices (P < 0.0001).

Table 4.1.2: Summary of impact estimates for genetic counseling					
intervention	**Maternal /Paternal**	**Pregnancy**	**Newborn**	**Infant**	**Others**
	known high-risk status. [AlHamdan 2007]*[128] 127 of 129 (98%) of this cohort ignored the PMS results and proceeded with their planned marriage, mainly due to previous family agreement and family pressures (48%), preexisting love story (34%). [Sulaiman 2010]*[129] The concept of genetic counseling was appreciated by most of the participants 107 (83%). 100 (88%) agreed for having the program applied on all the participants deciding to get married. One hundred and seventeen (91%) did not think that there is a major disadvantage in this program. [Sulaiman 2010]*[129] 99% of prospective carrier couples (152/154 of Extended Family Members and all from the OPD and College Group) married even after knowing their high-risk status and opted for prenatal diagnosis. (voluntary program) [Tamhankar 2009]*[130] An increasing percentage of carrier couples did not go ahead with their marriage in the successive years of			Affected birth rates showed a sharp decrease in contrast to an average of 18-20 cases per year before the implementation of the "Thalassaemia Prevention Programme." Between 1991 to 2001, only five thalassemic babies were born, one in every 2-3 years. No thalassemic babies have been born in the last 5 years.[Bozkurt 2007][139] Post-implementation of obligatory screening, there has been a reduction in the birth of children with b-thalassaemia major; 15 births in the year before implementation to 1 in yr 5 post-implementation from b-thalassaemia carrier couples who refused to separate. [Tarazi 2006]*[131] **<u>Detection rates:</u>** Frequency of b-	

Table 4.1.2: Summary of impact estimates for genetic counseling					
intervention	**Maternal /Paternal**	**Pregnancy**	**Newborn**	**Infant**	**Others**
	the programme, which was fitted to zero in the first year and reached 73.7% in the year 2005 (both partners were carriers in 19 couples, 14 decided to separate while five continued). [Tarazi 2006]*[131] Voluntary outreach screening: The mean percentage of volunteers requesting the test, both single and married, from the total population of subjects at child-bearing age was 32%. [Cao 1981][145] Hospital testing: 111 couples at thalassaemia risk identified have had a pregnancy. After counseling, 86 of these elected to have prenatal diagnosis, 502 parents of Cooley anemia patients were counseled and 116 (23.2%) had a pregnancy. After counseling, 91 of these had prenatal diagnosis. [Cao 1981][145] There was a steady decline of prenatal testing refusal from 1977 (28.1%) to 1980 (5.8%). Cascade testing and counseling All carriers reported that they have used the information provided in the testing and counseling process:			thalassaemia trait was 0.68%. If screening is mandatory, it should be performed by simple, rapid and less expensive tests like total blood count or enzyme-linked immunosorbent assay and not high-performance liquid chromatography (HPLC). [Acemoglu 2008][149] **Reduction in thalassaemia after screening coupled with prenatal diagnosis:** number of newborns with thalassaemia major has decreased by about 60% in the Cypriot, and 20% in the Asian, communities in the United Kingdom; by 60% in southern Sardinia and by 90% in Ferrara in Italy; by about 50% in Greece and by 70% in Cyprus [WHO Bulletin 1983][150] Two children with	

Table 4.1.2: Summary of impact estimates for genetic counseling					
intervention	**Maternal /Paternal**	**Pregnancy**	**Newborn**	**Infant**	**Others**
	carriers married to carriers with two or more healthy children have avoided further pregnancy, and most such couples with one or no healthy children have used prenatal diagnosis. Seven of eight new marriages and engagements are known not to be at risk. [Ahmed 2002][136] <u>School-screening:</u> With purpose of school screening, to detect healthy carriers and in due time couples at risk, 67% of the parents responded favorably and consented to carrier screening and prevention, and shared the information with their relatives. [Amato 2009][146] Six carrier couples were identified, four asked for genetic counseling and requested eight prenatal diagnoses, and two couples did not request genetic counseling and have had two affected children. Despite a mean time lapse of 14 years between screening, informing, and pregnancy, the information was well conserved and resulted in testing of the partner (86% of the partners of carriers asked had had a haemoglobin test performed).			thalassemia major have been born since inception of the program. One was the result of a false-negative thalassemia fetal diagnosis; the other was born to a non-screened couple. Incidence of the disease has fallen by 95% in the 13 years of the program, reflecting both a general decline in birthrate and a specific effect of the program. [Mitchell 1996][134] The voluntary program averted the birth of 33 thalassemic children; 28 in Extended Family Members (EFM) group (by screening of 394 individuals), 4 in the OPD group (by screening 1348 anemic patients), and 1 in College students (CG) group (by screening of 939 students). [Tamhankar 2009]*[130]	

Table 4.1.2: Summary of impact estimates for genetic counseling					
intervention	**Maternal /Paternal**	**Pregnancy**	**Newborn**	**Infant**	**Others**
	[Lena-Russo 2002][135] The high-school cohort harbored 16 carrier couples who would have children in the time frame of our analysis. There were nine carrier couples identified by screening who sought prenatal diagnosis, the predicted number in the screened cohort. They had 14 pregnancies, all monitored by prenatal diagnosis. One couple requested to have counseling only and elected to have no children. Fetal diagnosis detected three affected pregnancies; each was terminated, by choice. Ten unaffected offspring were born to the screened carrier couples. [Mitchell 1996][134] 32 couples have sought prenatal diagnosis since the origination of the program, 24 originating from the screening program. [Mitchell 1996][134] Of the 94 prospective couples of Latial extraction, 35 (more than a third) were the same students identified in the schools screening or through one of their close relatives. [Bianco 1984][133] **<u>Uptake rate:</u>**				

Table 4.1.2: Summary of impact estimates for genetic counseling					
intervention	**Maternal /Paternal**	**Pregnancy**	**Newborn**	**Infant**	**Others**
	School-based screening: Of the 2420 students who attended the informational meetings, 1812 (75 percent) obtained parental consent and agreed to undergo screening. [Lau 1997][147] **Reduction in rates:** The National Student Screening Project to determine the prevalence of genetic blood disorders and raise awareness among young Bahrainis: The 1.2% prevalence of Sickle Cell Disease homozygosity was lower than reported in two previous Bahraini studies—the 1994 premarital counselling study (1.6%) and the 1984 newborn screening study (2.1%). The prevalence of Sickle Cell Trait in the present study was 13.8%, approximately the same as in the premarital counseling study but higher than the newborn screening study, which reported 11% carrier prevalence. The prevalence of β-thalassaemia among students was 2.9%, which was almost the same as the 1994 premarital counseling study. Preventive measures such as health education, carrier screening and premarital counseling remain the best ways of dealing with inherited				

Table 4.1.2: Summary of impact estimates for genetic counseling					
intervention	**Maternal /Paternal**	**Pregnancy**	**Newborn**	**Infant**	**Others**
	blood disorders. [Al-Arrayed 2003][148] <u>School-screening:</u> Following universal acceptance of the strategy of school screening by the native population, the incidence of severe hemoglobinopathies approached zero since 1993. [Amato 2009][146] <u>Hospital testing:</u> A survey of all in- and outpatient admission in the hospitals of the counties showed a steady decline of thal-major incidence at birth from 1976 [1:213] to 1978 [1:290]. [Cao 1981][145] **<u>Detection rates:</u>** Population screening - 22.6% were carriers of a large variety of β-thalassemia mutations, 48.0% were suspected α-thalassemia carriers, 13.8% were carriers for HbS. In spite of screening and counseling there was an increase in number of severely affected subjects diagnosed during the same period; such an increase was related to immigrants. [Amato 2009][146] The yield of carriers from Extended Family Members (EFM), OPD and				

Table 4.1.2: Summary of impact estimates for genetic counseling					
intervention	**Maternal /Paternal**	**Pregnancy**	**Newborn**	**Infant**	**Others**
	College students (CG) groups was 78.17% (308/394), 19.51% (263/1348) and 4.04% (38/939), respectively. The numbers of prospective high-risk couples detected were 154, 48 and 2 from EFM, OPD and CG, respectively. [Tamhankar 2009]*[130]				
CF and/or Hemoglobinpathies/ Tay Sachs screening	**Attitudes towards screening/counseling (pre or post):** Ancestry based couple screening: Among all survey participants, 29% of the variance in intention to participate in the current preconceptional CF and/or HbPs carrier testing, as a result of the stepwise hierarchical linear regression, was explained by 'attitude' (19%), 'perceived behavioural control' (4%), and 'social influence' (7%) in the first step. [Lakeman 2009][151] 68% (167/247) of the offer decliners had a positive intention (score 43 on the future intention scale) to participate in the future in preconceptional CF and/or HbPs carrier screening if this became possible (M=3.5). Offer decliners without children were even more positive than those who already had children: 74% (114/154)				

Table 4.1.2: Summary of impact estimates for genetic counseling					
intervention	**Maternal /Paternal**	**Pregnancy**	**Newborn**	**Infant**	**Others**
	versus 57% (53/93) (P<0.004). [Lakeman 2009][151] 32% (80/247) of the offer decliners who were not interested in participating in this kind of screening in the future (score <= 3), compared with those who were interested, perceived significantly less social influence (M=1.8 versus 2.3 (P<0.001)); perceived less benefits from the screening (M=2.5 versus 4.1 (P<0.001)); would less often draw reproductive consequences from test results (M=2.6 versus 3.3 (P<0.001)); perceived more negative psychological effect (although still not much) (M=2.7 versus 2.3 (P<0.004)); perceived slightly more eugenetic feelings (M=2.9 versus 2.5 (P<0.005)). [Lakeman 2009][151] Non-Western offer decliners compared with Western offer decliners had a significantly higher mean score on the future intention scale: M=3.8 versus 3.4 (P<0.011), and 75% (51/68) and 65% (116/179), respectively, intended to participate in future screening if this became possible (P<0.08). [Lakeman 2009][151]				

Table 4.1.2: Summary of impact estimates for genetic counseling					
intervention	**Maternal /Paternal**	**Pregnancy**	**Newborn**	**Infant**	**Others**
	School-based screening: Percentage of students who had a positive attitude at baseline (pre-education session) significantly increased between 1995 (50%) and 1998 (73%) (p=0.009). Immediately after the education session, a significant increase from baseline in the percentage of students with a positive attitude was observed (50-79% in 1995; 73-84% in 1998) (p=0.008). Students who had testing had a significantly increased positive attitude towards genetic testing over 12 months (p=0.024). those tested post-session, had retained more knowledge 12 months later than those who had not had testing (p=0.012 for TSD and p=0.008 for CF) [Barlow-Stewart 2003][152] **Uptake rates:** School-based screening: Uptake for testing increased from 54% of eligible students in 1995 to 94% in 1998. [Barlow-Stewart 2003][152]				
Tay-Sachs	**Mode of information delivery:** School screening: No significant differences were found between the computer-based resource and oral presentation. [Gason 2004/2005][153, 154]			**Incidence:** School-based screening: Overall incidence of Tay-Sachs disease in the province has fallen by 90% in 20 years,	

Table 4.1.2: Summary of impact estimates for genetic counseling					
intervention	**Maternal /Paternal**	**Pregnancy**	**Newborn**	**Infant**	**Others**
	Mode of screening: School screening: There were significantly more students accepting a carrier test and anxiety was lower when a cheek-brush test was offered compared with when a blood test was offered. [Gason 2005][154] **Attitude:** School testing: 67% uptake for testing. Students (91%) had a high level of acceptance towards TSD genetic testing; however, both these attitudes and the students' predicted feelings were associated significantly with their decision to be tested (acceptance level: high, tested 94.1%; acceptance level: low, tested: 5.9%; $p < 0.001$)(Anxiety level: high, tested: 10.5%; anxiety level: mid-moderate, tested: 88.2%). [Gason 2003][155] The high-school cohort harbored 16 couples (rounded from 15.4) who would have their children within the time frame of our analysis. Ten carrier couples identified by screening sought prenatal diagnosis, the predicted			reflecting both a general decline in birthrate in Quebec and the effect of carrier screening. Only one affected infant has been born in the Ashkenazi-Jewish community since inception of the carrier screening program; the parents were a non-screened couple. [Mitchell 1996][134]	

Table 4.1.2: Summary of impact estimates for genetic counseling					
intervention	**Maternal /Paternal**	**Pregnancy**	**Newborn**	**Infant**	**Others**
	number in the screened cohort. They had 15 pregnancies, all monitored for an affected fetus. Three affected pregnancies were terminated voluntarily; 12 unaffected offspring were born. [Mitchell 1996][134]				

Key messages

- Premarital screening service for thalessemia provided in Iran, was the only valuable evidence showing a 70% reduction in thalassemia-affected birth post-screening.
- There is otherwise a lack of literature on the provision of comprehensive genetic counseling to couples planning a pregnancy
- A relative lack of literature exists to test effectiveness of preconception genetic screening
- Review of literature for cystic fibrosis shows majority of couples welcome the idea of a pre-pregnancy screening test.
- Attitudes of health professionals regarding preconception cystic fibrosis carrier screening varies considerably. Greatest support to the notion is given by General Practitioners; however this attitude is not translated into practice.

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Section V

Nutrition

5.1 Maternal pre-pregnancy weight

While obesity is a fast-growing epidemic, women of lower socioeconomic status and young age are also at risk of being undernourished and underweight. Prepregnancy overweight has been linked to two of the foremost causes of maternal mortality[3, 4]- hypertensive disorders of pregnancy[3-7] and gestational diabetes mellitus[5, 6] as well as an entire spectrum of adverse pregnancy outcomes,[7-14] including poor lactation practices,[7, 8] obstetric anesthesia-related complications,[9] prolonged gestation,[10, 11] maternal infectious morbidity,[12] and decreased success with trial of labor.[13-17] Maternal obesity is also a cause for fetal and neonatal death,[13-17] and childhood disease.[13] Moreover, perpetuates the obesity epidemic since children of obese women are more likely to be obese themselves.[5, 13-16]

Pre-pregnancy underweight poses major perinatal risks- stillbirths, preterm births, small for gestational age and low birth weight babies.[13-20] However, there is a dearth of reviews on the subject, or trials to support interventions to prevent undernutrition in women of reproductive age. The available literature focuses on maternal short stature as an indirect indicator for the risk of poor MNCH outcomes with maternal undernutrition.

Scope of Intervention

In order to define the categories of weight that are not normal, the World Health Organization and the National Institutes of Health grouped weight into four categories according to individuals' body mass index: underweight (<18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (30.0 kg/m^2). The literature shows a BMI-dependent relationship between prepregnancy obesity and adverse pregnancy outcomes.[14, 15] Further, excessive postpartum weight retention is a risk not only for subsequent pregnancies,[16, 17] but also for the development of maternal chronic diseases. For this reason, the Institute of Medicine has also developed recommendations for gestational weight gain according to maternal prepregnancy BMI, however gestational weight gain is not discussed further as it falls outside the scope of preconception care.

Preconception care- maternal weight, diet and exercise
• Calculate BMI for women of reproductive age at any contact with the healthcare system • Women of reproductive age should understand the risks associated with being overweight (gestational hypertension, GDM, stillbirths, C-section, PPH, congenital heart defects) or underweight (preterm birth, small-for-gestational-age neonates) during pregnancy, and should be encouraged to normalize their BMI before pregnancy since weight loss during pregnancy is not recommended, and weight gain during pregnancy does not sufficiently reduce the risk for pregravid underweight women • For women with a normal pre pregnancy BMI, a weight gain of around 0.4 kg/week during the second and third trimesters is recommended. For underweight women, a weight gain of 0.5 kg/week is the target, whereas for overweight women, 0.3 kg/week is recommended. Although restricting weight gain might seem an easy solution, there is little evidence of effect for this as the primary

intervention in overweight women (Guelinckx 2008)[18]

- Balanced protein energy supplementation and appropriate micronutrient supplementation could reduce the risk of prepregnancy underweight on adverse perinatal outcomes
- Reaffirm that difficulty maintaining healthy weight and eating habits are not due to lack of willpower, but also environmental pressures such as easy access to low-cost, high-calorie foods. Promote improvement in diet and exercise through sustained, daily changes, with the help of a support system and monitoring for weight loss, and increased physical activity. Encourage women to challenge outside influences and make healthier choices about their eating and physical activity.(Siega-Riz 2009)[19] Use simple, consistent messages such as "tame the tube" and "right-size your portions", and provide patients with a food diary.

Impact estimates

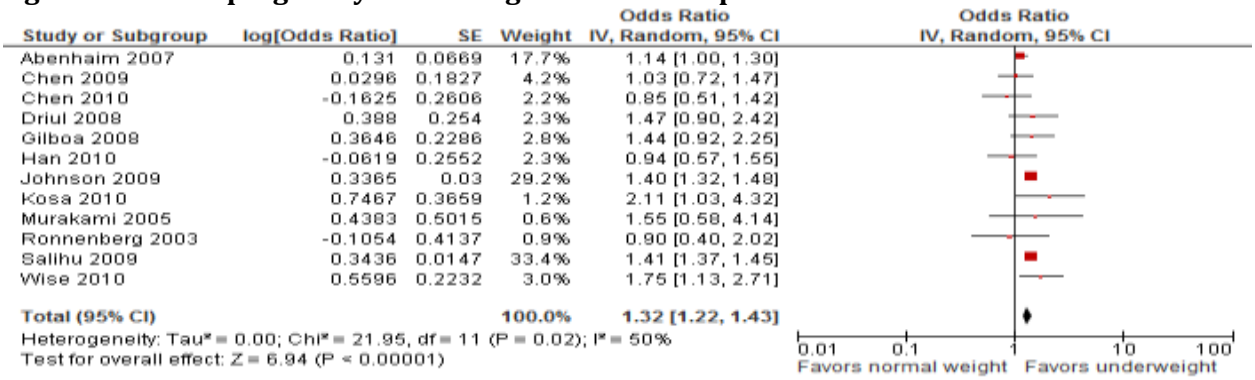
We pooled **risk-aversion** studies to assess which adverse MNCH outcomes maternal underweight or overweight significantly increases the risk for:

Underweight

This review found that prepregnancy underweight significantly increases the risk of preterm birth by 32% (RR 1.32, 95% CI: 1.22-1.43) (**Figure 5.1.1**), which is comparable to another meta-analysis which showed an increased risk of 29%[20] and a large population-based study[21]that demonstrated an increased risk of 37%.

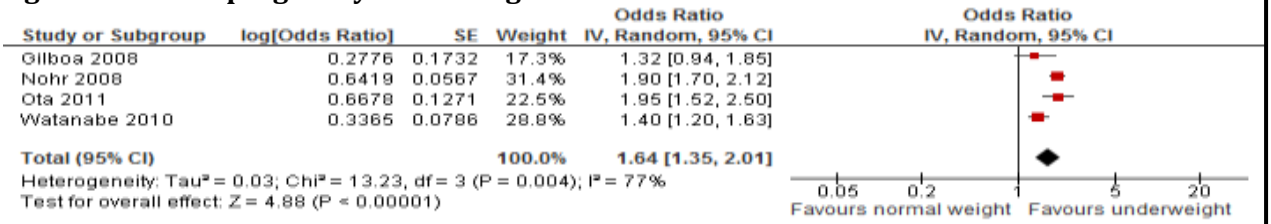
Prepregnancy underweight was also found to significantly increase the risk of small-for-gestational age babies (RR 1.64, 95% CI: 1.22-2.21) (**Figure 5.1.2**); this estimate is consistent with that reported by Salihu et al. 2009,[21] however the difference in effect size may be because we pooled only two observational studies.

Figure 5.1.1: Pre pregnancy underweight and risk for preterm birth



Citations to the included studies:
Abenhaim 2007[22], Chen 2009[23], Driul 2008[24], Johnson 2009 [25], Kosa 2010 [26], Murakami 2005[27], Ronnenberg 2003[28], Salihu 2009[29], Wise 2010[30], chen 2010[31], Gilboa 2008[32], Han 2010[33].

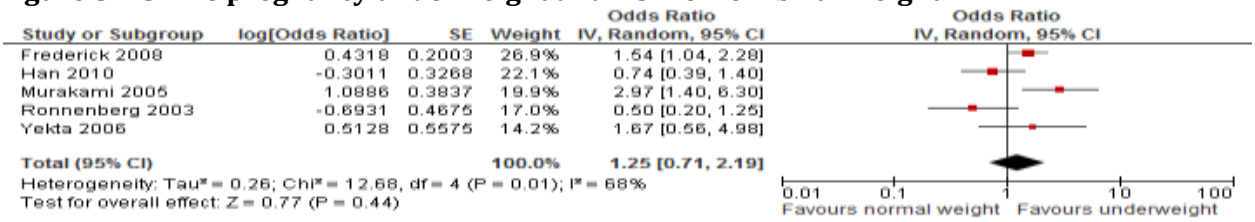
Figure 5.1.2: Pre pregnancy underweight and risk for SGA



Citations to the included studies:
Nohr 2008[34], Watanabe 2010[35], Gilboa 2008[32], Ota 2011[2].

Although previous work has found a significant effect of prepregnancy underweight on the risk of having low birthweight babies (aRR 1.64 (Han 2011)[20] and OR 1.82 (Salihu 2009),[21] this review found a non-significant risk (RR 1.37, 95% CI: 0.46-4.13) (**Figure 5.1.3**) perhaps because of the low number of studies included. One study (Shirima 2005)[36] demonstrated that perhaps, in addition to weight, height and hemoglobin levels, could be used as indicators of maternal undernutrition as a risk factor for poor MNCH outcomes.

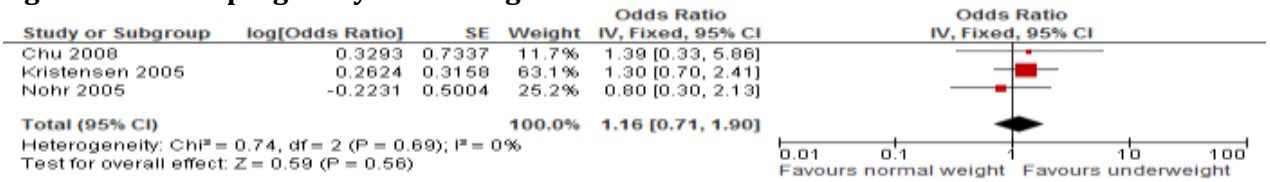
Figure 5.1.3: Pre pregnancy underweight and risk for low birth weight



Citations to the included studies:
Murakami 2005[27], Ronnenberg 2003[28], Frederick 2008[37], Han 2010[33], Yekta 2006[38].

Similarly, conflicting results were found for risk of stillbirths (**Figure 5.1.4**).

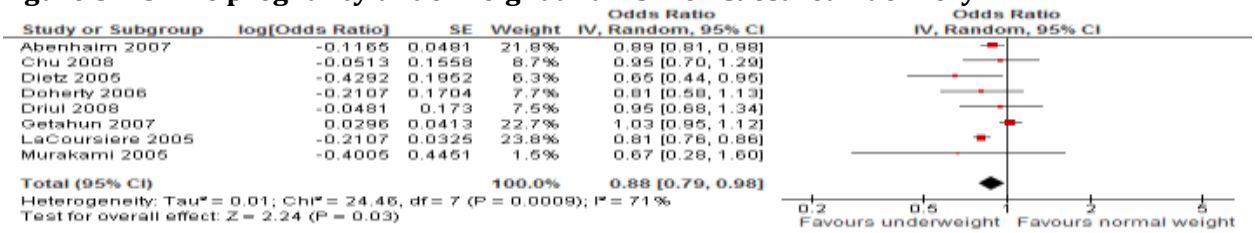
Figure 5.1.4: Pre pregnancy underweight and risk for stillbirths



Citations to the included studies:
Chu 2008 [39], Kristensen 2005[40], Nohr 2005[41].

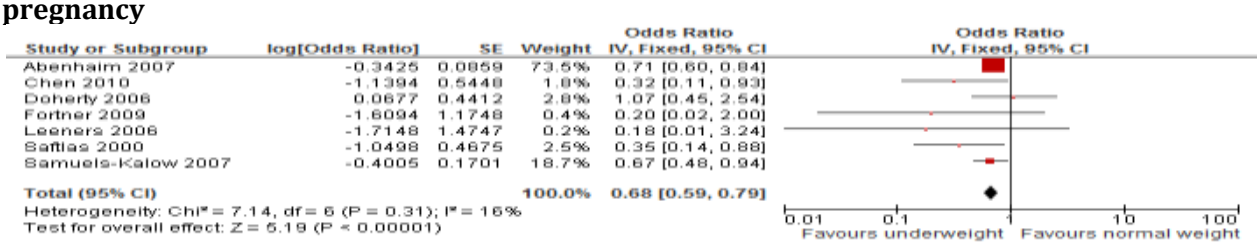
As expected, pre pregnancy underweight reduced the risk of Caesarean section (**Figure 5.1.5**), hypertensive disorders of pregnancy (**Figure 5.1.6**), pre-eclampsia (**Figure 5.1.7**), gestational diabetes mellitus (**Figure 5.1.8**), as well as congenital birth defects (**Figure 5.1.9**) (**Figure 5.1.10**) (**Figure 5.1.11**) (**Figure 5.1.12**).

Figure 5.1.5: Pre pregnancy underweight and risk for Caesarean delivery



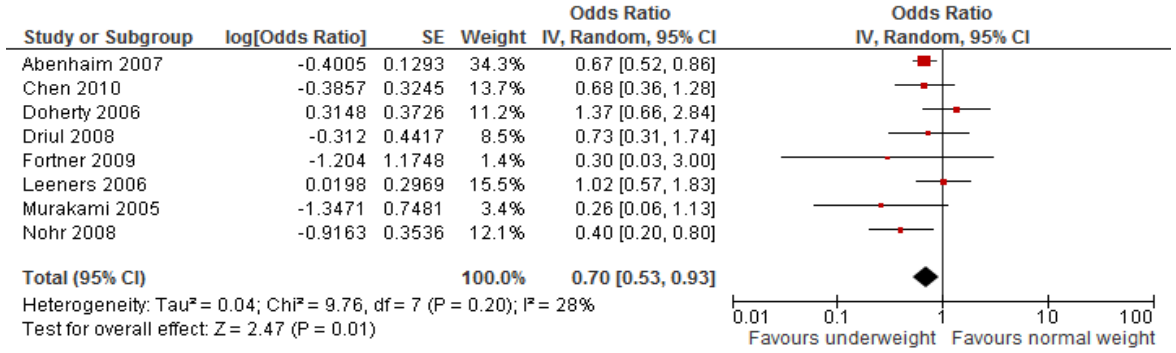
Citations to the included studies:
Abenhaim 2007[22], Chu 2008 [39], Dietz 2005 [42], Driul 2008[24], Getahun 2007[43], Murakami 2005[27], Doherty 2006[4], Lacoursiere 2005[44].

Figure 5.1.6: Pre pregnancy underweight and risk for hypertensive disorders of pregnancy



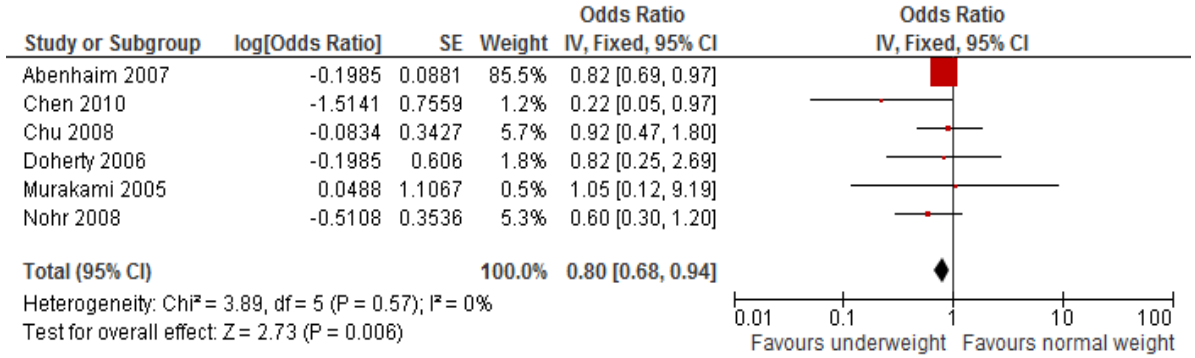
Citations to the included studies:
Abenhaim 2007[22],Fortner 2009[45], Samuels-kalow 2007[46], Chen 2010[31], Doherty 2006[4], Leeners 2006[47], Saftlas 2000[48].

Figure 5.1.7: Pre pregnancy underweight and risk for preeclampsia



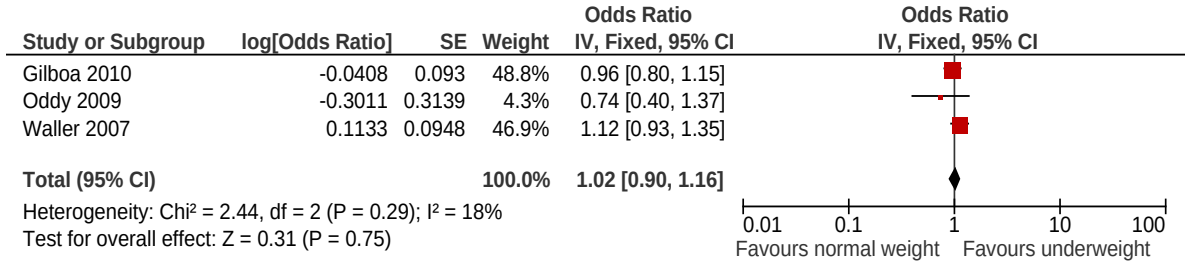
Citations to the included studies:
Abenhaim 2007[22], Driul 2008[24], Fortner 2009[45], Murakami 2005[27], Nohr 2008[34],Chen 2010[31], Doherty 2006[4], Leeners 2006[47]

Figure 5.1.8: Pre pregnancy underweight and risk for GDM



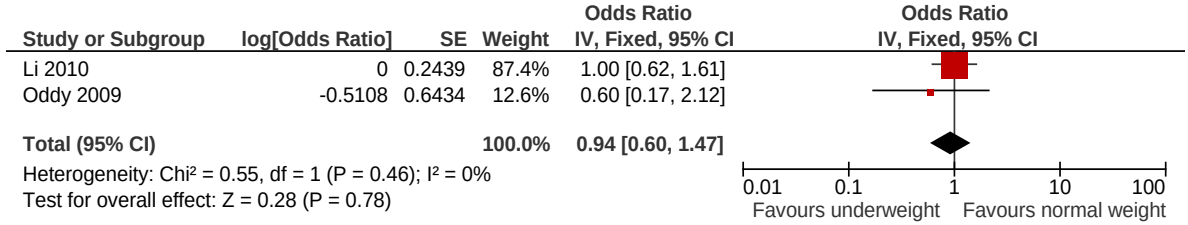
Citations to the included studies:
Abenhaim 2007[22], Chu 2008 [39], Murakami 2005[27], Nohr 2008[34], Chen 2010[31], Doherty 2006[4]

Figure 5.1.9: Pre pregnancy underweight and risk for CHDs



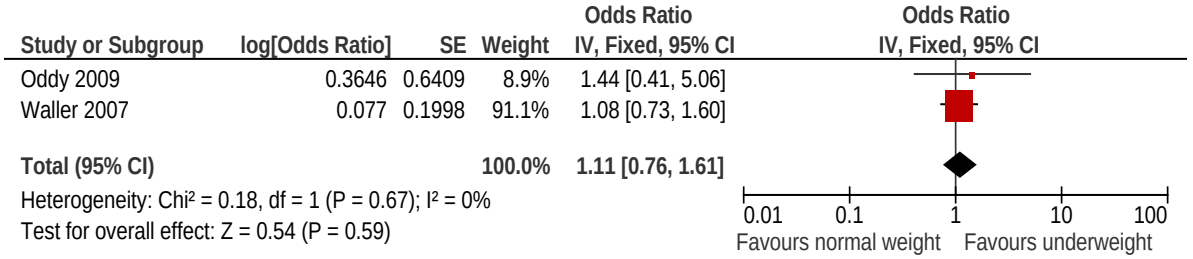
Citations to the included studies:
Gilboa 2010 [49], Oddy 2009[50], Waller 2007[51]

Figure 5.1.10: Pre pregnancy underweight and risk for NTDs



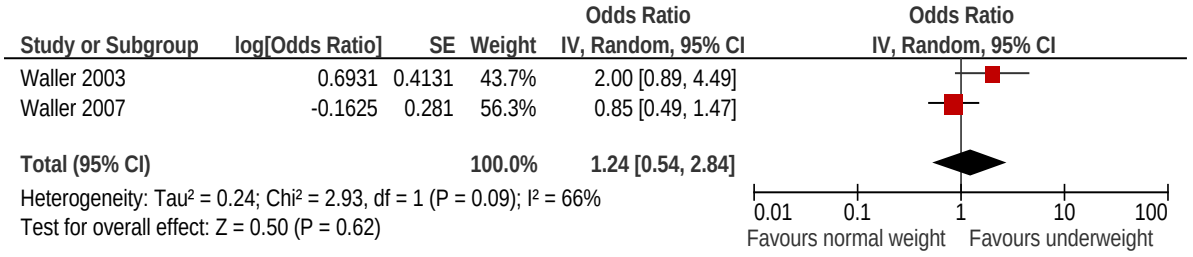
Citations to the included studies:
Li 2010[52], Oddy 2009[50]

Figure 5.1.11: Pre pregnancy underweight and risk for limb reduction defects



Citations to the included studies:
Oddy 2009[50], Waller 2007[51]

Figure 5.1.12: Pre pregnancy underweight and risk for congenital diaphragmatic hernia

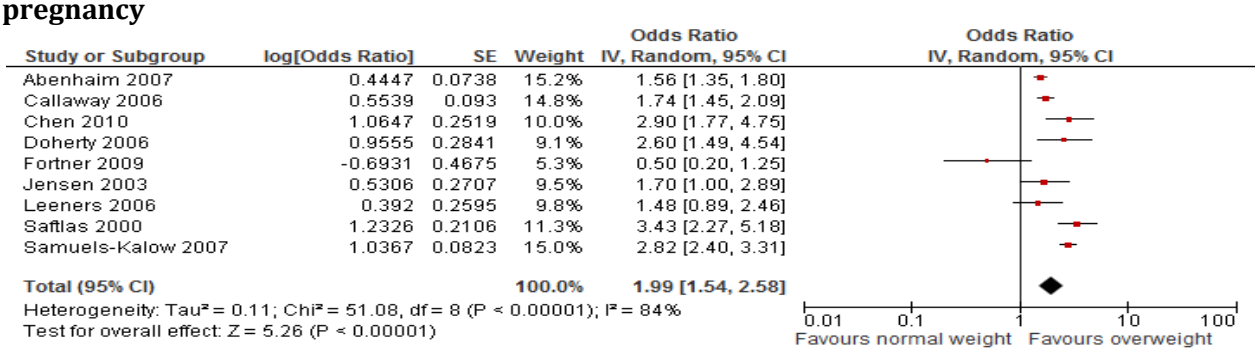


Citations to the included studies:
Waller 2003[53], Waller 2007[51]

Overweight

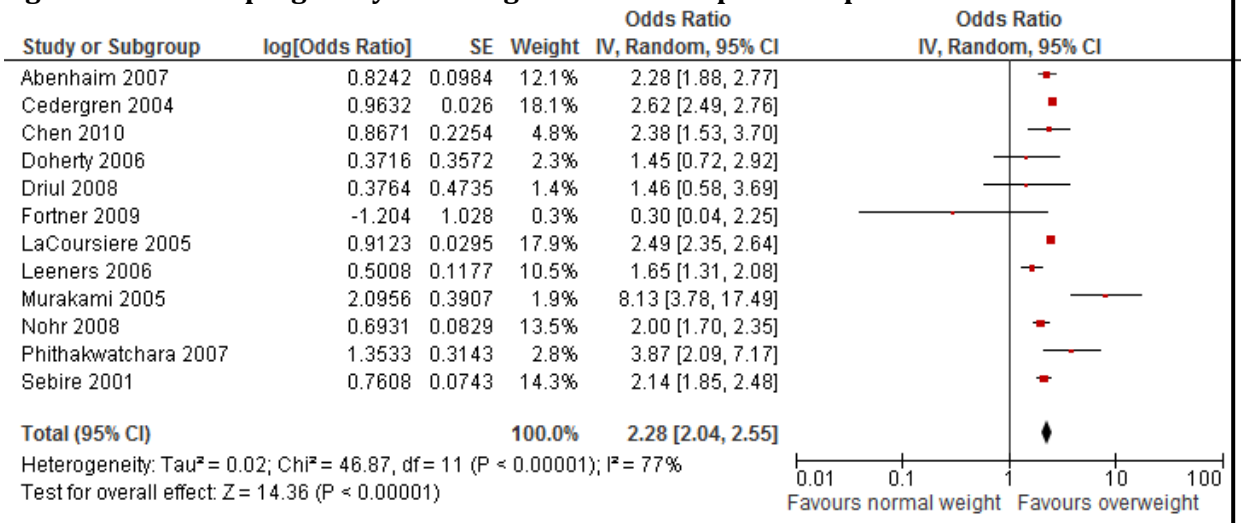
The results presented in this review for the increased risk of hypertensive disorders of pregnancy with maternal overweight are not truly representative of the association since various studies categorized this outcome differently (**Figure 5.1.13**), yet they concur with previous work[54, 55] showing a significantly increased risk of gestational hypertension among overweight women. The risk of preeclampsia (OR 2.28) (**Figure 5.1.14**) and gestational diabetes mellitus (OR 1.91) (**Figure 5.1.15**), however, approximately doubles with prepregnancy overweight, and the effect was even greater for prepregnancy obesity although this data was not presented as meta-views. This is consistent with previous reviews that show the risk of preeclampsia typically doubles for each 5 to 7kg/m2 increase in BMI;[56] and the OR of developing GDM is 1.97-2.14 for overweight women, and 3.01-3.56 for obese women.[6, 57] Besides preeclampsia, overweight women are also at increased risk for postpartum hemorrhage (pooled OR 1.18), the other leading cause of maternal mortality (**Figure 5.1.16**).[54, 55]

Figure 5.1.13: Pre pregnancy overweight and risk for hypertensive disorders of pregnancy



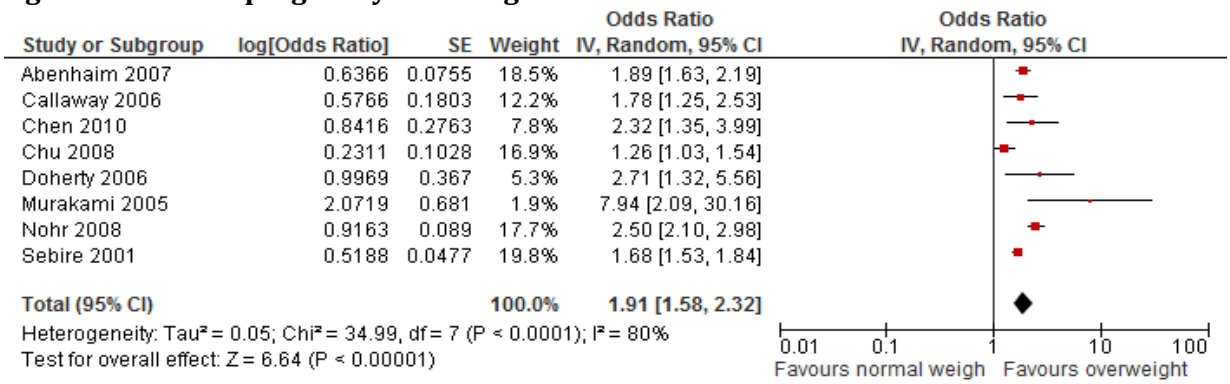
Citations to the included studies:
Abenhaim 2007[22], Fortner 2009[45], Samuels-kalow 2007[46],Callaway 2006[58], Chen 2010[31], Doherty 2006[4], Jensen 2003[59], Leeners 2006[47], Saftlas 2000[48]

Figure 5.1.14: Pre pregnancy overweight and risk for preeclampsia



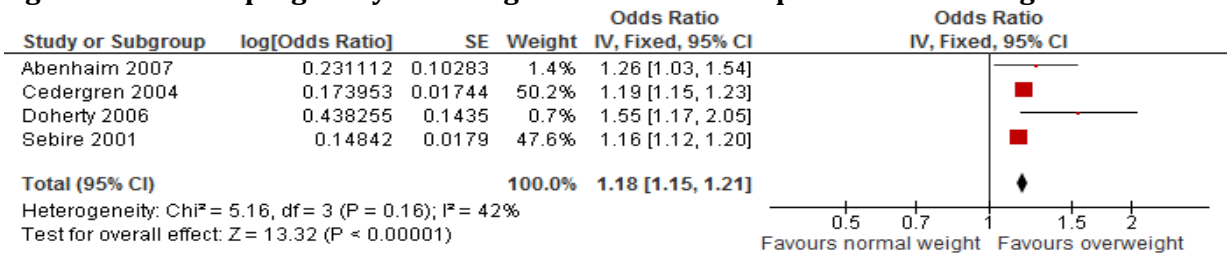
Citations to the included studies:
Abenhaim 2007[22], Driul 2008[24], Fortner 2009[45], Murakami 2005[27], Nohr 2008[34], Cedergren 2004[60], Chen 2010[31], Doherty 2006[4], Leeners 2006[47], LaCoursiere 2005[44], Phithakwatchara 2007[61], Sebire 2001[62]

Figure 5.1.15: Pre pregnancy overweight and risk for GDM



Citations to the included studies:
Abenhaim 2007[22], Chu 2008 [39], Murakami 2005[27], Nohr 2008[34], Callaway 2006[58], Chen 2010[31], Doherty 2006[4], Sebire 2001[62]

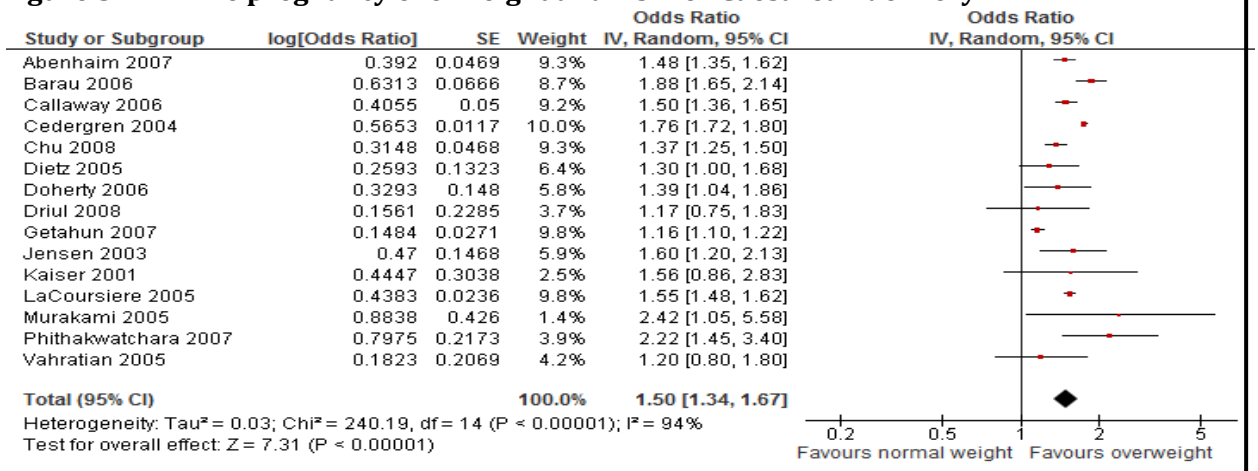
Figure 5.1.16: Pre pregnancy overweight and risk for Postpartum hemorrhage



Citations to the included studies:
Abenhaim 2007[22], Cedergren 2004[60], Doherty 2006[4], Sebire 2001[62]

Pooled analysis of observational studies showed a clear increase of 50% in caesarean delivery among overweight women (OR 1.42, 95% CI 1.21-1.66) (**Figure 5.1.17**), as has previously been demonstrated.[63, 64]

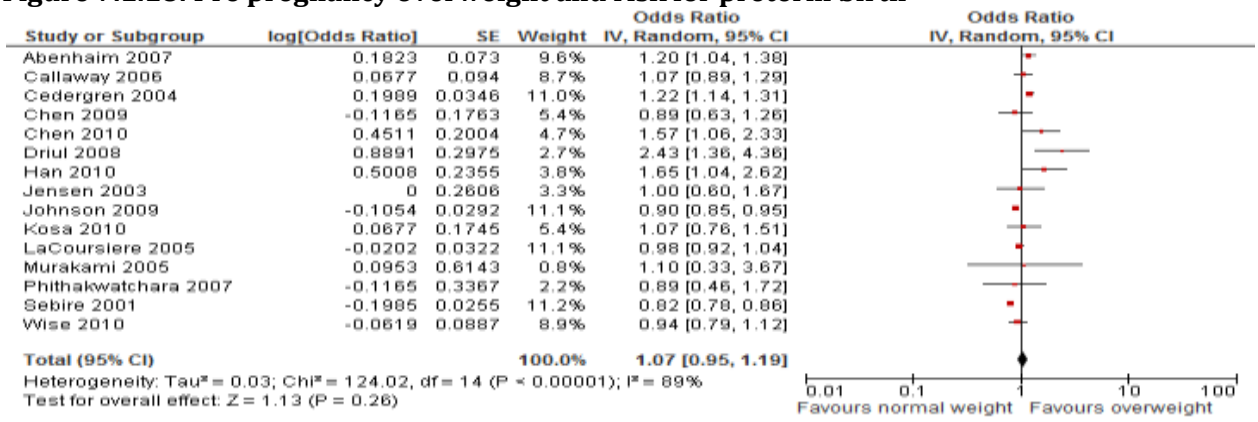
Figure 5.1.17: Pre pregnancy overweight and risk for Caesarean delivery



Citations to the included studies:
Abenhaim 2007[22], Chu 2008 [39], Dietz 2005 [42], Driul 2008[24], Getahun 2007[43], Murakami 2005[27], Barau 2006[65], Callaway 2006[58], Cedergren 2004[60], Doherty 2006[4], Jensen 2003[59], Kaiser 2001[66], LaCoursiere 2005[44], Phithakwatchara 2007[61], Vahratian 2005[67].

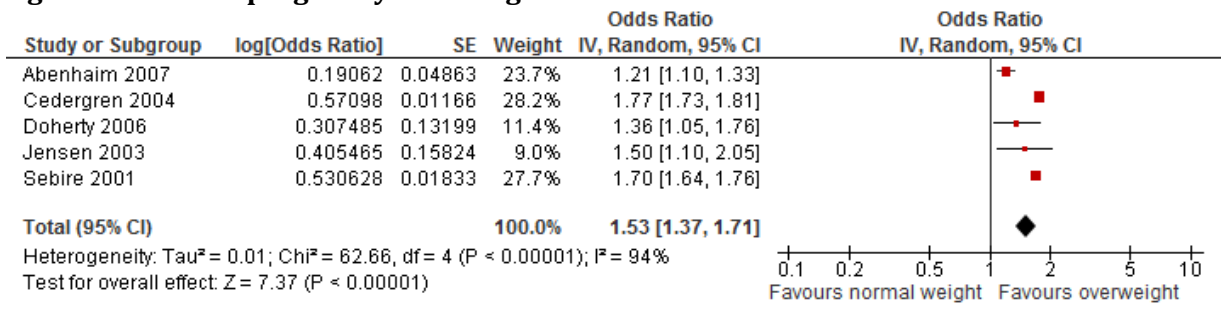
This review found that overweight status conferred an elevated risk for induction of labour **(Figure 5.1.18)**, stillbirths (**Figure 5.1.19**, which is consistent with other reviews.[54] The risk for preterm births (**Figure 5. 1.20**) and instrumental delivery (**Figure 5.1.21**) was slightly increased, which has also been previously illustrated.

Figure 7.1.18: Pre pregnancy overweight and risk for preterm birth



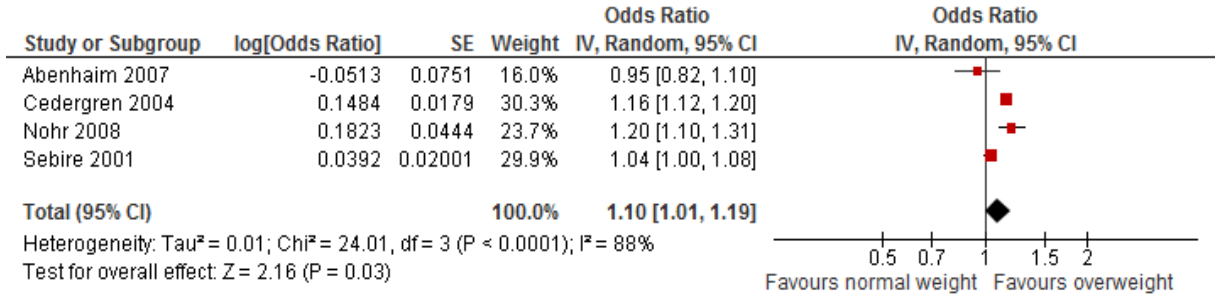
Citations to the included studies:
Abenhaim 2007[22], Chen 2009[23], Driul 2008[24], Johnson 2009 [25], Kosa 2010 [26], Murakami 2005[27], Wise 2010[30], Callaway 2006[58], Chen 2010[31], Cedergren 2004[60], Han 2010[33], Jensen 2003[59], Johnson 2009[25], Kosa 2010[26], LaCoursiere 2005[44], Phithakwatchara 2007[61], Sebire 2001[62]

Figure 5.1.19: Pre pregnancy overweight and risk for induction of labour



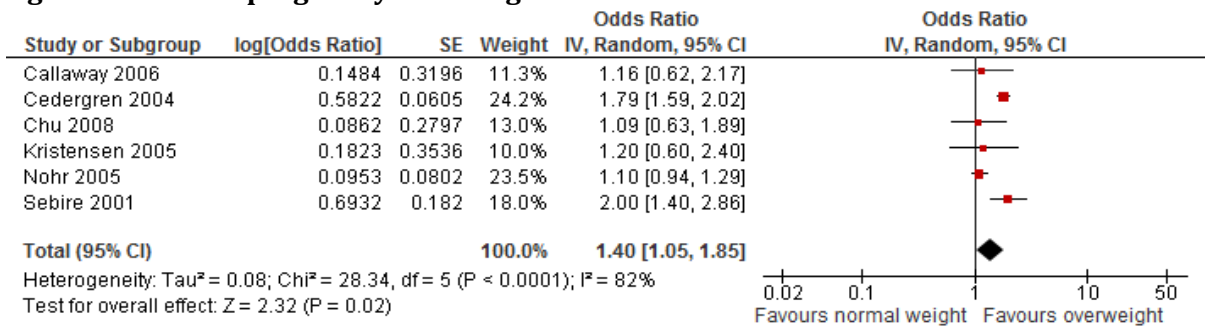
Citations to the included studies:
Abenhaim 2007[22], Cedergren 2004[60], Doherty 2006[4], Jensen 2003[59], Sebire 2001[62]

Figure 5.1.20: Pre pregnancy overweight and risk for instrumental delivery



Citations to the included studies:
Abenhaim 2007[22], Nohr 2008[34], Cedergren 2004[60], Sebire 2001[62]

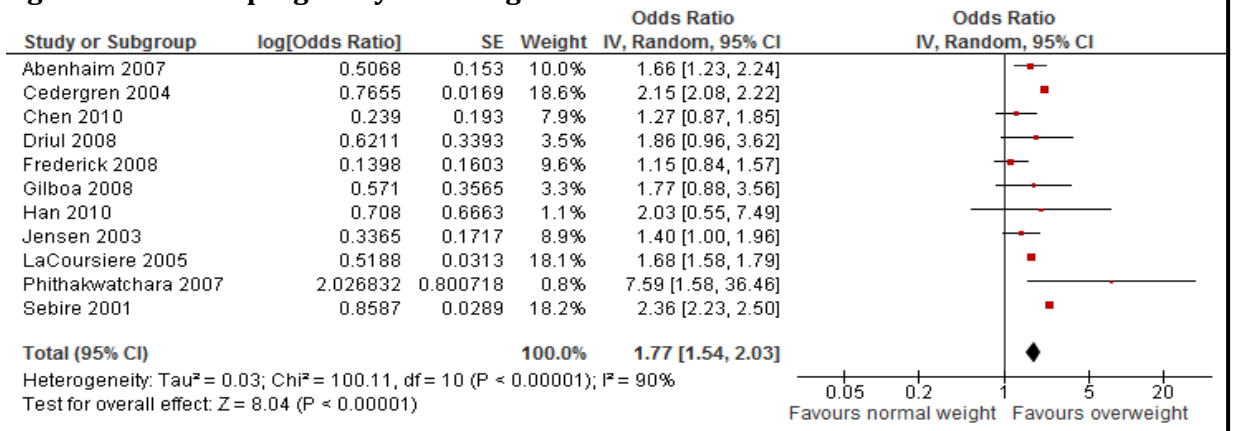
Figure 5.1.21: Pre pregnancy overweight and risk for stillbirths



Citations to the included studies:
Chu 2008 [39], Kristensen 2005[40], Callaway 2006[58], Cedergren 2004[60], Nohr 2005[41], Sebire 2001[62].

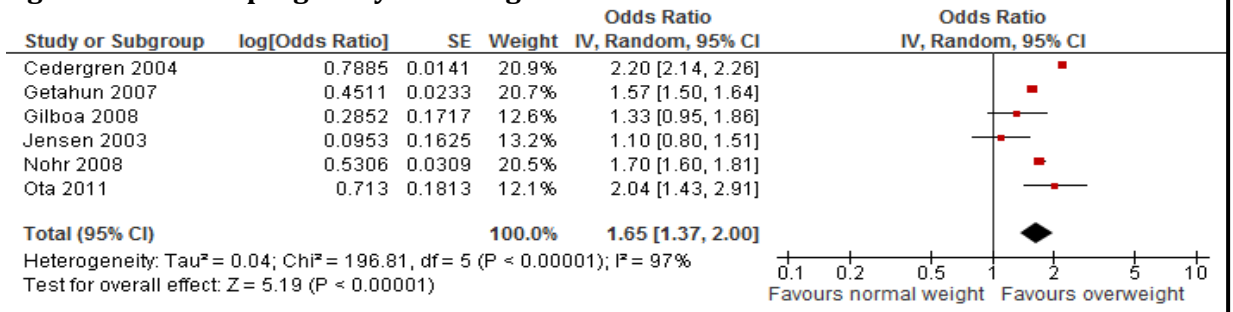
Perinatal outcomes that were significantly associated with maternal overweight before conception include macrosomia (OR 1.77, 95% CI: 1.54-2.03) (**Figure 5.1.22**), large-for-gestational age babies (OR 1.63, 95% CI: 1.51-1.76) (**Figure 5.1.23**), and birth defects (**Figure 5.1.24**) (**Figure 5.1.25**)-notably neural tube defects (**Figure 5.1.26**)and congenital heart defects (OR 1.15, 95% CI 1.07-1.24) (**Figure 5.1.27**), findings which are consistent with other reviews[68-70]

Figure 5.1.22: Pre pregnancy overweight and risk for macrosomia



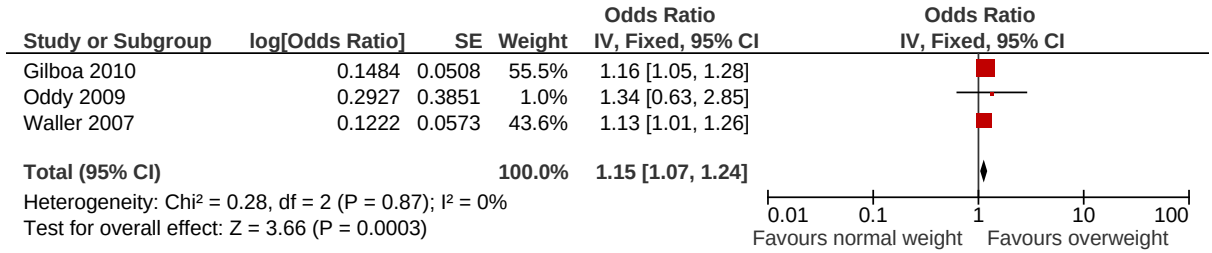
Citations to the included studies:
Driul 2008[24], Frederick 2006[71] Abenhaim 2007[22], Chen 2010[31], Cedergren 2004[60], Gilboa 2008[32], Han 2010[33], Jensen 2003[59], LaCoursiere 2005[44], Phithakwatchara 2007[61], Sebire 2001[62].

Figure 5.1.23: Pre pregnancy overweight and risk for LGA



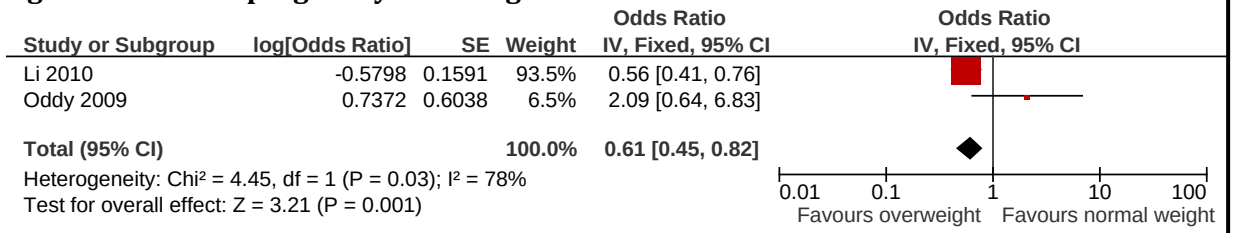
Citations to the included studies:
Getahun 2007[43], Nohr 2008[34], Cedergren 2004[60], Gilboa 2008[32], Jensen 2003[59], Ota 2011[2].

Figure 5.1.24: Pre pregnancy overweight and risk for CHDs



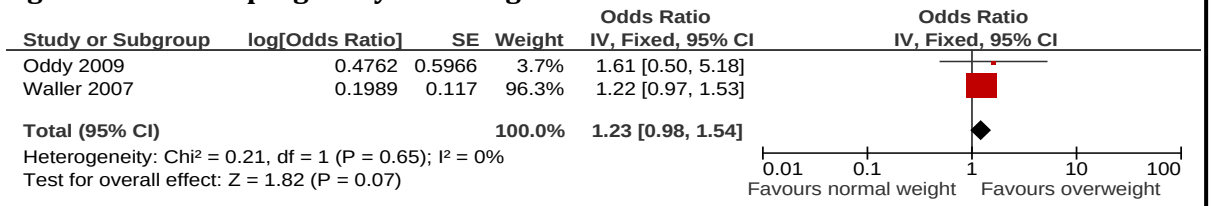
Citations to the included studies:
Gilboa 2010 [49], Oddy 2009[50], Waller 2007[51]

Figure 5.1.25: Pre pregnancy overweight and risk for NTDs



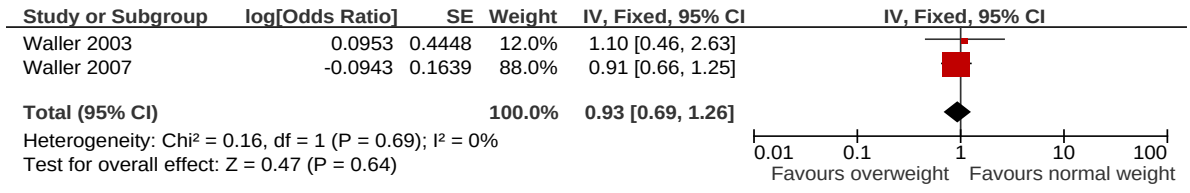
Citations to the included studies:
Li 2010[52], Oddy 2009[50]

Figure 5.1.26: Pre pregnancy overweight and risk for limb reduction defects



Citations to the included studies:
Oddy 2009[50], Waller 2007[51]

Figure 5.1.27: Pre pregnancy overweight and risk for congenital diaphragmatic hernia



Citations to the included studies:
Waller 2003[53], Waller 2007[51]

Although increasing maternal BMI showed a trend towards increased risk of multiple gestation, neonatal death, fetal distress and NICU admissions, as well as a reduced tendency to breastfeed and lack of success with VBAC, there were not enough individual studies to pool these results for meaningful analysis.

Conclusion

Maternal overweight and obesity is a growing problem across the world, but women in developing countries and lower socioeconomic strata continue to be at risk of undernourishment.[72] Both prepregnancy overweight and underweight are risk factors for poor maternal and child health outcomes, however overweight and obesity results in significantly greater health risks and associated costs. Given that weight is a modifiable risk factor, research must now focus on how healthcare providers and public health campaigns can reduce these risks.

Key messages:

- Maternal obesity is a fast-growing epidemic with serious consequences for maternal, pregnancy and child outcomes.
- Prepregnancy overweight approximately doubles the risk for hypertenseive disorders of pregnancy (OR 1.99), preeclampsia (OR 2.28) and gestational diabetes mellitus (OR 1.91).
- Women who are overweight are 1.5 times more likely to deliver by Caesarean section versus normal-weight women.
- Women who are overweight and obese are more likely to give birth to large-for-gestational age and macrosomic infants (OR 1.63).
- There is some evidence to suggest that birth defects, especially neural tube defects and congenital heart defects, are more common in children born to overweight women, and that this association becomes stronger with increasing maternal body mass index.
- Data is lacking to suggest an effect of pre pregnancy overweight on preterm births, instrumental delivery or fetal distress.
- Women who are underweight before pregnancy have a 32% increased risk of preterm birth, and a 64% increased risk of having small-for-gestational age babies.
- We found scarce evidence of an effect of pre pregnancy underweight on stillbirths, low birth weight, operative delivery including caesarean section, or congenital birth defects, although intervention studies of balanced energy protein supplementation during pregnancy do indicate significant benefit. The studies on maternal undernutrition largely focus on maternal short stature as a manifestation of the intergenerational effects of undernutrition, and thus indirectly link undernutrition with adverse MNCH outcomes.

Table 5.2.1: Summary impact estimates for maternal pre pregnancy weight			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
Prepregnancy BMI 28: 1.4 (95% CI 1.1-1.9) for vitamin D deficiency in pregnancy compared to BMI 22 [Bodnar 2007 Coh][73] Major depression during pregnancy: 2.3 (0.5, 11.1) for underweight women, 1.7 (0.9, 3.4) for overweight women [Bodnar 2009 Coh][74] Postpartum depression U: 1.22 (0.54–2.73), O: 1.09 (0.66–1.80), Obese: 1.06 (0.54–2.09) [LaCoursiere 2010 Coh][75] Unintended pregnancy: For	<u>Gestational weight gain:</u> Prepregnancy BMI <19.8: 23.1% women with inadequate weight gain versus 14.5% normal BMI. Prepregnancy BMI 26.1-29: 73.2% excessive weight gain versus 52.3% normal BMI, OR 2.26 (1.43-3.56) [Brawarsky 2005 Coh- referent BMI 19.8-26][77] In overweight and obese subjects, weight gain during pregnancy was significantly lower than in the underweight and normal subjects [Han 2010 CS- BMI cutoff at 23 for Asian population][33] <u>Miscarriage:</u> Early: OR 1.2 (1.01-1.46) for obese women Recurrent: OR 3.51 (1.03-12.01) [Lashen 2004 CC- referent BMI 19-24.9][78] <u>Gestational HTN:</u> U: 0.71 (0.60–0.83), O: 1.56 (1.35–1.81) [Abehnaim 2007 Coh][22] U: 0.2 (0.02-1.3), O: 0.5 (0.2-1.8), Obese: 2.5 (1.3-4.8) [Fortner 2009 Coh][45] U: 0.67 (0.48-0.92), O: 2.82 (2.40-3.31) [Samuels-Kalow 2007 Obs][46] O: aOR 1.74 (1.45–2.15) [Callaway 2006 Obs- referent BMI 20-25][58] U: 0.32 (0.11–0.88), BMI 24-27.9: 2.90 (1.77–4.75) [Chen 2010 Coh- referent BMI 18.5-23.9][31] U: aOR 1.07 (0.45–2.58), O: 2.60 (1.49–4.55) [Doherty 2006 Coh][4]	<u>Perinatal death:</u> U: 1.34 (0.91–1.98), O: 1.38 (0.89–2.15) [Abenhaim 2007 Coh][22] O: OR 1.8 (0.6-6.0), obese: 1.0 (0.2-1.3) [Jensen 2003 Coh][59] <u>Low APGARs:</u> U: 1.38 (0.95–2.02), O: 1.70 (1.30–2.70) [Abenhaim 2007 Coh][22] U: 0.8 (0.5-1.3), O: 1.3 (1.0-1.6) [Nohr 2008 Coh][34] BMI 29-35: aOR 1.58 (1.47-1.69) Greater effect size with increasing BMI [Cedergren 2004 Coh- referent BMI 19.8-26][60] <u>Meconium aspiration:</u> BMI 29-35: aOR 1.64 (1.30- 2.06)Greater effect size with increasing BMI [Cedergren 2004 Coh- referent BMI 19.8-26][60] <u>NICU admission:</u> U: 1.03 (0.93–1.14), O: 1.21 (1.08–1.36) [Abenhaim 2007 Coh][22] O: aOR 0.92 (0.73–1.16) , Obese: 1.25 (0.97–1.62) [Callaway 2006 Obs- referent BMI 20-25][58] Obese: 1.5 (1.09– 2.3) [Kiran 2005 Obs- referent BMI 20-30][87] <99 lbs: 1.1 (1.0-1.2), 150-199 lbs: 1.1 (1.0-1.1) [Rosenberg 2003 Obs- referent weight 100-149 lbs][84]	aOR that children with obese mothers (BMI>30) would have asthma at age 3= 1.34 (1.03–1.76) [Reichman 2008 Coh][115] 5 yr old children of underweight, overweight and obese mothers were more likely to have problems with inattention, hyperactivity and negative emotionality [Rodriguez 2010 Coh][116] <u>SIDS:</u> U:4.9 (1.7–14.2), O: 2.5 (0.6–10.4) [Wisborg 2003 Coh][117]

Table 5.2.1: Summary impact estimates for maternal pre pregnancy weight			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
women using contraception, U: 1.28 (0.92-1.79), O: 1.73 (1.26-2.36) [Bronner Huber 2005 CC][76] Stress: 1.05 [0.63, 1.74] for underweight, 2.25 [1.47, 3.43] for overweight [Han 2010 CS- referent BMI 18.5-22.9 for Asian population][33] Anesthetic complications: BMI>25: 1.48 (0.85-2.58) [LaCoursiere 2005 Obs][44] Anemia: O: 0.82 (0.79-0.85),obese: 0.66 (0.62-0.70) [Sebire 2001 Obs- referent BMI 20-25][62]	O: 1.7 (1.0-2.8) [Jensen 2003 Coh][59] U: 0.18 [0.01, 2.81], O: 1.48 [0.89, 2.48] [Leeners 2006 CC][47] Weight 90-120 kg: aOR 2.38, (2.24–2.52) [Robinson 2005 Coh- referent weight 55-70 kg][79] O: 1.9 (0.97–3.7) [Rode 2005 Coh- referent BMI <25][80] U:0.35 (0.14–0.87), obese: 3.43 (2.27-5.21) [Saftlas 2000 Coh- referent BMI 19.8-26][48] O: Severe preeclampsia at BMI 25 and 30 in white women were 1.7 (1.1–2.5) and 3.4 (2.1–5.6), respectively, and 2.1 (1.4 –3.2) and 3.2 (2.1–5.0) in black women. Severe transient hypertension of pregnancy at BMI values of 25 and 30 in white women were 3.6 (2.0–6.5) and 8.8 (4.4 –18), respectively, and 3.0 (1.6 –5.8) and 4.9 (2.5–9.6) in black women. [Bodnar 2007 Coh- referent white women with BMI=20][81] U: RR 0.85 (95% CI: 0.80 - 0.90), O: 1.37 (95% CI: 1.27 - 1.47) and obese (BMI>25): 1.88 (95% CI: 1.68 - 2.10) [Liu 2009 Obs- referent BMI 18.5-22.9][82] O: OR 1.99 (95% CI: 1.73-2.31) [Ehrenthal 2011 Coh] <u>Preeclampsia:</u> O: RR 2.99 (95% CI: 2.21–4.06), Obest: RR 5.68 (95% CI: 3.97–8.11) [Liu 2011 Coh- referent BMI 18.5-24, O:24-28] U: 0.67 (0.52–0.86), O: 2.28 (1.88–2.77) [Abenhaim 2007 Coh][22] U: 0.732 (0.308–1.738), O: 1.457 (0.576–3.689) [Driul 2008 Coh][24]	<u>Neonatal death:</u> O: 1.1 (0.7–1.6) [Cnattingius 1998 Coh- referent BMI < = 19][85] U: 1.3 (0.5– 2.9), O: 1.0 (0.4– 2.2), Obese: 2.7 (1.2– 6.1) [Kristensen 2005 Coh][40] BMI 29-35: aOR 1.59 (1.25-2.01). Greater odds with increasing BMI [Cedergren 2004 Coh- referent BMI 19.8-26][60] <u>Low birth weight:</u> U: aRR 1.54 (1.04–2.29), O: aRR 1.01 (0.58–1.77) [Frederick 2008 Coh][71] U: 1.67 [0.56, 4.98] [Yekta 2006 Coh- referent BMI 19.8-26][38] U: 2.97 (1.40-6.34), O: 0.20 (0.03-1.27) [Murakami 2005 Obs][27] U: 0.5 (0.2-1.6) [Ronnenberg 2003 Coh][28] MUAC: 1.9 Height: 1.7 Weight: 2.3 BMI: 1.8 [WHO 1995 MA][1] U: 0.74 [0.39, 1.43]O:1.97 [1.18, 3.28] [Han 2010 CS- referent BMI 18.5-22.9 for Asian population][33] BMI>27: OR 0.57 (0.29-1.14)[Phithakwatchara 2007 Coh- referent BMI 20-25]	

Table 5.2.1: Summary impact estimates for maternal pre pregnancy weight			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
U: RR 2.54 (95% CI:1.15–5.63) [Liu 2011 Coh]	U: 0.3 (0.03-2.03), O: 0.3 (0.04-2.2), Obese: 2.5 (1.3-4.8) [Fortner 2009 Coh][45] O: RR 1.7 (0.6–4.9) [Frederick 2006 Coh- referent < 20][71] U: 0.26 (0.06-1.09), O: 8.13 (3.78-17.49) [Murakami 2005 Obs][27] U: 0.4 (0.2-0.7), O: 2.0 (1.7-2.3) [Nohr 2008 coh][34] BMI 17: aOR 0.43 (0.25-0.76), BMI 26: 2.1 (1.4-3.4), BMI 30 2.9 (1.6-5.3) [Bodnar 2005 Coh- referent BMI=21][83] BMI 29-35: aOR 2.62 (2.49-2.76) [Cedergren 2004 Coh- referent BMI 19.8-26][60] U:0.68 (0.36–1.27), BMI 24-27.9: 2.38 (1.53–3.69) [Chen 2010 Coh- referent BMI 18.5-23.9][31] MUAC: 0.6 Height: 0.8 Weight: 0.7 BMI: 0.7 [WHO 1995 MA][1] U: aOR 1.37 (0.66–2.85) O: 1.45 (0.72–2.90) [Doherty 2006 Coh][4] BMI>25: 2.49 (2.35-2.64) [LaCoursiere 2005 Obs- referent BMI 19-24.9][44] U: 1.02 [0.57, 1.80], O: 1.65 [1.31, 2.08] [Leeners 2006 CC][47] BMI>27: OR 3.87 (2.09-7.25)[Phithakwatchara 2007 Coh- referent BMI 20-25][61] O: 1.44 (1.28 – 1.62), obese: 2.14 (1.85 – 2.47) [Sebire 2001 Obs-	O: 0.80 (0.76-0.84),obese: 0.79 (0.73-0.86) [Sebire 2001 Obs- referent BMI 20-25] O: 1.0 (0.5–2.0), obese: 2.8 (1.4–5.6) [Rode 2005 Coh- referent BMI <25][80] <u>SGA:</u> U: RR 1.67 (95% CI:1.07–2.61) [Liu 2011 Coh] O: 0.6 (0.5–0.6) [Cnattingius 1998 Coh- referent BMI < = 19][85] U: 1.9 (1.7-2.1), O: 0.7 (0.6-0.8) [Nohr 2008 Coh][34] U: 1.4 (1.2–1.7) [Watanabe 2010 Obs][35] BMI 29-35: aOR 0.98 (0.93-1.04). Increasing odds with increasing BMI [Cedergren 2004 Coh- referent BMI 19.8-26][60] U: aOR 1.95 (1.52–2.50, p<0.001) BMI>23 (overweight for Asian population): 0.95 (0.60–1.52) [Ota 2011 Coh][2] U: 1.32 (0.94–1.86), O: 0.77 (0.54–1.10) [Gilboa 2008 Obs][32] O: OR 1.0 (0.6-1.5) similar for obese [Jensen 2003 Coh][59] <u>Macrosomia:</u> U: 0.43 (0.28–0.68), O: 1.66 (1.23–2.24) [Abenhaim 2007 Coh][22] U: 0.662 (0.310–1.414), O: 1.965 (0.954–4.050) [Driul 2008	

Table 5.2.1: Summary impact estimates for maternal pre pregnancy weight			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
	referent BMI 20-25][62] O: 1.7 (1.2–2.4) [Rode 2005 Coh- referent BMI <25][80] <99 lbs: 0.6 (0.5-0.8), 150-199 lbs: 1.6 (1.5-1.7) [Rosenberg 2003 Obs- referent weight 100-149 lbs][84] GDM: O: RR 2.49 (95% CI: 1.82–3.39) [Liu 2011 Coh] U: 0.82 (0.69–0.97), O: 1.89 (1.63–2.19) [Abenhaim 2007][22] U: 9/259 versus normal weight 229/6091, O: 171/3634 [Chu 2008 Obs][39] U: 1.05 (0.12-9.46), O: 7.94 (2.09-30.18) [Murakami 2005 Obs][27] U: 0.6 (0.3-1.2), O: 2.5 (2.1-3.0) [Nohr 2008 Coh][34] O: aOR 1.78 (1.25–2.52) [Callaway 2006 Obs- referent BMI 20-25][58] U: 0.22 (0.05–0.92), BMI 24-27.9: 2.32 (1.35–3.97) [Chen 2010 Coh- referent BMI 18.5-23.9][31] U: aOR 0.82 (0.25–2.74)O: 2.71 (1.32–5.55) [Doherty 2006 Coh][4] O: 1.68 (1.53 – 1.84)obese: 3.6 (3.25 – 3.98) [Sebire 2001 Obs- referent BMI 20-25][62] O: 3.4 (1.7–6.8) [Rode 2005 Coh- referent BMI <25][80] <99 lbs: 0.6 (0.5-0.7), 150-199 lbs: 2.1 (2.0, 2.2) [Rosenberg 2003 Obs- referent weight 100-149 lbs][84]	Coh][24] U: aRR 0.55 (0.38–0.79), O: aRR 1.15 (0.84–1.57) [Frederick 2008 Coh][71] BMI 29-35: aOR 2.15 (2.08-2.23) [Cedergren 2004 Coh- referent BMI 19.8-26][60] U:0.48 (0.30–0.77), BMI 24-27.9: 1.27 (0.87–1.86) , BMI 28: 1.21 (0.61–2.41) [Chen 2010 Coh- referent BMI 18.5-23.9][31] O: 1.77 (0.88–3.55) [Gilboa 2008 Obs][32] U: 0.41 [0.05, 3.23], O: 2.03 [0.55, 7.46] Han 2010 CS- referent BMI 18.5-22.9 for Asian population][33] O: 1.4 (1.0-1.9) [Jensen 2003 Coh][59] Obese: 2.1 (1.6– 2.6) [Kiran 2005 Obs- referent BMI 20-30][87] BMI>25: 1.68 (1.58-1.79) [LaCoursiere 2005 Obs][44] BMI>27: OR 7.59 (1.98-29.09)[Phithakwatchara 2007 Coh- referent BMI 20-25] O: 1.57 (1.50-1.64),obese: 2.36 (2.23-2.50) [Sebire 2001 Obs- referent BMI 20-25] O: 1.3 (1.1–1.5) [Rode 2005 Coh- referent BMI <25][80] <99 lbs: 0.3 (0.3-0.4), 150-199 lbs: 2.0 (1.9-2.0) [Rosenberg 2003 Obs- referent weight 100-149 lbs][84]	

Table 5.2.1: Summary impact estimates for maternal pre pregnancy weight			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
	Antenatal admission: U: 0.96 (0.88–1.05), O: 1.15 (1.04–1.26) [Abenhaim 2007 Coh][22] Hospital admission >5 days- O: aOR 1.36 (1.13–1.63) [Callaway 2006 Obs- referent BMI 20-25][58] U: aOR 0.92 (0.70–1.23) O: 1.70 (1.32–2.19) [Doherty 2006 Coh][4] Placental: Abruption- BMI 29-35: aOR 1.00 (0.89-1.12) [Cedergren 2004 Coh- referent BMI 19.8-26][60] O: 0.86 (0.72-1.01),obese: 0.86 (0.68-1.10) [Sebire 2001 Obs- referent BMI 20-25][62] O: RR 1.84 (95% CI: 1.19–2.87) [Liu 2011 Coh] Previa- BMI 29-35: aOR 0.87 (0.73-1.02)Decreasing trend with increasing BMI [Cedergren 2004 Coh- referent BMI 19.8-26][60] O: 0.88 (0.72-1.08), obese: 0.81 (0.60-1.10)[Sebire 2001 Obs- referent BMI 20-25][62] Preterm birth: U: 1.14 (1.00–1.30), O: 1.20 (1.04–1.38) [Abenhaim 2007 Coh][22] U: aHR 1.03 (0.72-1.47), O: aHR 0.89 (0.63-1.26), for change in BMI between pregnancies <25th percentile 1.17 (0.90-1.53) and >75th percentile 1.08 (0.83-1.41) [Chen 2009 Coh][23] O: 0.8 (0.7–0.9) [Cnattingius 1998 Coh- referent BMI < = 19][85] U: 1.474 (0.896–2.424), O: 2.433 (1.358–4.359) [Driul 2008 Coh][24] U: 1.4 (1.32–1.50), O: 0.9 (0.85–0.92) [Johnson 2009 Obs][25]	LGA: O: RR 1.46 (95% CI: 1.02–2.08) [Liu 2011 Coh] U: 3.8% of 10,843 women versus 8.7% of 84,807 women with normal BMI. O: 13% of 29,047 women [Getahun 2007 Coh][98] U: 0.5 (0.4-0.5), O: 1.7 (1.6-1.8) [Nohr 2008 Coh][34] BMI 29-35: aOR 2.20 (2.14-2.26) [Cedergren 2004 Coh- referent BMI 19.8-26][60] U: aOR 0.51 (0.35-0.74, p<0.001) BMI>23 (overweight for Asian population):2.04 (1.43–2.91, p<0.001) [Ota 2011 Coh][2] O: 1.33 (0.95–1.86) [Gilboa 2008 Obs][32] O: 1.1 (0.8-1.5) [Jensen 2003 Coh][59] Pre-pregnancy overweight and obesity were associated with higher WAZ (linear regression coefficient [β], 0.32; 95% CI, 0.04-0.61) and WLZ (β, 0.39; 95% CI, 0.02-0.76), respectively [Deierlein 2011 Coh] [Congenital anomalies as quoted in Watkins 2003[99] and Nuthalapaty 2004] CHDs: U: 0.96 (0.80–1.16), O: 1.16 (1.05–1.29) [Gilboa 2010 CC][49] U: 0.74 (0.40-1.36), O: 0.79 (0.45-1.41) [Oddy 2009 CC][50] U: 1.12 (0.93-1.36), O: 1.13 (1.01-1.26) [Waller 2007 CC][51]	

Table 5.2.1: Summary impact estimates for maternal pre pregnancy weight			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
	U: 2.11 (1.03–4.32), O: 1.07 (0.76–1.51), Obese: 1.31 (0.86–2.00) [Kosa 2010 CC][26] U: 1.55 (0.58-4.15), O: 1.10 (0.33-3.65) [Murakami 2005 Obs][27] U: 0.9 (0.4-2.0) [Ronnenberg 2003 Coh][28] U: 1.41 (1.37–1.45) [Salihu 2009 Obs][29] U: 1.75 (1.13–2.71), O: 0.94 (0.79–1.12), Obese: 1.46 (1.17–1.81) [Wise 2010 Coh][30] O: aOR 1.07 (0.89–1.28) [Callaway 2006 Obs- referent BMI 20-25][58] BMI 29-35: aOR 1.22 (1.14-1.31) [Cedergren 2004 Coh- referent BMI 19.8-26][60] U: 0.85 (0.51–1.40), BMI 24-27.9: 1.57 (1.06–2.34), BMI 28: 1.45 (0.78–2.70) [Chen 2010 Coh- referent BMI 18.5-23.9][31] Pregnancies conceived in September to November were significantly shorter than those from better-fed months (gestational age at birth 38.6 vs 39.0 weeks, p< .0001). MUAC: 1.2 Height: 1.2 Weight: 1.4 BMI: 1.3 [WHO 1995 MA][1] U: OR 1.44 (0.92–2.26) [Gilboa 2008 Obs][32] U: 0.94 [0.57, 1.55], O:1.65 [1.04, 2.62] [Han 2010 CS- referent BMI 18.5-22.9 for Asian population][33]	U: 0.97 (0.81–1.17),O: 1.37 (0.92–2.03) [Watkins 2001 CC- referent BMI 19.9-22.7][100] BMI> 27: 6.5 (1.2-34.9, p=0.025) [Mikhail 2002 CC- referent BMI <27][101] BMI<19.8: 0.92 (0.84-1.00), O: 1.03 (0.96-1.11), Obese: 1.18 (1.09-1.27) [Cedergren 2003 CC- referent BMI 19.8-26][102] U: 1.7 (0.9–3.1), O: 2.0 (1.2–3.1) [Watkins 2003 CC][99] BMI>30: 0.8 (0.3–1.9) [Queisser-Luft 1998 CC- referent BMI <30][103] U: 1.00 (0.91-1.10), O: 1.00 (0.94-1.06), obese: 1.15 (1.07-1.23)[Mills 2010 CC] Conotruncal- U: 1.04 (0.75–1.44), O: 1.09 (0.91–1.31) [Gilboa 2010 CC][49] U: 1.06 (0.43-2.61), O: 0.69 (0.25-1.90), Obese: 2.59 (0.94-7.11) [Oddy 2009 CC][50] BMI>29: 1.0 (0.6-1.8)[Shaw 2000 CC- referent BMI<29][104] U: 1.09 (0.85-1.40), O: 1.08 (0.91-1.28), obese: 1.17 (0.97-1.41)[Mills 2010 CC] Left ventricular outflow defects- U: 0.92 (0.62–1.37), BMI> 25: 1.15 (0.97–1.37) [Gilboa 2010 CC][49] U: 1.09 (0.82-1.43), O: 1.15 (0.96-1.38), obese: 1.51 (1.25-1.82)[Mills 2010 CC] U: 1.2 (0.3–4.5), O: 3.3 (1.6–6.7), obese: 1.2 (0.4–3.9) [Watkins 2003 CC][99] Right ventricular outflow defects- U: 0.68 (0.43–1.07),	

Table 5.2.1: Summary impact estimates for maternal pre pregnancy weight			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
	O: OR 1.0 (0.6-1.9), obese: 1.6 (0.9-2.9)[Jensen 2003 Coh][59] BMI>25: 0.98 (0.92-1.04) [LaCoursiere 2005 Obs][44] BMI>27: OR 0.89 (0.46-1.71)[Phithakwatchara 2007 Coh- referent BMI 20-25][61] O: 0.82 (0.78-0.86),obese: 0.93 (0.87-1.00) [Sebire 2001 Obs- referent BMI 20-25][62] aOR=2.12 (1.20-3.74) [Hacini Afroukh 2008 CC][86] <u>IUGR:</u> U: 1.1 (0.5-2.2) [Ronnenberg 2003 Coh][28] MUAC: 1.6 Height: 1.9 Weight: 2.5 BMI: 1.8 [WHO 1995 MA][1] U: aOR 1.80 (1.26–2.56) O: 0.88 (0.57–1.36) [Doherty 2006 Coh][4] <u>Induction of labour:</u> U: 0.86 (0.79–0.94), O: 1.21 (1.10–1.32) [Abenhaim 2007 Coh][22] BMI 29-35: aOR 1.77 (1.73-1.81) [Cedergren 2004 Coh- referent BMI 19.8-26][60] U: aOR 0.77 (0.59–1.01) O: 1.36 (1.05–1.77) [Doherty 2006 Coh][4] O: 1.5 (1.1-2.2) [Jensen 2003 Coh][59] Obese: 1.6 (1.3– 1.9) [Kiran 2005 Obs- referent BMI 20-30][87]	BMI> 25: 1.34 (1.13–1.60) [Gilboa 2010 CC][49] U: 0.98 (0.76-1.26), O: 1.16 (0.99-1.36), obese: 1.30 (1.10-1.55)[Mills 2010 CC] U: 2.4 (0.7–7.9), O: 1.5 (0.5–4.3) [Watkins 2003 CC][99] Septal defects- U: 1.03 (0.80–1.31), BMI> 25: 1.15 (1.02–1.30) [Gilboa 2010 CC][49] U: 0.99 (0.89-1.12), O: 0.96 (0.89-1.04), obese: 1.08 (0.99-1.17)[Mills 2010 CC] U: 1.8 (0.7–4.6), O: 1.7 (0.8–3.6), obese: 2.2 (1.0–4.9) [Watkins 2003 CC][99] <u>NTDs:</u> U: 1.00 (0.62–1.62), O: 0.56 (0.41–0.76), Obese: 0.65 (0.29–1.49) [Li 2010 CC][52] U: 0.60 (0.17-2.12), O: 0.65 (0.21-2.01) [Oddy 2009 CC][50] Anencephaly- U: 0.82 (0.42-1.59), O: 0.94 (0.65-1.36) Spina bifida- U:0.91 (0.56-1.46), O: 1.03 (0.78-1.34) [Waller 2007 CC] BMI> 27: 0.6 (0.2 to 1.9)[Mikhail 2002 CC- referent BMI <27][101] U: 1.1 (0.3–3.8), O: 1.4 (0.6–3.3) [Watkins 2003 CC][99] BMI>30: 1.40 (0.80-2.47) [Hendricks 2001 CC- referent BMI <30][105] BMI>28: PR 0.74 (0.23-2.37) [Moore 2000 Coh- referent BMI <28][106] BMI>29: 1.9 (1.3–2.9) [Shaw 2000 CC- referent BMI<29][104]	

Table 5.2.1: Summary impact estimates for maternal pre pregnancy weight			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
	O: 2.14 (1.85 – 2.47)obese: 1.70 (1.64 – 1.76) [Sebire 2001 Obs- referent BMI 20-25][62] Weight 90-120 kg: aOR 1.94, (1.86–2.04) [Robinson 2005 Coh- referent weight 55-70 kg][79] <u>Shoulder dystocia:</u> U: 0.88 (0.80–0.96), O: 1.50 (1.37–1.65) [Abenhaim 2007 Coh][22] BMI 29-35: aOR 2.14 (1.83-2.49) [Cedergren 2004 Coh- referent BMI 19.8-26][60] O: OR 1.1 (0.5-2.5), obese: 0.9 (0.4-2.2) [Jensen 2003 Coh][59] Obese: 2.9 (1.4– 5.8) [Kiran 2005 Obs- referent BMI 20-30][87] BMI>25: 1.92 (1.82-2.03) [LaCoursiere 2005 Obs][44] <u>CPD:</u> BMI>27: OR 2.15 (1.35-3.42)[Phithakwatchara 2007 Coh- referent BMI 20-25][61] <u>Instrumental delivery:</u> U: 1.04 (0.93–1.17), O: 0.95 (0.82–1.10) [Abenhaim 2007 Coh][22] U: 1.2 (1.1-1.4), O: 1.2 (1.1-1.2) [Nohr 2008 Coh][34] BMI 29-35: aOR1.16 (1.12-1.21) [Cedergren 2004 Coh- referent BMI 19.8-26][60] Assited delivery: MUAC: 0.8 Height: 1.6 Weight: 1.0	BMI>29: 1.8 (1.1-3.0) [Shaw 2000 CC- referent BMI<29][104] BMI>26: 1.35 (1.00-1.83)[Kallen 1998 Coh- referent BMI <26][107] BMI>29: 2.0 (1.0-4.0) [Werler 1996 CC- referent BMI 19-23.9][108] BMI>29: 1.92 (1.08-3.40)[Watkins 1996 CC- referent BMI 19.8-26][109] BMI>29: 1.9 (1.3-2.9) [Shaw 1996 CC- referent BMI <29][110] BMI>31: 1.8 (1.1-3.0)[Waller 1994 CC- referent BMI 19-27][111] Obese: 2.6 (1.7–4.0) [Anderson 2005 CC][112] <u>Orofacial defects:</u> U: 1.07 (0.46-2.51), O: 1.55 (0.73-3.30) [Oddy 2009 CC][50] CL/P- U: 1.35 (1.04-1.76), O: 0.97 (0.81-1.15) and CPO- U: 0.92 (0.62-1.36), O: 1.03 (0.82-1.28) [Waller 2007 CC][51] CL/P- BMI>29: 1.0 (0.6-1.6) and CPO- BMI>29: 1.1 (0.6-2.0) [Shaw 2000 CC- referent BMI<29][104] U: 0.7 (0.3–1.8), O: 1.2 (0.6–2.2), Obese: 0.8 (0.4–1.8) [Watkins 2003 CC][99] BMI>28: PR 3.69 (1.19-11.44) [Moore 2000 Coh- referent BMI <28][106] BMI>30: 2.8 (1.0-8.9) [Queisser-Luft 1998 CC- referent BMI	

Table 5.2.1: Summary impact estimates for maternal pre pregnancy weight			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
	BMI: 0.7 [WHO 1995 MA][1] Obese: 1.6 (1.4– 2) [Kiran 2005 Obs- referent BMI 20-30][87] O: 1.04 (1.00-1.08)obese: 0.95 (0.90-1.00) [Sebire 2001 Obs- referent BMI 20-25][62] <u>Perineal tears:</u> O: RR 2.89 (95% CI: 1.44–5.81) [Liu 2011 Coh] U: 1.07 (0.94–1.22), O: 1.03 (0.87–1.21) [Abenhaim 2007 Coh][22] BMI 29-35: aOR 1.01 (0.95-1.07) [Cedergren 2004 Coh- referent BMI 19.8-26][60] U: aOR 0.70 (0.49–0.99) O: 1.24 (0.90–1.70) [Doherty 2006 Coh][4] <u>C-section:</u> O: RR 1.47 (95% CI: 1.27–1.70) [Liu 2011 Coh] U:0.89 (0.81–0.97), O: 1.48 (1.35–1.62) [Abenhaim 2007 Coh][22] O: 1.88 (1.65–2.14) [Barau 2006 Obs][65] U: 53/259 versus normal weight 1295/6091, O: 983/3634 [Chu 2008 Obs][39] U: aRR 0.7 (0.5–1.0), O: aRR 1.4 (1.0–1.8) [Dietz 2005 Obs][42] U: 0.953 (0.679–1.338), O: 1.169 (0.747–1.831) [Driul 2008 Coh][24] U: 1.03 (0.95-1.11), O: 1.16 (1.10-1.23) [Getahun 2007 Coh][43] U: 0.67 (0.28-1.60), O: 2.42 (1.05-5.58) [Murakami 2005 Obs][27]	<30][103] <u>Urinary tract defects:</u> U: 0.86 (0.44-1.68), O: 0.96 (0.52-1.78) [Oddy 2009 CC][50] U: 0.9 (0.4–2.0), O: 0.8 (0.5–1.5) [Watkins 2003 CC][99] BMI>30: 1.7 (1.1-2.8) [Queisser-Luft 1998 CC- referent BMI <30][103] <u>Limb reduction defects:</u> U: 1.44 (0.41-5.00), O: 1.61 (0.50-5.13) [Oddy 2009 CC][50] U: 1.08 (0.73-1.61), O: 1.22 (0.97-1.54) [Waller 2007 CC][51] U: 1.1 (0.4–3.3), O: 1.1 (0.5–2.5) , Obese: 0.8 (0.3–2.5) [Watkins 2003 CC][99] BMI>29: 0.8 (0.4-1.6)[Shaw 2000 CC- referent BMI<29][104] <u>Congenital Diaphragmatic hernia:</u> U: 2.0 (0.89–4.5),O: 1.1 (0.46–2.7) [Waller 2003 CC][53] U: 0.85 (0.49-1.47), O: 0.91 (0.66-1.26) [Waller 2007 CC][51] U:1.4 (0.3–6.8), O: 1.1 (0.3–3.9) [Watkins 2003 CC][99] BMI>31: 2.6 (0.3-20.7) [Waller 1994 CC- referent BMI 19-27][111] <u>Multiple congenital anomalies:</u> U: 1.3 (0.6–3.1), O: 1.9 (1.1–3.4) [Watkins 2003 CC][99] BMI>29: 3.2 (1.4-7.8) [Shaw 2002 CC- referent BMI<29][113]	

Table 5.2.1: Summary impact estimates for maternal pre pregnancy weight			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
	O: aOR 1.50 (1.36–1.66) [Callaway 2006 Obs- referent BMI 20-25][58] BMI 29-35: aOR1.76 (1.72-1.80) [Cedergren 2004 Coh- referent BMI 19.8-26][60] BMI>29: aOR 1.66 (1.51-1.82) [Crane 1997 Obs- referent BMI<29][88] U: aOR 0.81 (0.58–1.14) O: 1.39 (1.04–1.86) [Doherty 2006 Coh][4] O: 1.6 (1.2-2.3) [Jensen 2003 Coh][59] O: 1.56 [0.86, 2.82], BMI>29: 1.94 [1.25, 3.03] [Kaiser 2001 Obs- referent BMI 19.8-26][66] Obese: 2.0 (1.2– 3.5) [Kiran 2005 Obs- referent BMI 20-30][87] U:0.81 (0.76-0.86) , O: 1.55 (1.48-1.63) [LaCoursiere 2005 Obs][44] BMI<20: 15/180, O: 44/194 versus control 84/540 [Young 2002 Obs- referent BMI 20-25- unclear if true prepregnancy BMI taken][89] BMI>27: OR 2.22 (1.45-3.49)[Phithakwatchara 2007 Coh- referent BMI 20-25][61] O: aRR 1.2 (0.8-1.8), Obese: 1.5 (1.05-2.0)[Vahratian 2005 Coh- referent BMI 19.8-26][67] Weight 90-120 kg: aOR 1.60, (1.53–1.67) [Robinson 2005 Coh- referent weight 55-70 kg][79] O: 1.5 (1.3–1.8) [Rode 2005 Coh- referent BMI <25][80]	BMI>31: 2.2 (0.3-17.7) [Waller 1994 CC- referent BMI 19-27][111] <u>Major malformations:</u> BMI>30: PR 1.24 (1.09-1.40) [Naeye 1990 Coh- referent BMI 20-24][114] BMI>30: 1.3 (1.0-1.7) [Queisser-Luft 1998 CC- referent BMI <30][103] BMI>28: PR 0.95 (0.62-1.5) [Moore 2000 Coh- referent BMI <28][106] <u>Vitamin D deficiency:</u> aOR=1.5 (95% CI 1.1-1.9) for prepregnancy BMI 28 versus BMI 22 <u>Hypoglycemia:</u> O: aOR 0.78 (0.36–1.66), Obese: 2.57 (1.39–4.78) [Callaway 2006 Obs- referent BMI 20-25][58] U: aOR 0.56 (0.33–0.96) O: 1.06 (0.69–1.63) [Doherty 2006 Coh][4] O: OR 1.2 (0.6-2.1), obese: 0.9 (0.5-1.8) [Jensen 2003 Coh][59] <u>Jaundice:</u> O: aOR 1.02 (0.92–1.12) [Callaway 2006 Obs- referent BMI 20-25][58] O: OR 1.0 (0.6-1.8) [Jensen 2003 Coh][59] BMI>27: OR 0.94 (0.50-1.80)[Phithakwatchara 2007 Coh- referent BMI 20-25]	

Table 5.2.1: Summary impact estimates for maternal pre pregnancy weight			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
	<99 lbs: 0.9 (0.9-1.0), 150-199 lbs: 1.4 (1.3-1.4) [Rosenberg 2003 Obs- referent weight 100-149 lbs][84] Stillbirths: U: 2/259 versus normal weight 34/6091, O: 22/3634 [Chu 2008 Obs][39] O: 1.3 (0.9–1.8) [Cnattingius 1998 Coh- referent BMI < = 19][85] U: 1.3 (0.7–2.6), O: 1.2 (0.6–2.2), Obese: 3.1 (1.6–5.9) [Kristensen 2005 Coh][40] O: aOR 1.16 (0.62–2.17) [Callaway 2006 Obs- referent BMI 20-25][58] BMI 29-35: aOR 1.79 (1.59-2.01) [Cedergren 2004 Coh- referent BMI 19.8-26][60] O: 1.10 (0.94-1.28),obese: 1.40 (1.14-1.71) [Sebire 2001 Obs- referent BMI 20-25][62] U: aOR 0.8 (0.3–2.2), O: 2.0 (1.4–2.9). Similar in pregnancies without obesity-related disease. Fetal death- U: aHR 1.0 (0.2–4.0), O: 1.7 0.9–3.0 [Nohr 2005 Coh][41] O: aOR 1.9 (1.2-2.9) [Stephansson 2001CC- referent BMI <19.9][90] O: aOR=1.71 (1.03-2.84) [Hacini Afroukh 2008 CC][86] PPH: O: RR 2.31 (95% CI: 1.51–3.54) [Liu 2011 Coh] U: 0.93 (0.46–1.14), O: 1.26 (1.03–1.55) [Abenhaim 2007 Coh][22]	Breastfeeding: Obese women were less likely to initiate breast-feeding and fed for ~2 wks less on average, than were women with a normal BMI before pregnancy who also gained the recommended weight during pregnancy. [Li 2003 Obs- referent BMI 19.8-26][7] O: 0.86 (0.84 – 0.88),obese: 0.58 (0.56 – 0.60) [Sebire 2001 Obs- referent BMI 20-25]	

Table 5.2.1: Summary impact estimates for maternal pre pregnancy weight			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
	BMI 29-35: aOR 1.19 (1.15-1.23) [Cedergren 2004 Coh- referent BMI 19.8-26][60] MUAC: 0.6 Height: 0.7 Weight: 0.6 BMI: 0.8 [WHO 1995 MA][1] U: aOR 0.79 (0.57–1.11) O: 1.55 (1.17–2.06) [Doherty 2006 Coh][4] Obese: 1.5 (1.2– 1.8) [Kiran 2005 Obs- referent BMI 20-30][87] O: 1.16 (1.12 – 1.21)obese: 1.39 (1.32 – 1.46) [Sebire 2001 Obs- referent BMI 20-25][62] <u>Post-term delivery:</u> BMI 29-35: aOR 1.37(1.33-1.41) [Cedergren 2004 Coh- referent BMI 19.8-26][60] Obese: 1.4 (1.2– 1.7) [Kiran 2005 Obs- referent BMI 20-30][87] O: 1.21 (0.93-1.58),obese: 1.72 (1.23-2.42) [Sebire 2001 Obs- referent BMI 20-25][62] BMI <19.8: aOR 0.96 (0.86-1.07), O: 1.17 (1.01-1.34) [Stotland 2007 Coh- referent BMI 19.8-26][91] <u>PROM:</u> U: 0.43 (0.17–1.09), BMI 24-27.9: 2.44 (1.43–4.16) [Chen 2010 Coh- referent BMI 18.5-23.9][31] <u>VBAC:</u> O: 2463/3309, obese: 1688/2607 versus control 636/802 [Bujold 2005 Obs- referent BMI<25][92]		

Table 5.2.1: Summary impact estimates for maternal pre pregnancy weight			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
	<200 versus 200 to 300 lbs: OR 3.37 (1.06-10.76). 200 to 300 versus >300 lbs OR 8.67 (2.38-31.55) [Carroll 2003 Coh][93] BMI<19.8: 50/59, O: 75/115, Obese: 89/163 versus control 122/173 [Durnwald 2004 Obs- referent BMI 19.8-24.9][94] O: 152/191, obese: 184/257 versus control 238/277[Goodall 2005- referent BMI<25][95] <u>Twins:</u> U: 0.88 [0.69, 1.12], O: 1.27 [0.99, 1.64] [Reddy 2005 Coh][96] <u>Plasma Zinc in early pregnancy:</u> Mean Zn Z-score (Standard deviation):highest BMI quartile -0·2 (0·9) versus lowest BMI quartile 0·17 (1·0), p for trend<0.0001 [Tamura 2004 CS][97]		

Where there was a stronger effect with increasing BMI, only overweight was quoted; for unexpected trends the category "obese" or any other pertinent BMI category (eg. BMI>25) was quoted. Some studies provided the category "morbidly obese", however this was not quoted since the number of participants was usually small and thus resulted in wide confidence intervals. Note: studies showed that there was an interaction between gestational weight gain and

WHO 1995[1]s and Ota 2011[2] used anthropometric indicators during the first trimester or recalled prepregnancy anthropometric indicators

5.2 Diet and exercise

Background

The world is increasingly facing a double burden of disease- a simultaneous rise in the prevalence of obesity and undernutrition. Soaring food inflation and physical inactivity are concerning for the health of all people, but disproportionately affect mothers and their young children. Fortunately, weight is a modifiable risk factor and evidence supports weight change as an intervention to improve MNCH outcomes. [15, 14, 43,98,23, 118]

Scope of Intervention

Although we have demonstrated that maternal underweight increases the chances of preterm birth (25%), and small-for-gestational age babies (64%), we found a scarcity of evidence for interventions to improve the macro-nutritional status of women before pregnancy. A single **interventional** study demonstrated that a change in the micronutrient-to-energy ratio of food rations in Bhutanese refugee camps, reduced the rate of low birth weight from 16% to 8%, over a period of 2 years.[280]

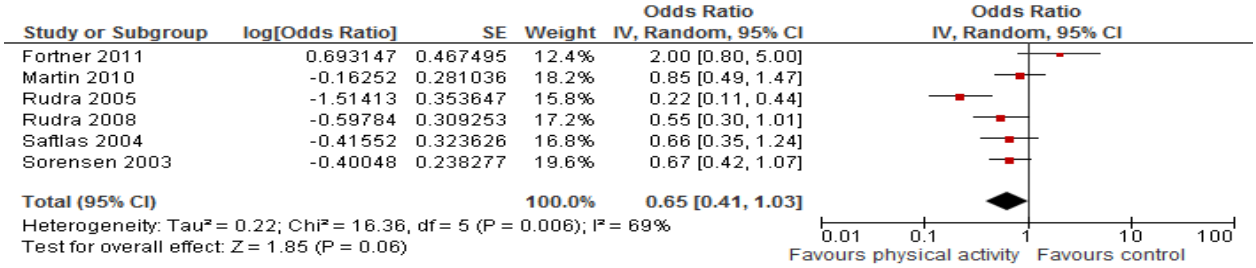
As shown in the previous section, maternal overweight and obesity is a major risk factor for poor maternal and child outcomes. There is some evidence to support exercise as an intervention to decrease the risk of gestational diabetes mellitus, preeclampsia, and maternal weight gain, improve birth weight, and increase the chance of a normal delivery.[119] This review expands upon previous work[120,121] and examines whether diet and/or exercise are effective in reducing weight in women, and if this impacts MNCH outcomes.

Impact estimates

The **interventional** trials assessing weight loss interventions in women all used a control group; however they were carried out in women of different ages, and included different interventions. Women in the intervention group lost an average of up to 3.5kg. Interventions that combined calorie restriction and physical activity, involved a support system and monitoring, and were sustained over longer periods effected more weight change. This is consistent with previous evidence-based reviews that have examined interventions for weight loss[122, 123] and prevention of weight gain[124] in adults. Since weight loss is difficult to achieve and sustain, a more sensible approach might be to screen and intervene in adolescence, however there is a need to expand the body of evidence in this area to determine how weight loss interventions might be adapted to this special population.[64]

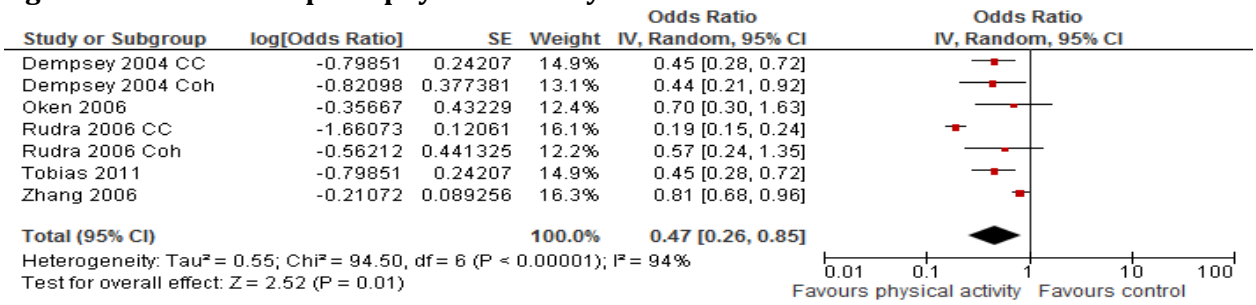
For physical activity before pregnancy, likewise, exposure in **observational** studies was too heterogeneous to be pooled. Overall, there seemed to be a reduced, although insignificant, risk of gestational hypertension, perhaps because the included studies only examined “any” activity versus “none” or “highest” versus “lowest” total activity (**Figure 5.2.1**). The evidence of benefit for physical activity on GDM was more convincing, especially when studies used subgroups based on increased intensity of physical activity or used objective measurements of energy expenditure. Physical activity seemed to have varied effects on risk for congenital defects (**Figure 5.2.2**). From studies of work during pregnancy, it can be inferred that beyond a threshold, increasing intensity of exercise will adversely affect pregnancy outcomes.

Figure 5.2.1: Preconception physical activity and risk of hypertensive disorders of pregnancy



Citations to the included studies
Fortner 2011[125], Martin 2010[126], Rudra 2005[127], Rudra 2008[128], Saftlas 2004[129], Sorensen 2003[130].

Figure 5.2.1: Preconception physical activity and risk of GDM



Citations to the included studies:
Dempsey 2004cc[131], Dempsey 2004[132], Oken 2006[133], Rudra 2006[134], Tobias 2011[135], Zhang 2006[136]

Table 5.2.1: Interventions related to diet and exercise

Intervention	Outcome
Physical activity and dietary counseling, 5 follow-ups, exercise plan, optional group exercise sessions, printed material for participants, notebook log of dietary and exercise compliance [Kinnunen 2007][137]	50% of the intervention group and 30% of the control group returned to their pre-pregnancy weight by 10 months postpartum (p = 0.06). aOR for returning to pre-pregnancy weight was 3.89 (95% CI 1.16–13.04, p = 0.028) for the intervention group compared with control
Group pram-walking or supervised aerobic exercise sessions Individualized diet/exercise plans Printed material or correspondence, including telephone contact Diets were all low-calorie [Adegboye 2008][138]	-Women who exercised did not lose significantly more weight than women in the usual care group (WMD 0.00 kg; 95% CI -8.63 to 8.63). -Women who took part in a diet (WMD -1.70 kg; 95% CI -2.08 to -1.32), or diet plus exercise programme (WMD -2.89 kg; 95% CI -4.83 to -0.95), lost significantly more weight than women in the usual care. -There was no difference in the magnitude of weight loss between diet and diet plus exercise group (WMD 0.30 kg; 95% CI -0.60 to 0.66).
12-session mentorship at **adolescents'** homes focusing on healthy eating and physical activity through motivation [Black 2010][139]	Overweight/obese adolescents in intervention group dropped from 45% to 40% to 39% versus in controls increased from 32% to 34% to 43% No change in physical activity between intervention and control
Individualized informational and self-help material on diet, exercise and weight control for **young women**. Initial in-person contact, followed by regular 1 year contact via phone, email, and occasional group sessions, booster dietitian visits and lectures [Eiben 2006][140]	Women in the intervention group lost weight (-3.2 ±2.0 kg) whereas women in the control group gained weight (2.6 ±1.9 kg), p=0.046 Physical activity score in intervention group was 1464 ±96 versus control group 200 ±383 (p=0.03)

Table 5.2.1: Interventions related to diet and exercise	
Intervention	**Outcome**
Women (not postpartum) received 4 2-hour classes on portion control with low-cost quick foods, incentives for each class [Faucher 2010][141]	Women in the intervention group lost more weight on average (-6.5 ±7.5 lb) versus women in the control group (-2.8 ±10.2 lb)
Weekly, then monthly, meetings for 8 weeks each focusing on weight control, monitoring. Two different interventions were compared- large and small changes- to diet and physical activity [LaRose 2010][142]	LC group had an overall weight loss of 3.5±3.1 kg compared to 1.5±1.8 kg in SC (p=0.006)
Healthy-eating and physical activity group sessions, telephone counseling, study notebook, pedometer, stroller, low-calorie. Intervention over 9 months [Østbye 2009][143]	Mean weight loss was 0.90 kg (±5.1 kg) in the intervention group and 0.36 kg (±4.9 kg) in the control group; this difference was not significant. There were also no significant group differences in improvement of diet or increased physical activity
DVDs and peer group teleconferences to promote healthful eating, physical activity and stress reduction to prevent weight gain (Mothers in Motion) [Chang 2010][144]	Intervention group weighed less than the control group at 2 months (3.19 lbs) and 8 months (0.3 lbs) post intervention, but no significant effect size was detected (-0.26, and -0.03 respectively). At 2 months, physical activity was 7.58 MET greater in intervention and at 8 months 17.18 MET, but no significant effect size (0.25 and 0.57 respectively)
In-person, online or mixed intervention including low-calorie, low-fat diet, exercise and journal [Harvey-Berino 2010][145]	Mean weight loss in kg (SD) for online intervention −5.5(5.6), for in person −8.0(6.1) and for mixed intervention −6.0 (5.5), p<0.01 Mean physical activity in k Cal/week post-intervention for online 1877.5, for in person 1930.4, for mixed 1613.1, p= 0.49
Home-based exercise program (both intervention and control received initial counseling for slight caloric restriction) [Mediano 2010][146]	Mean weight loss: −1.1 kg intervention versus −1.0 control, p=0.20
Weekly in person or telephone counseling and prepackaged food (low calorie, low fat) versus usual care (montly counseling by dietitian regarding healthy eating and exercise) [Rock 2010][147]	Mean weight change for in person −8.2 (95% CI −9.5 to −6.8), for telephone-based −6.7 (95% CI −8.2 to −5.2), for usual care −2.1 (95% CI −3.6 to −0.7)
Interactive group sessions for mothers with young children, messages and handouts on healthy eating, physical activity and behavior change. Pedometer provided. Once a month, support via email, text message or phone call. Aim to prevent weight gain, not promote weight loss[Lombard 2009]	Mean measured weight decreased significantly in the intervention group (-0.78 kg 95% CI;-1.22 to -0.34, p < 0.001). Using self-reported weight, both the intervention andcomparison groups decreased weight, -0.75 kg (95% CI; -1.57 to 0.07, p = 0.07) and -0.72 kg (95% CI; -1.59 to 0.14 p = 0.10) with no significant difference between groups (-0.03 kg, 95%CI; -1.32 to 1.26, p = 0.95). More women lost or maintained weight in the intervention group. Theintervention group tended to have the greatest effect in those who were overweight at baselineand in those who weighed themselves regularly.

Conclusion

There is a strong need for evidence to demonstrate the effectiveness of interventions to achieve optimal prepregnancy weight, especially for those women who areunderweight. This review confirms earlier evidence[148] that promoting improvement in diet and exercise through sustained, daily changes, with the help of a support system results in weight loss and higher levels of physical activity. Although preceding work[149] illustrates examples of population-scale interventions, more research is needed to support how small-scale initiatives targeted at women with childbearing potential can be

Table 5.2.2: Summary impact estimates for maternal work or physical activity			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
Postpartum depression: aOR 0.80 (0.63-1.02) for feeling depressed and 0.67 (0.53-0.86, significant) for lack of interest in women who exercised 3 months preconception [Ersek 2009 Obs][150]	[quoted in Gavard 2008 SR][119] Hypertensive disorders of pregnancy: aOR 2.0 (0.8–4.8) for highest versus lowest total physical activity, aOR 2.1 (0.7–6.2) for preeclampsia with highest versus lowest total physical activity in the year before pregnancy [Fortner 2011 Coh][125] aOR 0.85 (0.49–1.46) for >5d/wk physical activity in the 3 months preconception [Martin 2010 Obs][126] Preeclampsia- aOR 0.55 (0.30–1.02) for any activity, for >7h/wk versus none aOR 0.63 (0.31–1.26), for high energy expenditure aOR 0.60 (0.30–1.20), for perceived exertion 0.63 (0.38–1.06) [Rudra 2008 Coh][128] Any vs. none aOR 0.67 (0.42-1.08) for physical activity in year before pregnancy. Vigorous vs. none aOR 0.40 (0.23-0.69) [Sorensen 2003 CC][130] aOR 0.66 (0.35-1.22) for leisure time physical activity in the year before pregnancy. aOR 0.71 (0.37-1.36) for women with non-sedentary work versus those with sedentary work [Saftlas 2004 CC][129] aOR 0.22 (0.11-0.44) for maximal versus minimal perceived physical exertion in the year before pregnancy [Rudra 2005 CC][127] GDM: aOR 0.70 (0.30–1.68) for >=14h/wk physical activity versus less than 2h/wk in year before pregnancy [Oken 2006 Coh][133] aOR 0.19 (0.15–0.50) for maximum versus minimum perceived exertion, aOR 0.49 (0.28–0.87) for actual energy expenditure during physical activity in the year before pregnancy. Effect greater for perceived physical exertion and for BMI>25 [Rudra 2006 CC][134] aOR 0.57 (0.24–1.37) for maximum versus minimum perceived exertion, aOR 0.14 (0.05–0.38) for actual energy expenditure during physical	NTDs: Prevalence OR: 0.67 (0.27–1.65) for women not employed, but began taking multivitamins 3 months preconception. No effect if not taking multivitamins. Effect similar for first trimester use of multivitamins For each 5-unit change in the physical activity index, POR 0.72 (0.56–0.94). Effect nullified for any periconceptional intake of multivitamins[Carmichael 2002 CC][151] Orofacial clefts: OR 1.75 (1.07-2.88) for mothers in an occupation that requires standing >75% (compared to mixed activity). No significant effect on NTDs [Lin 1998 CC][152]	

Table 5.2.2: Summary impact estimates for maternal work or physical activity			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
	activity in the year before pregnancy. [Rudra 2006 Coh][134] Any vs. none aOR 0.45 (0.28-0.74). Vigorous vs. none 0.29 (0.16-0.51) for physical activity in the year before pregnancy [Dempsey 2004 CC][131] aRR=0.44 (95% CI 0.21-0.91) for physical activity in the year before pregnancy. Effect greater for higher frequency aRR 0.24 (0.10-0.64) and greater exertion aRR 0.26 (0.10-0.65) [Dempsey 2004 Coh][132] Highest vs. lowest quintile aRR 0.81 (0.68-1.01)for total physical activity prepregnancy. Highest vs. lowest quintile aRR 0.77 (0.69-0.94) for vigorous activity. Effect greater for brisk walking and stair climbing. [Zhang 2006 Coh][136] For women in the highest physical activity quantiles compared with those in the lowest pooled OR =0.45 (95% CI 0.28–0.75, p=0.002). Walking with increased intensity and duration had pooled OR= 0.59 (95% CI 0.30 – 0.87). Stair climbing pooled OR=0.49 (95% CI 0.26–0.72). Vigorous activity pooled OR= 0.47 (95% CI 0.19–0.75) [Tobias 2011 MA][135]		

implemented on a wider scale, or to reassess previous clinical trials for outcomes in women only as a subgroup.

Physical activity without the goal of weight loss or maintenance is also important for the health of women themselves. While more study is needed to establish what the type of exercise and goals should be in this population, research has demonstrated that counseling by physicians is not sufficient to encourage greater physical activity[153]

Stronger evidence is also needed to analyse effect sizes of preconception physical activity on MNCH outcomes.

Key messages

- Evidence for the effect of physical activity or nutritional supplements (such as balanced energy protein) on MNCH outcomes is limited .
- With the burgeoning obesity epidemic, a disproportionate amount of maternal and neonatal morbidity could be reduced if overweight women optimized their BMI status before pregnancy.
- Diet and exercise and diet (calorie-restricted) alone are successful interventions for weight loss (average 3 kg) in women (including postpartum). Interventions are more effective when they are more intensified and women must make bigger behavioural changes, and when they have a support group. Programs also have a greater impact if they include regular monitoring of compliance with the intervention and of how much weight loss has occurred. A major issue with such programs however is that initial weight loss is not sustained.

5.3. Vitamin and mineral supplements

The role of nutrition in promoting health is well defined. What women eat determines more than just their own health, it is also vital to healthy pregnancies and newborns, and in fact research now shows that nutritional status in early childhood affects health throughout life. Pregnancy, or planning for pregnancy, provides an impetus for women to change non-healthful behaviours. Many women are still unaware of how much their nutritional status impacts their pregnancy outcomes, and improving women's eating behaviors should therefore begin during their earlier reproductive years.

Preconception care- micronutrients

- In addition to calculating BMI and optimizing prepregnancy weight, providers should assess women's dietary habits and discuss the importance of micronutrients as part of routine preconception counseling. Other relevant points in the medical history should also be inquired about, such as sun exposure (vitamin D)
- If necessary, perform laboratory testing to establish a nutritional deficiency such as anemia
- Help women develop individualized dietary plans including consumption of a variety of healthy foods in appropriate amounts, and dietary supplements (especially a multivitamin containing at 400 μg of folic acid, Calcium and vitamin D, and Iron)
- Providers should ask about previous pregnancy outcomes, since women who have previously given birth to an infant with a NTD require higher levels of folic acid supplementation (800 μg)
- Women of reproductive age with iodine deficiency should be counseled on the risks of this condition to pregnancy outcomes and the importance of maintaining adequate daily dietary iodine intake of 150 μg during preconception and at least 200 μg when pregnant or lactating. All women of reproductive age should consume iodized salt in areas of deficiency
- Women should be advised against consuming excess vitamin A (maximum upper intake level in pregnancy 10,000 IU/day).

- Women should be advised to refrain from eating certain kinds of fish (danger of high mercury levels), and soft cheeses (listeriosis). Other fish and cheese should be consumed in appropriate quantities, since they provide essential fatty acids and calcium, respectively.
- Women should thoroughly wash all fruits and vegetables, cook all food properly, and ensure that hands and cooking surfaces/utensils are clean, to prevent the risk of other infections.
- Providers should specifically ask if women are using any other herbal products, folk remedies, weight loss or sport supplements or over-the-counter medications, and counsel them regarding the possible risks to the fetus

5.3.1. Periconceptional folic acid and multivitamin supplementation

Background

Folic acid is a B-vitamin whose bioavailability from dietary sources lags behind that achieved through supplementation, and whose deficiency is associated with congenital abnormalities, especially neural tube defects.[154] Following the pioneering work of Laurence and Smithells in the 1980's, there were concerns that the apparent effect of folic acid on neural tube defects might be the result of differences in socioeconomic and other risk factors among women of reproductive age- a study by Mills in 1989 showed no effect of folic acid or multivitamins. Since then, multiple case-control, cohort and quasi-randomised controlled trials have been carried out that provide a strong evidence base to support the effectiveness of folic acid supplementation in preventing birth defects and their consequent morbidity and mortality. Folic acid supplementation has thus become a primary periconceptional intervention.

Although major health organizations promote the use of folic acid by women of reproductive age through clinical guidelines and recommendations,[155] and the prevalence of folic acid use is reportedly high in the prenatal period, most women do not use folic acid in the periconceptional period, even if they are aware of its benefits .[156] A recent systematic review[157] demonstrated that even in developed countries, only half of all women use folic acid before conception, therefore protective levels cannot be achieved before the critical period of neural tube closure. Reasons for low prevalence of use are confirmed by other studies[158-166] and include low maternal education and socioeconomic status; young maternal age; lack of a partner; and unplanned pregnancy. It is necessary therefore to improve awareness and use of folic acid supplements among all women of reproductive age so that even women with unplanned pregnancies are protected.

Scope of the intervention (Folate and Multivitamin)

There is incontrovertible data to support the routine use of multivitamins by women of reproductive age, to improve their own health as well as their potential mother and child outcomes. Although previous systematic reviews and meta-analyses have analysed the unique role of periconceptional folic acid (versus multivitamins) on MNCH outcomes, they have included only randomised and quasi-randomised trials. In addition, while periconceptional supplementation is in itself an intervention, it would have a greater impact if it were implemented for all women with the potential to become mothers.

Research has proposed that folic acid prevents birth defects through its influence on the methylation pathway[154, 167-169] and that women at risk for recurrence of birth defects require higher levels of folic acid.[170] In spite of this, mass campaigns to promote the use

of folic acid before conception have failed to show a post-intervention prevalence of use greater than 50%.[157, 171] In order to provide all women (including those at risk of recurrence) with an adequate dose of folic acid, public health policy in some countries now mandates that staple foods, such as flour, be fortified with folic acid.

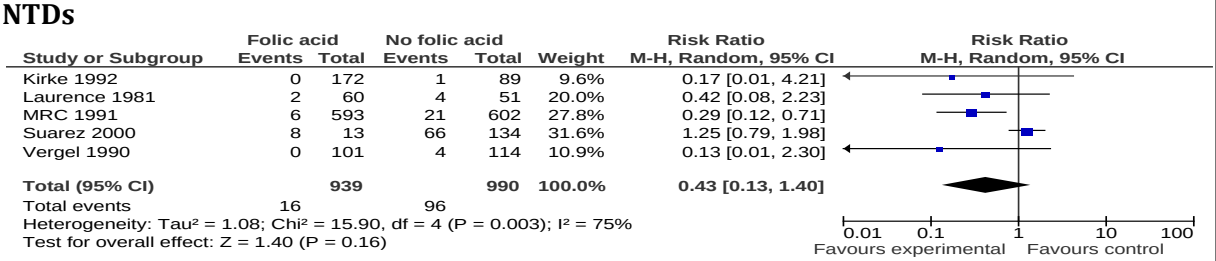
This review re-emphasizes the effect of periconceptional folate-containing multivitamin intake on MCH outcomes. It then presents a separate analysis on the role of folic acid, including papers where the authors have compared folate use alone to multivitamins or trace elements, or where participants were given multivitamins but the authors presented only results on folate. Studies are included irrespective of whether periconceptional intake was through diet, supplementation or fortification. Data are presented for strictly preconceptional use where available, in preference to periconceptional or early first trimester use. Meta-analyses for dietary intake and fortification are presented, although it is noted that such intake persists throughout pregnancy. Most importantly, the review then draws together studies that demonstrate the impact of interventions to increase maternal awareness and use of multivitamins and folic acid, during the crucial periconceptional period.

Impact estimates

Folic acid and multivitamin supplementation

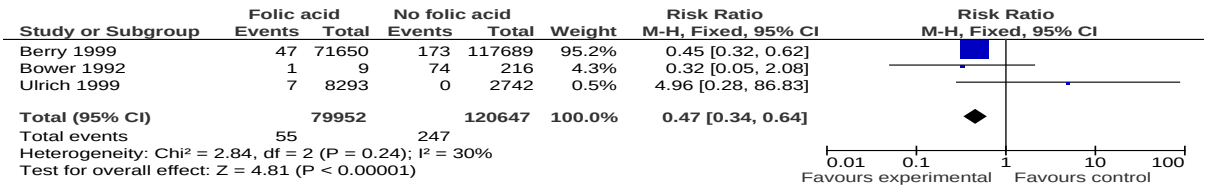
The recent Cochrane review[172] found a strong protective effect (RR 0.28; 95% CI: 0.13-0.58) of folic acid on recurrent neural tube defects. Other meta-analyses of randomized and observational studies showed a reduction in recurrence risk of 69 to 100%[173] and a reduction in occurrence risk of 42[168] to 62%.[174] Our analyses yielded similar results for recurrent NTDs with a RR of 0.31, 95% CI: 0.14-0.66 when it was restricted to randomized double-blind placebo-controlled studies, however this effect was no longer significant when two observational studies were included- RR 0.43, 95% CI: 0.13-1.40 (**Figure 5.3.1**). However, for occurrent NTDs the impact of folic acid supplementation had protective effect (RR 0.47; 95% CI: 0.34-0.61) (**Figure 5.3.2**).

Figure 5.3.1: Periconceptional folic acid supplementation for the prevention of *recurrent* NTDs



Citations to the included studies:
Kirke 1992[175], Laurence 1981[176], MRC 1991[177], Suarez 2000[178], Vergel 1990[179]

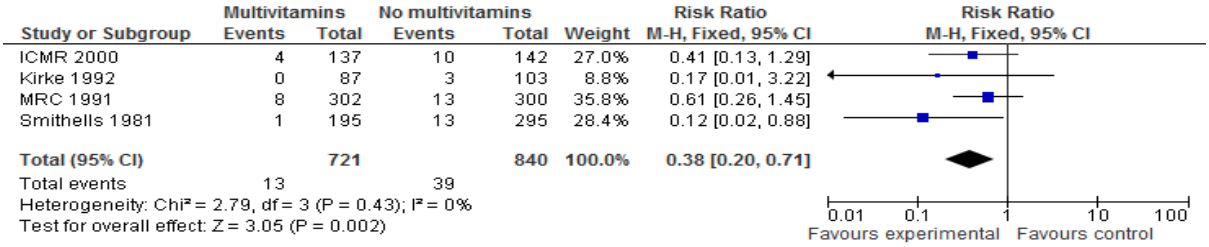
Figure 7.3.2: Periconceptional folic acid supplementation for the prevention of *occurrent* NTDs



Citations to the included studies:
Berry 1999[180], Bower 1992[181], Ulrich 1999[182]

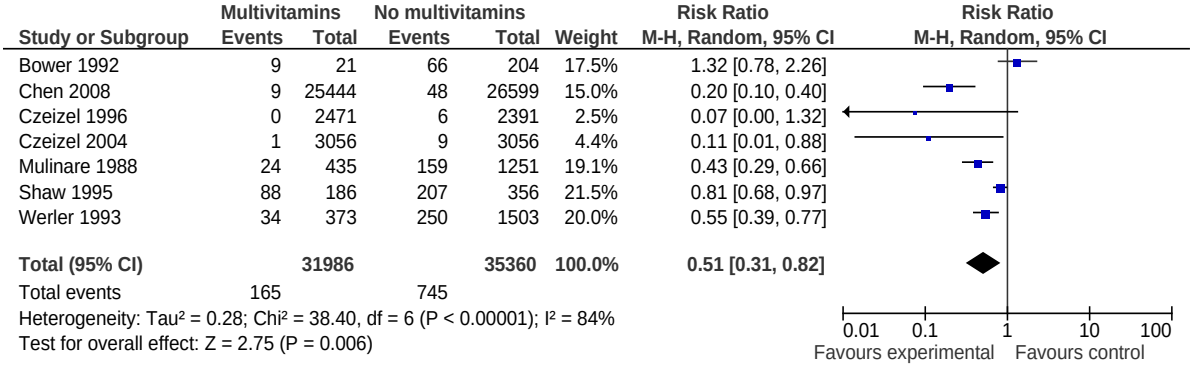
We also found a significant effect of multivitamin supplementation in preventing neural tube defects, both occurrent and recurrent. The pooled analysis for recurrent NTDs included only prospective studies; however the analysis for occurrent NTDs also includes case-control trials. The only included study that did not show a beneficial effect actually separated folic acid from multivitamins, while the rest included folic-acid containing supplements. Hence, it is doubtful that multivitamins without folic acid have a protective effect against neural tube defects, which is confirmed by the MRC study (RR for multivitamins versus placebo 0.61, 95% CI: 0.26-1.45) (**Figure 5.3.3**) (**Figure 5.3.4.**) (**Figure 5.3.5**) (**Figure 5.3.5**).

Figure 5.3.3: Periconceptional multivitamin supplementation for the prevention of *recurrent* NTDs



Citations to the included studies:
ICMR 2000[183], Kirke 1992[175], MRC 1991[177], Smithells 1981[184]

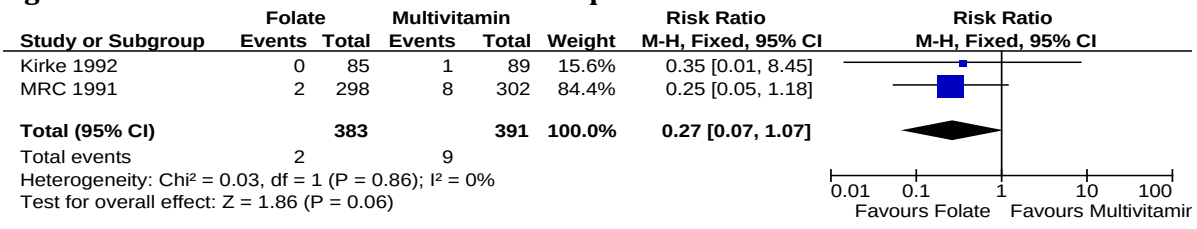
Figure 5.3.4: Periconceptional multivitamin supplementation for the prevention of *occurrent* NTDs



Citations to the included studies:
Bower 1992[181], Chen 2008[185], Czeizel 1996[186], Czeizel 2004[187], Mulinare 1988[188], Shaw 1995[189], Werler 1993[190]

When periconceptional folic acid supplementation was compared with supplementation with multivitamin alone or with folate and multivitamin in randomised controlled trials, it showed a non-significant decrease in NTDs with folate alone (**Figure 5.3.5**), (**Figure 5.3.6**).

Figure 5.3.5: Folate versus multivitamin for prevention of recurrent NTDs

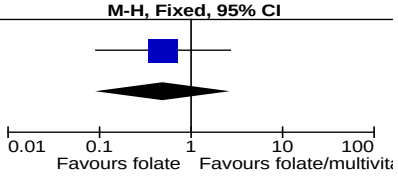


Citations to the included studies:
Kirke 1992[175], MRC 1991[177]

Figure 5.3.6: Folate versus Folate/multivitamin for prevention of recurrent NTDs

Study or Subgroup	Folate Events	Folate Total	Multivitamin Events	Multivitamin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kirke 1992	0	85	0	87		Not estimable
MRC 1991	2	298	4	295	100.0%	0.49 [0.09, 2.68]
Total (95% CI)		**383**		**382**	**100.0%**	**0.49 [0.09, 2.68]**
Total events	2		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.82 (P = 0.41)



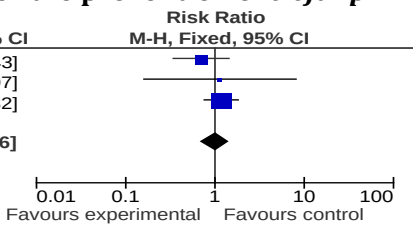
Citations to the included studies:
Kirke 1992[175], MRC 1991[177]

Previous reviews have not shown a benefit of folic acid/multivitamin supplementation on orofacial clefts, and although this review added three case-control studies and two prospective cohorts, the effect sizes adhered to unity. However, reviews that include all studies on folic acid/multivitamin supplementation simultaneously do show a modest protective effect[191-194], especially for cleft lip. (**Figure 5.3.7**) (**Figure 5.3.8**) (**Figure 7.3.9**) (**Figure 5.3.10**) (**Figure 5.3.11**).

Figure 5.3.7: Periconceptional folic acid supplementation for the prevention of *cleft lip*

Study or Subgroup	Folic acid Events	Folic acid Total	No folic acid Events	No folic acid Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bower 2006	9	174	33	446	34.0%	0.70 [0.34, 1.43]
Czeizel 1999	2	3017	2	3431	3.4%	1.14 [0.16, 8.07]
Hayes 1996	69	511	24	209	62.6%	1.18 [0.76, 1.82]
Total (95% CI)		**3702**		**4086**	**100.0%**	**1.01 [0.70, 1.46]**
Total events	80		59			

Heterogeneity: Chi² = 1.49, df = 2 (P = 0.47); I² = 0%
Test for overall effect: Z = 0.07 (P = 0.95)

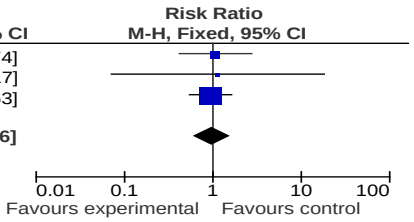


Citations to the included studies:
Bowes 2006[195], Czeizel 1999[196], Hayes 1996[197], Johnson 2008[193]

Figure 5.3.8: Periconceptional folic acid supplementation for the prevention of *cleft palate*

Study or Subgroup	Folic acid Events	Folic acid Total	No folic acid Events	No folic acid Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bower 2006	6	171	14	427	24.4%	1.07 [0.42, 2.74]
Czeizel 1999	1	3018	1	3432	2.8%	1.14 [0.07, 18.17]
Hayes 1996	38	480	17	202	72.8%	0.94 [0.54, 1.63]
Total (95% CI)		**3669**		**4061**	**100.0%**	**0.98 [0.61, 1.56]**
Total events	45		32			

Heterogeneity: Chi² = 0.07, df = 2 (P = 0.97); I² = 0%
Test for overall effect: Z = 0.09 (P = 0.92)

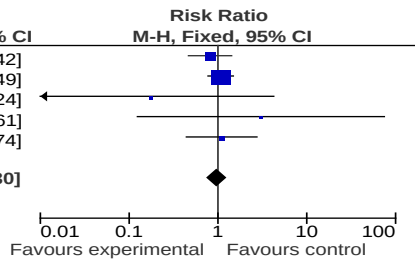


Citations to the included studies:
Bowes 2006[195], Czeizel 1999[196] , Hayes 1996[197]

Figure 5.3.9: Periconceptional folic acid supplementation for the prevention of orofacial clefts

Study or Subgroup	Folic acid Events	Folic acid Total	No folic acid Events	No folic acid Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bower 2006	15	180	47	460	27.5%	0.82 [0.47, 1.42]
Hayes 1996	107	549	41	226	60.5%	1.07 [0.78, 1.49]
Kirke 1992	0	169	1	88	2.1%	0.17 [0.01, 4.24]
MRC 1991	1	593	0	602	0.5%	3.05 [0.12, 74.61]
Ulrich 1999	20	8293	6	2742	9.4%	1.10 [0.44, 2.74]
Total (95% CI)		**9784**		**4118**	**100.0%**	**1.00 [0.76, 1.30]**
Total events	143		95			

Heterogeneity: Chi² = 2.37, df = 4 (P = 0.67); I² = 0%
Test for overall effect: Z = 0.02 (P = 0.98)

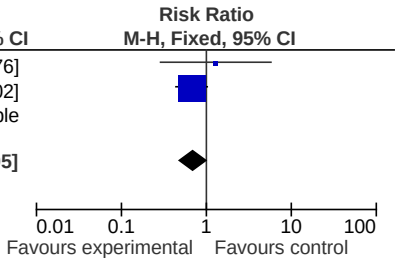


Citations to the included studies:
Bowes 2006[195], Hayes 1996[197], Kirke 1992[175], MRC 1991[177], Ulrich 1999[182]

Figure 5.3.10: Periconceptional multivitamin supplementation for the prevention of cleft lip

Study or Subgroup	Multivitamins Events	Total	No multivitamins Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Czeizel 1996	4	2471	3	2391	5.2%	1.29 [0.29, 5.76]
Itikala 2001	25	467	105	1314	94.8%	0.67 [0.44, 1.02]
Kirke 1992	0	87	0	103		Not estimable
Total (95% CI)		**3025**		**3808**	**100.0%**	**0.70 [0.47, 1.05]**
Total events	29		108			

Heterogeneity: Chi² = 0.68, df = 1 (P = 0.41); I² = 0%
Test for overall effect: Z = 1.71 (P = 0.09)

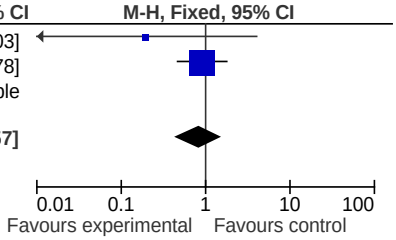


Citations to the included studies:
Czeizel 1996[186], Itikala 2001[198], Kirke 1992[175]

Figure 5.3.11: Periconceptional multivitamin supplementation for the prevention of cleft palate

Study or Subgroup	Multivitamins Events	Total	No multivitamins Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Czeizel 1996	0	2471	2	2391	12.5%	0.19 [0.01, 4.03]
Itikala 2001	11	467	34	1314	87.5%	0.91 [0.47, 1.78]
Kirke 1992	0	87	0	103		Not estimable
Total (95% CI)		**3025**		**3808**	**100.0%**	**0.82 [0.43, 1.57]**
Total events	11		36			

Heterogeneity: Chi² = 0.96, df = 1 (P = 0.33); I² = 0%
Test for overall effect: Z = 0.60 (P = 0.55)



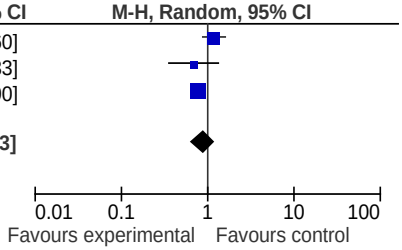
Citations to the included studies:
Czeizel 1996[186], Itikala 2001[198], Kirke 1992[175]

The evidence on folic acid/multivitamin supplementation and congenital heart defects is mixed at best- pooling of two randomized trials, one cohort and one case-control trial showed a risk reduction of 42% in our analysis. The reviews that simultaneously examine all studies on folic acid/multivitamin supplementation find a non-significant benefit with the effect leaning towards multivitamins, whereas an observational study by van Beynum[199] seems to find folic acid valuable for all subtypes of congenital heart defects. For limb reduction defects (RR ranges from 0.43-0.59 for all analyses) and congenital urinary tract anomalies (RR ranges from 0.17-0.68 for all analyses), the evidence shows a modest but persistent risk reduction with the use of *multivitamins*, rather than folic acid. (**Figure 5.3.12**) (**Figure 5.3.13**) (**Figure 5.3.14**) (**Figure 5.3.15**) (**Figure 5.3.16**) (**Figure 5.3.17**) (**Figure 5.3.18**) (**Figure 5.3.19**) (**Figure 5.3.20**).

Figure 5.3.12: Periconceptional folic acid supplementation for the prevention of CHDs

Study or Subgroup	Folic acid Events	Total	No folic acid Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bower 2006	50	215	101	514	36.3%	1.18 [0.88, 1.60]
Ulrich 1999	27	8293	13	2742	16.9%	0.69 [0.35, 1.33]
van Beynum 2010	342	2502	254	1437	46.8%	0.77 [0.67, 0.90]
Total (95% CI)		**11010**		**4693**	**100.0%**	**0.88 [0.64, 1.23]**
Total events	419		368			

Heterogeneity: Tau² = 0.06; Chi² = 6.59, df = 2 (P = 0.04); I² = 70%
Test for overall effect: Z = 0.73 (P = 0.47)

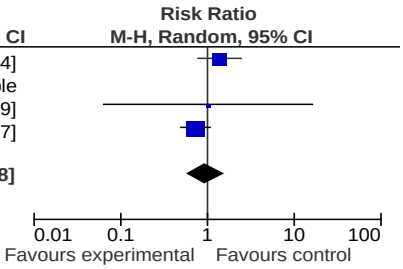


Citations to the included studies:
Bowes 2006[195], Ulrich 1999[182], Van Beynum 2010[200]

Figure 5.3.13: Periconceptional folic acid supplementation for the prevention of conotruncal CHDs

Study or Subgroup	Folic acid Events	Total	No folic acid Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bower 2006	17	182	30	443	40.5%	1.38 [0.78, 2.44]
Kirke 1992	0	170	0	88		Not estimable
MRC 1991	1	593	1	602	3.2%	1.02 [0.06, 16.19]
van Beynum 2010	57	2502	45	1437	56.3%	0.73 [0.49, 1.07]
Total (95% CI)		**3447**		**2570**	**100.0%**	**0.95 [0.58, 1.58]**
Total events	75		76			

Heterogeneity: Tau² = 0.08; Chi² = 3.34, df = 2 (P = 0.19); I² = 40%
Test for overall effect: Z = 0.19 (P = 0.85)

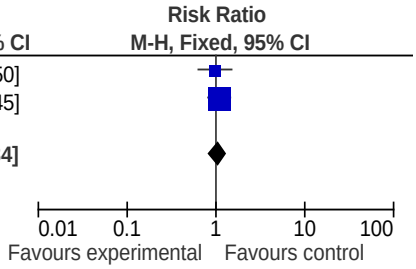


Citations to the included studies:
Bowes 2006[195], Kirke 1992[175], MRC 1991[177], Van Beynum 2010[200]

Figure 5.3.14: Periconceptional folic acid supplementation for the prevention of CHDs-outflow tract defects

Study or Subgroup	Folic acid Events	Total	No folic acid Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Scanlon 1998	21	137	105	668	29.0%	0.98 [0.63, 1.50]
van Beynum 2010	131	2502	69	1437	71.0%	1.09 [0.82, 1.45]
Total (95% CI)		**2639**		**2105**	**100.0%**	**1.06 [0.83, 1.34]**
Total events	152		174			

Heterogeneity: Chi² = 0.18, df = 1 (P = 0.67); I² = 0%
Test for overall effect: Z = 0.46 (P = 0.65)

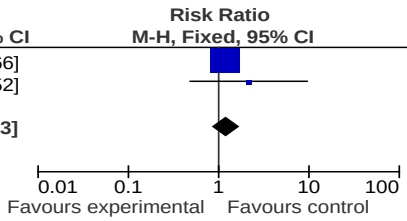


Citations to the included studies:
Scanlon 1998[201], Van Beynum 2010[200]

Figure 5.3.15: Periconceptional folic acid supplementation for the prevention of urinary tract defects

Study or Subgroup	Folic acid Events	Total	No folic acid Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bower 2006	38	203	79	492	93.9%	1.17 [0.82, 1.66]
Ulrich 1999	13	8293	2	2742	6.1%	2.15 [0.49, 9.52]
Total (95% CI)		**8496**		**3234**	**100.0%**	**1.23 [0.87, 1.73]**
Total events	51		81			

Heterogeneity: Chi² = 0.63, df = 1 (P = 0.43); I² = 0%
Test for overall effect: Z = 1.16 (P = 0.24)

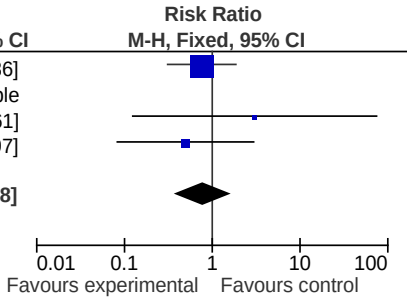


Citations to the included studies:
Bowes 2006[195], Ulrich 1999[182]

Figure 7.3.16: Periconceptional folic acid supplementation for the prevention of limb reduction defects

Study or Subgroup	Folic acid Events	Total	No folic acid Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bower 2006	6	171	20	433	76.4%	0.76 [0.31, 1.86]
Kirke 1992	0	169	0	88		Not estimable
MRC 1991	1	593	0	602	3.3%	3.05 [0.12, 74.61]
Ulrich 1999	3	8293	2	2742	20.3%	0.50 [0.08, 2.97]
Total (95% CI)		**9226**		**3865**	**100.0%**	**0.78 [0.37, 1.68]**
Total events	10		22			

Heterogeneity: Chi² = 0.95, df = 2 (P = 0.62); I² = 0%
Test for overall effect: Z = 0.63 (P = 0.53)

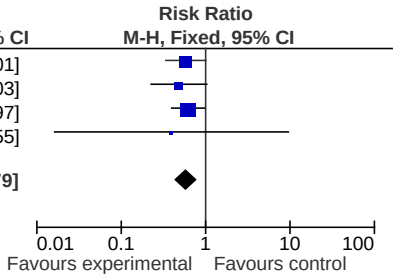


Citations to the included studies:
Bowes 2006[195], Kirke 1992[175], MRC 1991[177], Ulrich 1999[182]

Figure 5.3.17: Periconceptional multivitamin supplementation for the prevention of CHDs

Study or Subgroup	Multivitamins Events	Total	No multivitamins Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Botto 1996	15	446	72	1251	34.5%	0.58 [0.34, 1.01]
Czeizel 1996	10	2471	20	2391	18.6%	0.48 [0.23, 1.03]
Czeizel 2004	31	3056	50	3056	45.6%	0.62 [0.40, 0.97]
Kirke 1992	0	87	1	103	1.3%	0.39 [0.02, 9.55]
Total (95% CI)		**6060**		**6801**	**100.0%**	**0.58 [0.42, 0.79]**
Total events	56		143			

Heterogeneity: Chi² = 0.36, df = 3 (P = 0.95); I² = 0%
Test for overall effect: Z = 3.42 (P = 0.0006)

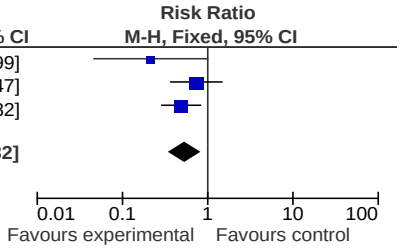


Citations to the included studies:
Botto 1996[202], Czeizel 1996[186], Czeizel 2004[187], Kirke 1992[175]

Figure 5.3.18: Periconceptional multivitamin supplementation for the prevention of urinary tract defects

Study or Subgroup	Multivitamins Events	Total	No multivitamins Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Czeizel 1996	2	2471	9	2391	19.8%	0.22 [0.05, 0.99]
Czeizel 2004	14	3056	19	3056	41.2%	0.74 [0.37, 1.47]
Li 1995	43	185	10	21	39.0%	0.49 [0.29, 0.82]
Total (95% CI)		**5712**		**5468**	**100.0%**	**0.54 [0.35, 0.82]**
Total events	59		38			

Heterogeneity: Chi² = 2.31, df = 2 (P = 0.31); I² = 14%
Test for overall effect: Z = 2.84 (P = 0.005)

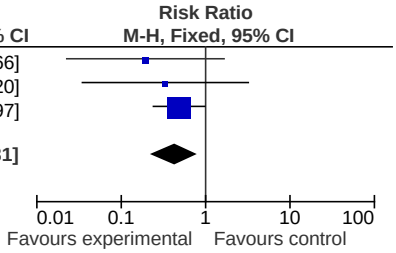


Citations to the included studies:
Czeizel 1996[186], Czeizel 2004[187], Li 1995[203]

Figure 5.3.19: Periconceptional multivitamin supplementation for the prevention of limb reduction defects

Study or Subgroup	Multivitamins Events	Total	No multivitamins Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Czeizel 1996	1	2471	5	2391	14.3%	0.19 [0.02, 1.66]
Czeizel 2004	1	3056	3	3056	8.5%	0.33 [0.03, 3.20]
Yang 1997	9	440	52	1231	77.2%	0.48 [0.24, 0.97]
Total (95% CI)		**5967**		**6678**	**100.0%**	**0.43 [0.23, 0.81]**
Total events	11		60			

Heterogeneity: Chi² = 0.69, df = 2 (P = 0.71); I² = 0%
Test for overall effect: Z = 2.62 (P = 0.009)

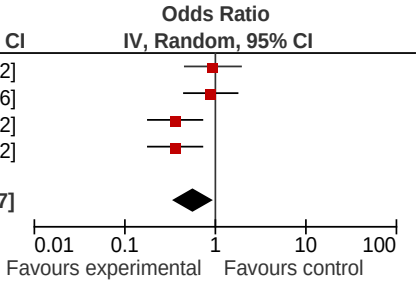


Citations to the included studies:
Czeizel 1996[186], Czeizel 2004[187], Yang 1997[204]

Figure 5.3.20: Periconceptional multivitamin supplementation for the prevention of multiple congenital anomalies

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Bitsko 2007	-0.0619	0.3646	24.4%	0.94 [0.46, 1.92]
Czeizel 2003	-0.1165	0.3479	25.4%	0.89 [0.45, 1.76]
Khoury 1996	-1.0217	0.3536	25.1%	0.36 [0.18, 0.72]
Shaw 2000	-1.0217	0.3536	25.1%	0.36 [0.18, 0.72]
Total (95% CI)			**100.0%**	**0.57 [0.34, 0.97]**

Heterogeneity: Tau² = 0.16; Chi² = 6.90, df = 3 (P = 0.08); I² = 57%
Test for overall effect: Z = 2.07 (P = 0.04)

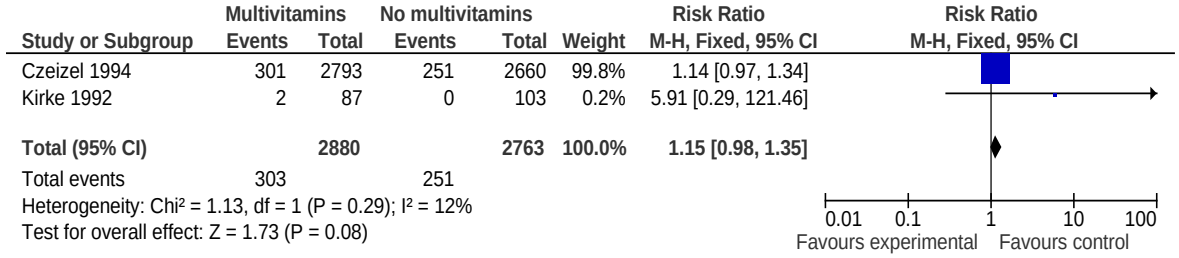


Citations to the included studies:
Bitsko 2007[205], Czeizel 2003[206], Khoury 1996[207], Shaw 2000[208]

No review has shown a consistent effect of folic acid/multivitamin supplementation on maternal and pregnancy outcomes- including ectopic pregnancy, miscarriage, stillbirths, preterm births, low birth weight, and other birth defects. Further, the apprehension that

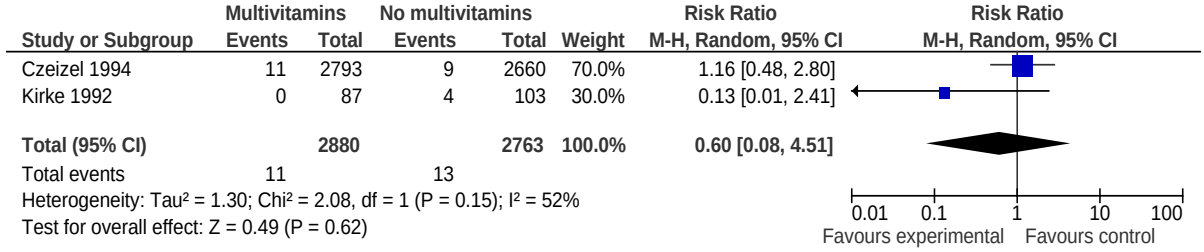
widespread folic acid supplementation or fortification would lead to increased rates of multiple gestation was not shown to be significant in this review RR 0.99, 95% CI 0.94-1.05 or previous work (aOR 1.02 with supplementation and maximum annual increase in twinning rates of 4.6% with fortification).[209] Pooling two cohort studies, we also found a significant 27% reduction in the risk of preeclampsia by maternal periconceptional multivitamin supplementation. This review also found a 43% risk reduction of multivitamins for multiple congenital abnormalities (**Figure 5.3.21**) (**Figure 5.3.22**) (**Figure 5.3.23**) (**Figure 5.3.24**) (**Figure 5.3.25**) (**Figure 5.3.26**) (**Figure 5.3.27**).

Figure 5.3.21: Periconceptional multivitamin supplementation for the prevention of miscarriage



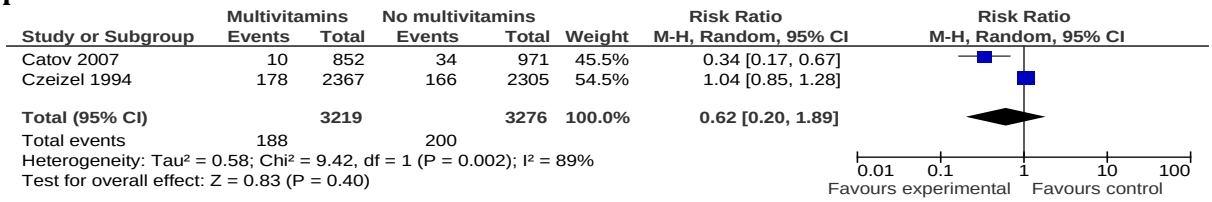
Citations to the included studies:
Czeizel 1994[210],Kirke 1992[175]

Figure 5.3.22: Periconceptional multivitamin supplementation for the prevention of stillbirths



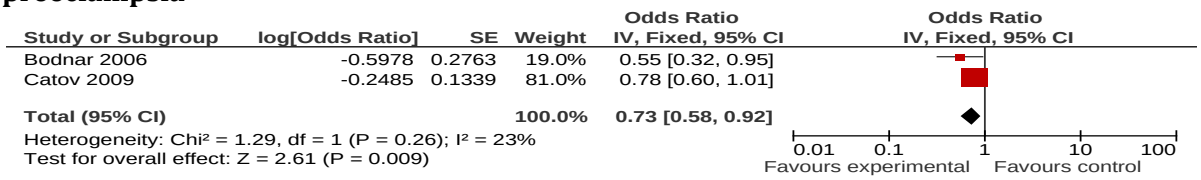
Citations to the included studies:
Czeizel 1994[210],Kirke 1992[175]

Figure 5.3.23: Periconceptional multivitamin supplementation for the prevention of preterm birth



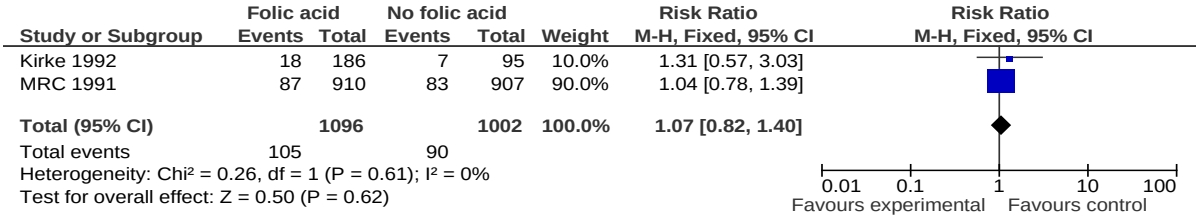
Citations to the included studies:
Catov 2007[211], Czeizel 1994[210]

Figure 5.3.24: Periconceptional multivitamin supplementation for the prevention of preeclampsia



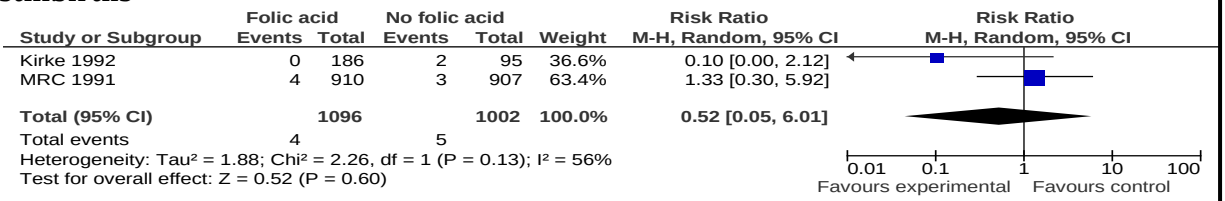
Citations to the included studies:
Bodnar 2006[212], Catov 2009[213]

Figure 5.3.25: Periconceptional folic acid supplementation for the prevention of miscarriage



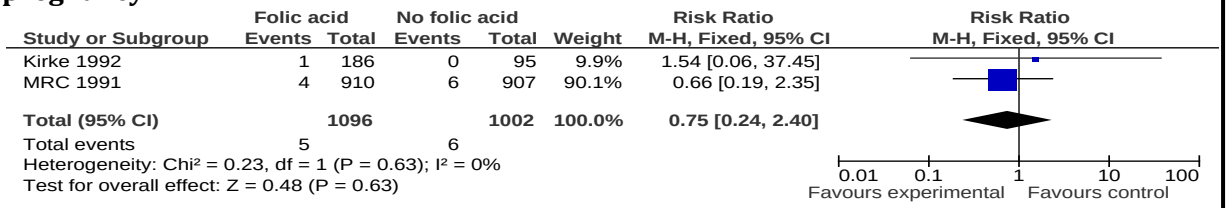
Citations to the included studies:Kirke 1992[175], MRC 1991[177]

Figure 5.3.26: Periconceptional folic acid supplementation for the prevention of stillbirths



Citations to the included studies:Kirke 1992[175], MRC 1991[177]

Figure 5.3.27: Periconceptional folic acid supplementation for the prevention of ectopic pregnancy

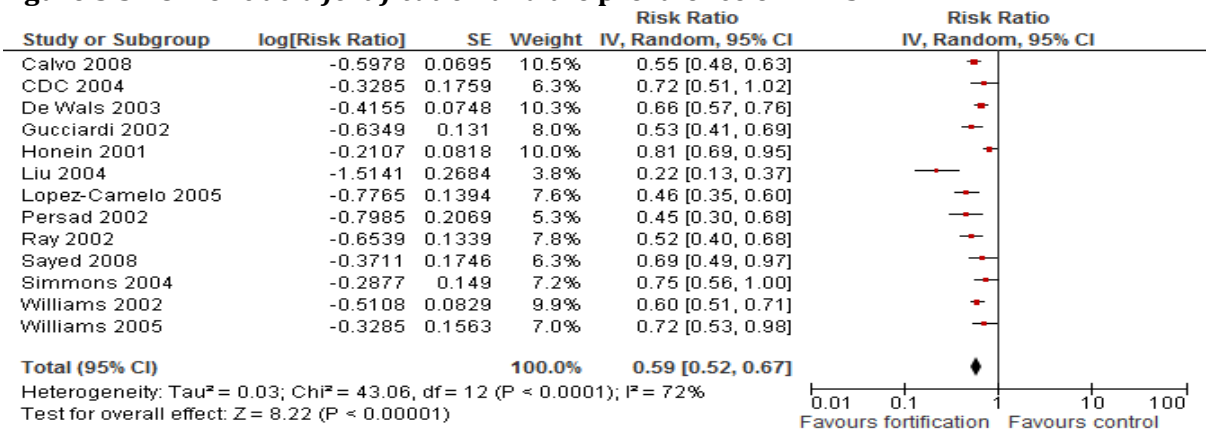


Citations to the included studies:
Kirke 1992[175], MRC 1991[177]

Folic acid Fortification

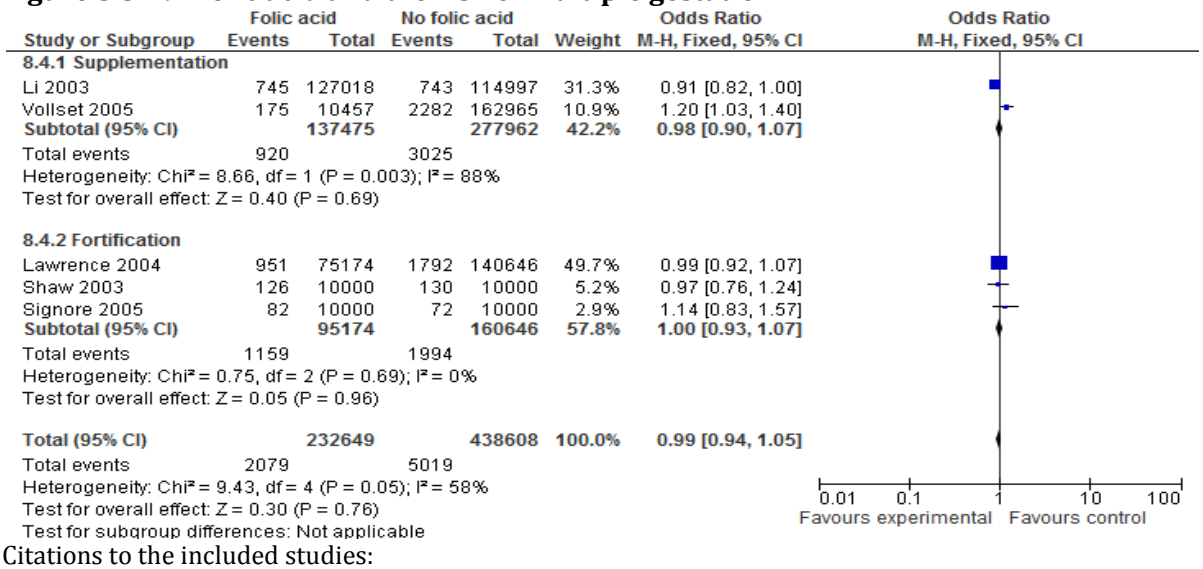
Periconceptional folic acid fortification also showed a significant impact on reduction of NTDs prevalence by 41% (RR 0.59; 95% CI: 0.52-0.67) (**Figure 5.3.28**).. However, when risk of multiple gestations was compared between folic acid supplementation versus folic acid fortification, it had no difference on the outcome (**Figure 5.3.29**).

Figure 5.3.28: Folic acid *fortification* and the prevalence of NTDs



Citations to the included studies:
Calvo 2008[214]; CDC 2004[215], De Wals 2003[216]; Gucciardi 2002[217], Honein 2001[218], Liu 2004[219]; Lopez-Camelo 2005[220], Persad 2002[221]; Ray 2002[222]; Sayed 2008[223]; Simmons 2004[224]; Williams 2002[225]; Williams 2005[226]

Figure 5.3.29: Folic acid and the risk of multiple gestation

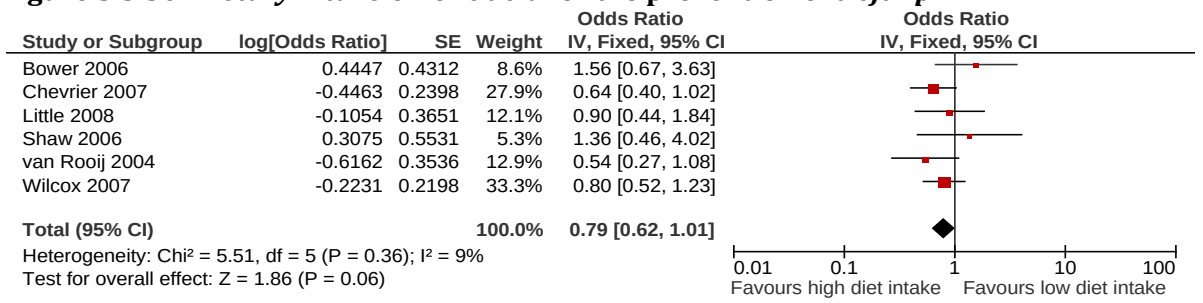


Citations to the included studies:
Li 2003[227], Vollset 2005[228], Lawrence 2004[229], Shaw 2003[230], Signore 2005[231]

Dietary intake

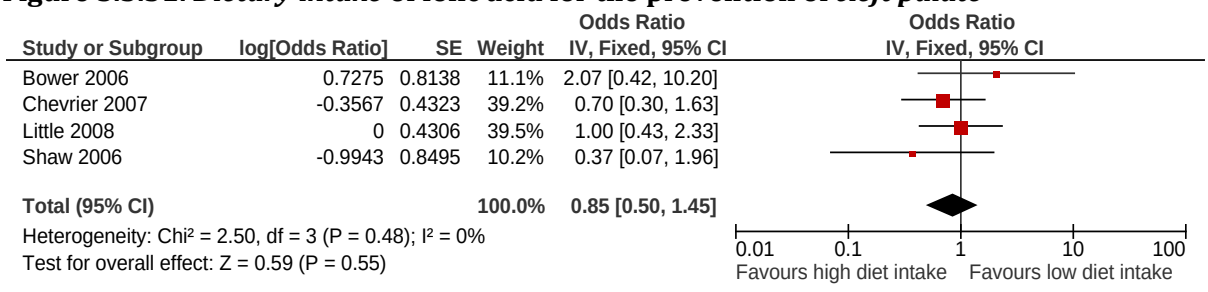
We also looked for the impact of dietary intake of folic acid on prevention of congenital anomilies like cleft lip and palate. However, results should a non-significant reduction on prevention of these anamolies (RR 0.79; 95% CI: 0.62-1.01) and (RR 0.85; 95% CI: 0.50-1.45) respectively (**Figure 5.3.30**) and (**Figure 5.3.31**).

Figure 5.3.30: *Dietary intake* of folic acid for the prevention of *cleft lip*



Citations to the included studies:
Bowes 2006[195], Chevrier 2007[232], Little 2008[233], Shaw 2006[234], Van Rooij 2004[235], Wilcox 2007[236]

Figure 5.3.31: *Dietary intake* of folic acid for the prevention of *cleft palate*



Citations to the included studies:
Bowes 2006[195] Chevrier 2007[232], Little 2008[233], Shaw 2006[234]

Table 5.3.1.2: Other interventions for folate	
Promotional Intervention	**Outcomes**
Mass media campaign [de Walle	17/342 before to 161/452 after, women who used periconceptional

Table 5.3.1.2: Other interventions for folate	
Promotional Intervention	**Outcomes**
2002][237]	folate supplements
Point-of-purchase nutrition education (recipe card, supermarket helper, posters) and short curriculum for community organizations [Kannan 2007][238]	Of 160 women surveyed, 153 (96%) women expected to change their intake of folic acid based on the educational event. Of the 153 women who indicated positive behavioral intent, 136 (89%) reported that they planned to eat more folic acid–rich foods every day, whereas 111 (73%) chose to pay more attention to food product labels, and 98 (64%) plan to take a multivitamin pill every day.
Educational session by medical students, leaflets, posters [Kari 2008][239]	From 12% pre-intervention who knew about folate and NTDs, post-intervention, 78% knew the timing and 84% the dose of supplementation, 82.9% would use folate pre-conception, but only 63.6% knew the correct sources of folate.
Television and magazine announcements to increase awareness of , and access to, fortified foods and supplements [Sillender 2000][240]	71/262 before to 36/75 after, women who used periconceptional folate supplements
Media aimed at public and letters sent to GPs [van der Pal- de Bruin 2000][241]	78/1636 before to 339/1612 after, women who used periconceptional folate supplements
Telephone messages, letters, leaflets, television and newspaper announcements [Chan 2001][242]	50/187 before to 77/167 after, women who used periconceptional folate supplements
Telephone counselling [Pastuszak 1999][243]	105/145 women were taking folic acid (correct dose) at follow-up, most before conception. In control group, only 25/147 women started taking folic acid preconception. Of the 66 women who became pregnant, 47 took folic acid at the correct time. Of those who had not conceived, 34 were not taking folic acid, but 14 were still planning pregnancy.
Individual genetic counseling to prevent recurrence, communication with health service providers and public health campaign (public service announcements for television and radio, a television documentary film, billboards, advertisements, payroll envelope inserts for businesses, a calendar, and a series of brochures and posters) to prevent occurrence [Stevenson 2000][244]	Prevalence of NTDs fell from 1.89 to 0.95 over 5 years. However, among the women who experienced an NTD recurrence, 113/132 used folic acid periconceptionally (83 women took 4mg daily). Use of folic acid among controls increased from 8 to 30%. By year 6, 35% of women of childbearing age were taking folic acid 4 times/week.
Brief counseling, bottle of 30 folic acid tablets, booster phone call, and a pamphlet [Robbins 2005][245]	More than one quarter of women (26%) who received the brief message and a starter bottle of 30 tablets moved from no intake of folic acid to weekly intake average of 5.1 days per week ($p<0.001$). Weekly folic acid intake increased 68% in intervention versus 20% in control group. Women who were of lower socioeconomic strata and not planning pregnancy were influenced more.
Poster, leaflet, brochures, magnetized card distributed and displayed in strategic public places [Watson 1999[246] and 2001[247]]	Post-intervention background increase in the comparison communities of 3.4% ($p=0.02$), and an increase above this owing to the intervention of 4.0%. 4 times as many women reported seeing the leaflet as any other intervention material. Pharmacies 2% and MCHCs 1% were reported as the source of intervention material least frequently, but these women had the highest folate awareness 75% and 83.3% respectively because of the information kit. Women were more likely to be aware if they saw more than one source, or the source was trusted- doctor, family. A second survey evaluated the long-term effect of the intervention- there was a significant increase from 1997 to 2000 aOR=1.43, $p=0.02$ in the number of women who had heard of spina bifida. There was a significant and persistent impact of the intervention on women's

Table 5.3.1.2: Other interventions for folate	
Promotional Intervention	**Outcomes**
	awareness of the association between folate and NTDs (aOR=1.24, *p*=0.007) - this impact decreased over the survey time but not significantly. Sustained increase in women knowing correct folate food sources (aOR= 1.90) and correct timing for folate supplementation (aOR= 1.67) and that folate prevents against birth defects including NTDs (aOR= 2.21) and knowing food s with added folate (aOR= 3.75) between surveys. The aOR for using folate-enriched foods over time was 1.50
Folic acid education program at community clinic, and 3 month supply of multivitamins [Chacko 2003][248]	Pre-intervention 44-52% was aware of multivitamins for the prevention of birth defects; post-intervention 88-92% was aware. However only 38% knew that all women of childbearing age should take folic acid. Of the 97% who received vitamins from the clinic, only 9% took them daily.
Articles in state professional publications, presentations at continuing medical education courses, direct mailings, and educational booths at professional meetings [Hauser 2004][249]	Pre-intervention 58% of healthcare providers knew the correct dose of folic acid for prevention of NTD occurrence, post-intervention 70% did. There was a rise from 26% to 36% of healthcare providers who knew the correct folic acid dose for NTD recurrence prevention. Although the number of providers with knowledge of the correct timing to start folic acid was initially high and rose only from 80% to 85%, the number of providers who would recommend folic acid to all women of reproductive age rose from 45% to 57%. (all results p<0.0001)
Free folic acid supplement program at family planning clinics- folic acid pills and educational material; fortified cereal and educational material; educational material only provided. [Watkins 2004][250]	Pill and cereal interventions significantly ($p < 0.05$) increased participants' reported knowledge about the appropriate time to take folic acid. The pill intervention also significantly increased participants' knowledge that folic acid prevents birth defects (41–54%, $p = 0.03$). Only the pill intervention was associated with a significantly increased self-reported consumption of folic acid (23–42%, $p= 0.03$). OR that participants answered knowledge questions correctly at second clinic visit were 1.94 (greater for education than pill than cereal). OR that participants reported folic acid consumption at second clinic visit was 1.18 (greater for cereal than pill than education). OR=2.09 for reported consumption for participants who answered knowledge questions correctly versus those who did not. However, interventions did not directly increase mean serum folate levels at second visit.
Direct mailing of starter kit of 100 *multivitamins* to participants versus education for healthcare providers to promote multivitamin use (with written materials) versus brochure (control) [Lawrence 2003][251]	Direct mail/pharmacy intervention change in percentage of participants taking regular multivitamin 4.8% versus 3.7% for provider education versus 3.5% for control (Direct mail/pharmacy intervention transient spike during intervention)
Information brochure for pharmacies, promotion among healthcare providers, mass media campaign[Egen 2003][252]	Pre-intervention 5/131 (3.8%) and post-intervention 11/118 (9.3%) number of women taking folic acid at the correct time. Significant increase in women knowing the importance of folic acid (28 to 42% post-intervention) however this benefit translated only to women with planned pregnancies (5.3 to 14.7% post-intervention taking folic acid at the correct time)
Social marketing media campaign, outreach to consumers using a lay health education program, an extensive health care provider education program, a multivitamin distribution program, and a Latino-focused campaign. Encourages women especially between the ages of 18 and 24 years to consume	40% decline in NTD prevalence in North Carolina between 1995 and 1996 (9.95 per 10,000 live births) and 2004 and 2005 (6.05 per 10,000 live births). By comparison, the national NTD rate declined by 23%-26% in the years after fortification of the US food supply beginning in 1998.

Table 5.3.1.2: Other interventions for folate	
Promotional Intervention	**Outcomes**
multivitamins containing folic acid [Mullenix 2009][253]	
Multivitamin/mineral fortified dairy product [Baro 2004- abstract only][254]	Increased levels of plasma folate and B12 within one month
Physician counseling for women to take folic acid before pregnancy[de Weerd 2002][255]	Estimated mean red cell folate levels of women who reported no use of folic acid supplements before counseling increased significantly from 540 nmol/L to 680 nmol/L. Red cell folate levels of women who reported taking supplements remained stable up to 1 year after counseling. Women with low precounseling folate levels showed a highly significant mean increase in red cell folate from 475 nmol/L to 689 nmol/L after counseling.

Grade Table

Pooling data from 5 case-control and 2 cohort-controlled trials conducted in relatively high-income countries, resulted in a significant 49% decrease in risk (RR 0.51, 95% CI 0.31-0.82) of occurrent neural tube defects due to periconceptional multivitamin supplementation. The case-control study by Bower 1992 was inconsistent with the other study results, possibly owing to the small total number of women using periconceptional multivitamins, or to recall bias among case mothers. There was substantial heterogeneity between studies; however repeat analysis using random effects did not change the results. In comparison, Lumley did not find an effect on occurrent neural tube defects when multivitamins alone or in combination were compared to folic acid.

For Folate

Results from 3 randomised double-blind placebo-controlled studies were pooled to yield a relative risk of 0.31, 95% CI 0.14-0.66 for recurrent neural tube defects with periconceptional folic acid supplementation. The MRC study probably provides the most

Multivitamin compared to Placebo for Occurent Neural Tube defects

Patient or population: patients with Occurent Neural Tube defects
Settings: Australia, China, Hungary, USA and Canada
Intervention: Multivitamin
Comparison: Placebo

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Placebo	Corresponding risk Multivitamin	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Occurent Neural tbe defects Multivitamin Follow-up: mean 1.5 years	Study population		RR 0.51 (0.31 to 0.82)	67346 (7 studies)	⊕⊕⊕⊖ very low[1]	
	21 per 1000	11 per 1000 (7 to 17)				
	Low risk population					
	2 per 1000	1 per 1000 (1 to 1)				
	Medium risk population					
	127 per 1000	65 per 1000 (39 to 104)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Funnel plot showing mild publication bias

accurate estimate for this intervention since it was a multicenter prospective randomized trial. The remaining studies all suffer from low response rates, however, only Suarez 2000 has results inconsistent with the pooled analysis. This could be attributed to recall and selection bias in the study, or to primary intake in this population being from dietary sources with lower bioavailability. Our results are confirmed by the meta-analyses undertaken by De-Regil and Lumley, who also cite a 68% risk reduction.

Folate compared to Placebo for Recurrent neural tube defects

Patient or population: patients with Recurrent neural tube defects
Settings: Ireland; UK; Australia; Israel; Hungary; Canada; Russia; France
Intervention: Folate
Comparison: Placebo

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Placebo	Corresponding risk Folate	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Recurrent neural tube defects Follow-up: 9 years	**Study population**		RR 0.31 (0.14 to 0.66)	1549 (3 studies)	⊕⊕⊕⊕ **high**[1]	
	36 per 1000	11 per 1000 (5 to 24)				
	Low risk population					
	11 per 1000	3 per 1000 (2 to 7)				
	High risk population					
	78 per 1000	24 per 1000 (11 to 52)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Randomisation unclear. Did not reach planned sample size

Conclusion

Increasing the dietary intake of folic acid among women of reproductive age is not sufficient to prevent birth defects, especially neural tube defects. Folic acid supplementation has been proven to reduce the risk of neural tube defects, both recurrent and occurrent. However, further research is needed to show whether this benefit extends to prevention of orofacial clefts and congenital cardiovascular abnormalities. Despite recommendations and guidelines to promote folic acid use in this population, less than half of all potential mothers use daily folic acid supplements. Multicomponent interventions[244, 245] increase use transiently and do not achieve universal coverage, although those with personal counseling in addition to mass campaigns have been shown to be more effective.[293] It has also been shown that inclusion of a specific health claim, such as that folic acid prevents birth defects, is more successful in increasing uptake and use.[294] Fortification has thus been proposed as a means to prevent approximately half of all neural tube defects occurring annually and 13% of neonatal mortality attributed to neural tube defects,[174]especially in areas with high prevalence of neural tube defects.[295-297] However, ongoing efforts must be made to supplement women at risk of a recurrent neural tube defect and women who are more folate-depleted.[167, 169]

Key messages:

- Less than half of all women use folic acid/multivitamins in the periconceptional period despite evidence to support their effectiveness in preventing birth defects and mass campaigns to promote their use in this population
- Folic acid supplementation during the periconceptional period is proven to reduce the risk of neural tube defects- occurrent by 16-44% and recurrent by 72-76%
- There is inconclusive evidence to support the use of folic acid or multivitamins to reduce orofacial clefts and congenital heart defects
- Multivitamin supplementation reduces the risk of limb defects (19-76%), congenital urinary tract defects (18-65%).
- This review also demonstrates that periconceptional multivitamin supplementation reduces the risk of multiple congenital anomalies by 43% and preeclampsia by 27%.
- The evidence does not support a significantly increased risk of multiple gestations as a result of folic acid supplementation, RR 0.99-1.02, however a previous review found a pooled annual increase of 4.6% in twinning rates from retrospective cohort studies that merits substantiation

Table 5.3.1.2: Summary impact estimates of periconceptual multivitamins			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
Anaemia: RR= 0.59, 95% CI 0.46-0.76 [Gulati 2009 RCT][256] Folate levels: Mean erythrocyte folate rose from 250 to 482 ng/ml by the 8th week of pregnancy Mean serum folate rose from 8.3 to 26.5 ng/ml by the 8th week of pregnancy [Schorah 1983 Coh][257]	Ectopic pregnancy: 3/2170 supplemented versus 3/2133 unsupplemented [Czeizel 1993 RCT][258] 7/2793 supplemented versus 4/2660 unsupplemented [Czeizel 1994 RCT][210] Miscarriage: 2/87 supplemented versus 0/103 unsupplemented 5.91, 95% CI 0.29-121.46 [Kirke 1992[175], as quoted in De-Regil 2010 MA][259] 228/2170 supplemented versus 196/2133 unsupplemented [Czeizel 1993 RCT][258] 301/2793 supplemented versus 251/2660 unsupplemented [Czeizel 1994 RCT][210] Nausea and vomiting in early pregnancy: 18/500 supplemented	Neural Tube Defects (NTDs): Recurrent NTDs: 0/87 supplemented versus 3/103 unsupplemented Risk ratio= 0.17, 95% CI 0.01-3.22 [Kirke 1992[175], as quoted in De-Regil 2010 MA][259] Recurrent NTDs: 8/302 supplemented versus 13/300 unsupplemented, Risk ratio= 0.61, 95% CI 0.26-1.45 [MRC 1991[177], as quoted in Lumley 2009][172] 0/2104 supplemented versus 6/2052, p= 0.029. [Czeizel 1992 RCT][265] 0/2471 supplemented versus 6/2391 unsupplemented (x^2: = 6.21; P = 0.01) [Czeizel 1996 RCT][186] 1/3056 supplemented versus 9/3056 unsupplemented, aOR= 0.11 (95% CI 0.01-0.91) [Czeizel 2004 Coh][187] 9/25444 supplemented versus 48/26599 unsupplemented, RR= 0.20, 95% CI 0.10–0.40, OR=0.13 for total compliance and 0.18 for those with greater fruit/vegetable consumption. [Chen 2008 Coh][185] Recurrent NTDs: From 9/250 to 4/198 reduction in recurrence risk = 2.4 times in low prevalence area, and from 14/293 to 3/226 = 5.4 times high prevalence area [Seller 1984 Coh-controlled][266] Recurrent NTDs: 1/195 supplemented versus 13/295 unsupplemented [Smithells 1981 Coh][184] 24/435 supplemented versus 159/1251 unsupplemented, aOR= 0.51 (with negative control aOR= 0.41 95% CI 0.26-0.66 [Mulinare 1988 CC][188] 34/373 supplemented versus 250/1503, aOR= 0.6 95% CI 0.4-0.8. Results similar for highest vs. lowest quintile of dietary intake [Werler 1993 CC][190] 88/186 supplemented versus 207/356 unsupplemented, OR= 0.65 (95% CI 0.45-0.94). For highest versus lowest quartile of dietary intake, OR= 0.69 (95% CI 0.47-1.0) [Shaw 1995 CC][189] aOR= 4.46, for negative control 9/21 supplemented versus 66/204 unsupplementd aOR= 1.37 (95% CI 0.44-4.33). [Bower 1992[181] CC] Anencephaly: 73/458 supplemented versus 68/306 unsupplemented, aOR= 0.8, 95% CI 0.5–1.3.	The occurrence of atopic dermatitis and diseases of the digestive, urinary and respiratory systems, as well as anthropometric, audiological and ophthalmological examination did not reveal significant differences between 2 and 6 year old children whose mothers had received periconceptional multivitamins and those who had received trace elements. Intelligence tests did not reveal a significant difference. However children in the multivitamin

Table 5.3.1.2: Summary impact estimates of periconceptual multivitamins			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
	versus 44/500 unsupplemented. (However, constipation and diarrhoea were more frequently reported in the supplement group 25 vs. 10) [Czeizel 1992 RCT][260] Preeclampsia: 3.8% of users versus 4.4% of nonusers. aOR= 0.55, 95% CI 0.32-0.95. Stratified by prepregnancy BMI (> or < 25 kg/m^2), aOR= 0.29 for lean mothers and 1.08 for overweight mothers. Sensitivity analysis for fruit/vegetable consumption aOR= 0.63 [Bodnar 2006 Coh][212] aHR= 0.78, 95% CI 0.60-0.99. Effect stronger for use immediately post conception. No effect for obese women or of supplementation with folate only. [Catov	Spina bifida: 107/492 supplemented versus 82/320 unsupplemented aOR= 0.8, 95% CI 0.6–1.2 [Carmichael 2010 CC][267] aOR among fully-supplemented women 0.95 (0.78 to 1.14) compared to positive controls and 1.00 (0.83 to 1.20) compared to negative controls. [Mills 1989 CC][268] SGA: 31/852 supplemented versus 57/971 unsupplemented, aOR= 0.64, 95% CI 0.40-1.03. For no obese women aOR= 0.54, and for obese women 0.87 [Catov 2007 Coh][211] HR: 0.83; 95% CI: 0.73, 0.95 [Catov 2011 Coh periconception] Low birth weight: 110/2170 supplemented versus 80/2133 unsupplemented [Czeizel 1993 RCT][258] 101/2367 supplemented versus 81/2305 unsupplemented [Czeizel 1994 RCT][210] Periconceptional use in African American women: 536-gram increased birth weight (p=0.001) [Burris 2010 Coh] Orofacial clefts: CL/P 0/87 supplemented versus 0/103 unsupplemented. CPO 0/87 supplemented versus 0/103 unsupplemented [Kirke 1992[175], as quoted in De-Regil 2010 MA][259] CL/P OR= 0.35, 95% CI 0.09–0.95 [Tolarova 1995[269], as quoted in Botto 2004 SR][192] Isolated CL/P OR= 0.50 (0.36–0.68), isolated CPO OR= 0.73 (0.46–1.20) [Shaw 1995[270], as quoted in Botto 2004 SR][192] CL/P OR= 0.7 (0.4–1.1) CPO OR= 0.4 (0.2–0.9) [Werler 1999[271], as quoted in Botto 2004 SR][192] CL/P OR= 0.59 (0.33–1.09) CPO OR= 0.70 (0.31–1.56) [Beaty 2001[272], as quoted in Botto 2004 SR][192] CL/P 4/2104 supplemented versus 3/2052 unsupplemented, CPO 0/2104 and 2/2052 respectively [Czeizel 1992 RCT][265]	group had a higher rate of acute ear infections [Dobo 1998 Coh][276] Health, growth, behaviour, development and clinical examination did not reveal a difference between children of mothers who used periconceptional vitamins and the general population. However, these children had greater birth weight for gestational age [Holmes-Siedle 1992 Coh][277] Risk of childhood leukemia 82/192 supplemented

Table 5.3.1.2: Summary impact estimates of periconceptual multivitamins			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
	2009 Coh][213] <u>Preterm birth:</u> 178/2367 supplemented versus 166/2305 unsupplemented [Czeizel 1994 RCT][210] 10/852 supplemented versus 34/971 unsupplemented, aOR= 0.29 95% CI 0.13-0.64. For spontaneous preterm birth aOR=0.40 [Catov 2007 Coh][211] RR 0.50 (95% CI 0.20-1.25) [Vahratian 2004][261] HR: 0.84; 95% CI: 0.73, 0.95 [Catov 2011 periconception with BMI <25] <u>Stillbirth:</u> 0/87 supplemented versus 4/103 unsupplemented, Risk ratio= 0.13, 95% CI 0.01-2.41 [Kirke 1992[175], as quoted in	CL/P 4/2471 supplemented versus 3/2391 unsupplemented. CPO 0/2471 supplemented versus 2/2391 unsupplemented [Czeizel 1996 RCT][186] 4/3056 supplemented versus 3/3056 unsupplemented, aOR= 1.63 (95% CI 0.31-28.8) [Czeizel 2004 Coh][187] CL/P 25/467 supplemented versus 101/1314 unsupplemented, aOR= 0.63 95% CI 0.37-1.06. CPO 11/467 supplemented versus 34/1314 unsupplemented, aOR= 0.75 0.35-1.62 [Itikala 2001 CC][198] <u>Cardiovascular malformations:</u> CHDs 0/87 supplemented versus 1/103 unsupplemented, Risk ratio= 0.39, 95% CI 0.02-9.55 [Kirke 1992[175], as quoted in De-Regil 2010 MA][259] Outflow tract defects OR= 0.70 (0.46–1.1) [Shaw 1995[270], as quoted in Botto 2004 SR][192] CHDs 0.76 (0.60–0.97) Outflow tract defects 0.46 (0.24–0.86) VSD 0.61 (0.38–0.99) [Botto 2000[273], as quoted in Botto 2004 SR][192] Outflow tract defects 1.00 (0.70–1.50) VSD 1.20 (0.80–1.80) [Werler 1999[271], as quoted in Botto 2004 SR][192] 6/2104 supplemented versus 9/2052 [Czeizel 1992 RCT][265] 10/2471 supplemented versus 20/2391 unsupplemented (x^2= 3.69; P = 0.055). RR 0.48 (95% CI 0.23-1.03) [Czeizel 1996 RCT][186] 31/3056 supplemented versus 50/3056 unsupplemented, aOR= 0.60 (95% CI 0.38-0.96 [Czeizel 2004 Coh][187] 15/446 supplemented versus 72/1251 unsupplemented. Conotruncal OR= 0.64, 0.57 with negative control. TGA OR= 0.41, 0.36 with negative control. TOF OR= 0.54, 0.48 with negative control. [Botto 1996 CC][202]	versus 76/139 unsupplemented, aOR= 0.63 (95% CI 0.39–1.00) [Ross 2005 CC][278] No significant difference in somatic, mental or behavioral development between children whose mothers received periconceptional multivitamins and those who had received trace elements. Postnatal mortality 18/1809 for multivitamin group versus 13/1782 for unsupplemented. 64/1809 supplemented and 53/1782 unsupplemented had serious or chronic

Table 5.3.1.2: Summary impact estimates of periconceptual multivitamins			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
	De-Regil 2010 MA][259] 7/2170 supplemented versus 6/2133 unsupplemented [Czeizel 1993 RCT][258] 11/2793 supplemented versus 9/2660 unsupplemented [Czeizel 1994 RCT][210] <u>Twins:</u> 50/2170 supplemented versus 40/2133 unsupplemented [Czeizel 1993 RCT][258] 44/2198 supplemented versus 29/2170 unsupplemented [Czeizel 1994 RCT-attributed to clomiphene-ovarian stimulation][262] 93/2471 supplemented versus 64/2391 unsupplemented [Czeizel 1994 RCT][210]	<u>Urinary tract defects:</u> 0.6 (0.4–0.9) [Werler 1999[271], as quoted in Botto 2004 SR][192] 2/2471 supplemented versus 9/2391 unsupplemented (x^2= 4.70; *P* = 0.03). RR = 0.22 (95% CI 0.05-0.99) [Czeizel 1996 RCT][186] 14/3056 supplemented versus 19/3056 unsupplemented, aOR= 0.71 (95% CI 0.33-1.50) [Czeizel 2004 Coh][187] 43/185 supplemented versus 10/21 unsupplemented, aOR= 0.14 95% CI 0.05-0.41 [Li 1995 CC][203] <u>Limb reduction defects:</u> 0.64 (0.41–1.0) [Shaw 1995[270], as quoted in Botto 2004 SR][192] 0.5 (0.2–1.1) [Werler 1999[271], as quoted in Botto 2004 SR][192] 1/2104 supplemented versus 5/2052 unsupplemented [Czeizel 1992 RCT][265] 1/2471 supplemented versus 5/2391 unsupplemented *(x^2*= 2.80; *P* = 0.094). [Czeizel 1996 RCT][186] 1/3056 supplemented versus 3/3056 unsupplemented, OR= 0.33 (95%CI 0.01-3.71) [Czeizel 2004 Coh][187] 9/440 supplemented versus 52/1231 OR=0.47 95% CI 0.23-0.97 [Yang 1997 CC][204] <u>Multiple congenital anomalies:</u> 51/5527 supplemented versus 53/5447 unsupplemented, OR= 0.89, 95% CI 0.45-1.68 [Czeizel 2003 MA][206] NTDs combined with other multiple defects OR = 0.36, 95% C.I. 0.18-0.72 [Khoury 1996 MA][207] 5/3980 supplemented versus 5/3889 unsupplemented [Czeizel 1993 RCT][274] 22/62 supplemented versus 24/65 unsupplemented, aOR= 1.12, 95% CI 0.75–1.69 (including supplements and intake of fortified foods). When those with family history excluded, aOR= 1.05	disorders (significant difference when asthma, atopic dermatitis and wheezy bronchitis combined:26 in multivitamin versus 8 in trace element group [Czeizel 1994 RCT][279] Retinoblastoma: Daily vitamin use 2-12 months prepregnancy OR 0.7 (0.4-1.1)[Olshan 2002 CC]

Table 5.3.1.2: Summary impact estimates of periconceptual multivitamins			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
	84/2471 supplemented versus 64/2391 unsupplemented [Czeizel 1998 RCT][263] OR 0.9 (0.2–3.9) to 1.6 (0.7–3.7) for two different cohorts [Werler 1997][264] aOR 0.98 (0.83–1.17) [Vollset 2005][228]	[Bitsko 2007 CC][205] 23/234 supplemented versus 17/73 unsupplemented [Shaw 2000 CC][208] Multivitamin use >3 times/week during periconceptional period aOR=2.4, 95% CI 0.9-6.7 [Yuskiv 2005 CC][275] <u>Congenital malformations:</u> 20.64/1000 supplemented versus 40.57 unsupplemented ($x^2 = 16.35$; $P < 0.0001$). RR = 0.51, 95% CI 0.36-0.71, including NTDs and familial cases. [Czeizel 1996 RCT][186] 25/1909 supplemented versus 42/1899 unsupplemented [Czeizel 1993 RCT][258] 28/2104 supplemented versus 47/2052 unsupplemented [Czeizel 1992 RCT][265] Mild congenital anomalies 75/3980 supplemented versus 70/3889 unsupplemented [Czeizel 1993 RCT][274] <u>Pyloric stenosis:</u> 2/2471 supplemented versus 8/2391 unsupplemented ($x2 = 3.81$; $P = 0.051$). [Czeizel 1996 RCT][186] 1/3980 supplemented versus 4/3889 unsupplemented [Czeizel 1993 RCT][274] <u>Imperforate anus:</u> 0.50 (0.29–0.88) [Myers 2001, as quoted in Botto 2004 SR][192] <u>Omphalocele:</u> 0.4 (0.2–1.0) [Botto 2002, as quoted in Botto 2004 SR][192]	

Table 7.3.1.3: Summary impact estimates of periconceptual folic acid			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**

Table 7.3.1.3: Summary impact estimates of periconceptual folic acid			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
Folate levels: 46% increase in serum folate with 5mg/week, 136% increase with 1 mg daily (p< 0.0001). 25% increase in RBC folate with 5mg/week, 48% increase with 1 mg daily (p< 0.0001) [Rosenthal 2008 RCT][280] For all women to achieve protective levels, supplementation with 5 mg daily requires >40% adherence vs. 1.1mg >80% adherence. At 100% adherence, 5mg would yield protective levels in 6 wks, whereas 1.1 mg would achieve protection in 90% of women only [Nguyen	Spontaneous Preterm birth: 70% decrease in risk from 20-28 weeks (aHR= 0.31 p=0.031) and 28-32 weeks (aHR= 0.53, p= 0.046) for >1 yr preconception use. PPROM with preterm birth <32 weeks NS [Bukowski 2009 Coh][282] aOR= 0.88, 95% CI 0.63-1.21 [Timmermans 2009 Coh][283] Placental abruption: aHR=0.80-0.86 by duration of use, NS. [Bukowski 2009 Coh][282] Miscarriage: 18/186 folate versus 7/95 control [Kirke 1992 RCT][175] 87/910 folate versus 83/907 control [MRC 1991 RCT][177]	NTD occurrence: Prevalence decreased from 17.5/10,000 to 8.0/10,000with fortification [Lopez-Camelo 2005[220], as quoted in Heseker 2009 SR][286] Prevalence decreased from 7.6/10,000 to 5.5/10,000 with fortification [CDC 2004[215], as quoted in Heseker 2009 SR][286] Prevalence decreased from 16.2/10,000 to 8.6/10,000 with fortification [Gucciardi 2002[217], as quoted in Heseker 2009 SR][286] and from 45.6/10,000 to 7.6/10,000 (high prevalence area) [De Wals 2007[287], as quoted in Heseker 2009 SR][286] Prevalence decreased from 10.6/10,000 to 7.6/10,000 with fortification [Williams 2005[226], as quoted in Heseker 2009 SR][286] Risk ratio= 0.15 (high prevalence area) and 0.60 (low prevalence area) for >80% compliance [Berry 1999 Coh][180] Prevalence 6/4165 with 2.5 mg, 1/4128 with 1 mg, 0/2742 with none [Ulrich 1999 Coh][182] 7/944 cases versus 14/944 controls (x^2 for critical period= 4.33, p= 0.04) [Czeizel 1996 CC][288] Prevalence decreased from 1.9-2.0/1000 births pre-fortification, to 1.4-1.6/1000 with promotion and optional fortification [Bower 2006 Obs][195] Spina bifida: Prevalence decreased from 0.91/1000 to 0.91/1000 to 0.70/1000 with promotion and fortification. Anencephaly: Prevalence went from 0.86/1000 to 0.96/1000 to 0.59/1000. Encephalocele: Prevalence went from 0.17/1000 to 0.21/1000 to 0.12/1000. [Bower 2009 Obs][195] Spina bifida: Prevalence decreased from 4.9/1000 to 3.2/1000 with fortification. Anencephaly: Prevalence decreased from 2.2/1000 to 1.8/1000 [Canfield 2005 Obs][289] RR 0.55, 95% CI 0.48-0.63 [Calvo 2008][214] RR 0.66, 95% CI 0.57-0.76 [De Wals 2003][216]	Nervous system tumours: All tumours OR= 0.44 preconception NS, aOR= 0.26 when supplementation started at <21 days gestation. Central tumours OR= 0.34 preconception, 0.19 <21 days gestation. Sympathetic tumours OR= 0.65 preconception, 0.63 <21 days gestation [Ortega-Garcia 2010 CC][291] NTD survival: Spina bifida: 80/824 pre-fortification, 67/702 optional, 104/1315 mandatory (aHR with mandatory 0.66) [Bol, 2006 Coh][292] Encephalocele: 51/210 pre-fortification, 31/151 optional, 58/277 mandatory (aHR 0.70) [Bol, 2006 Coh][292]

Table 7.3.1.3: Summary impact estimates of periconceptual folic acid			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
2009 ROS][281]	<u>Ectopic pregnancy:</u> 1/186 folate versus 0/95 control [Kirke 1992 RCT][175] 4/910 folate versus 6/907 [MRC 1991 RCT][177] <u>Stillbirth:</u> 0/186 folate versus 2/95 control [Kirke 1992 RCT][175] 4/910 folate versus 3/907 control [MRC 1991 RCT][177] <u>Pre-eclampsia:</u> aHR= 1.03-1.05 by duration of use, NS. [Bukowski 2009, Coh][282] <u>Twinning:</u> With supplementation, Dizygotic aOR=1.26, Monozygotic aOR= 0.70, All twins aOR= 1.02 [Vollset 2005 Coh[228], as quoted in Muggli 2007 SR][209]	RR 0.81, 95% CI 0.69-0.95[Honein 2001][218] RR 0.22, 95% CI 0.13-0.37[Liu 2004][219] RR 0.46, 95% CI 0.35-0.60[Lopez-Camelo 2005][220] RR 0.45, 95% CI 0.30-0.68[Persad 2002][221] RR 0.52, 95% CI 0.40-0.68[Ray 2002][222] RR 0.69, 95% CO 0.49-0.97[Sayed 2008][223] RR 0.75, 95% CI 0.56-1.00[Simmons 2004][224] RR 0.60, 95% CI 0.51-0.71[Williams 2002][225] <u>NTD recurrence [as quoted in Grosse 2007 SR]:</u> 2/60 supplemented versus 4/51 unsupplemented, 58% risk reduction with intent-to-treat, NS. However 100% risk reduction with actual use [Laurence 1981 RCT][176]- 0/84 diet, 6/17 poor diet and unsupplemented (p= 0.04) 71% risk reduction with intent-to-treat. However 83% risk reduction with actual use [MRC 1991 RCT][177] 100% risk reduction with intent-to-treat [Kirke 1992 RCT][175] 8/13 supplemented versus 66/134 unsupplemented, aOR=1.12 [Suarez 2000 CC][178] For total intake (diet and supplements) aOR with 0.4-1 mg folic acid= 0.96, 95% CI 0.54-1.71 and for >1mg aOR= 0.73, 95% CI 0.31-1.72 [Suarez 2000 CC][178] 100% risk reduction [Vergel 1990 Obs][179]	

Table 7.3.1.3: Summary impact estimates of periconceptual folic acid			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
	With fortification, maximum 2.4-4.6% annual increase in rates across all maternal ages [Muggli 2007 SR][209] 34% increase in frequency, relative risk ratio 1.32 [Nazer 2006 Obs[284], RRR quoted in Muggli 2007 SR][209] 3/186 folate versus 1/95 control [Kirke 1992 RCT][175] 7/593 folate versus 5/600 control [MRC 1991 RCT][177] aOR 1.71 (95%CI 1.21–2.42) [Kallen 2004][285] OR 0.91, 95% CI 0.82-1.00 [Li 2003][227] OR 0.99, 95% CI 0.92-1.07 [Lawrence 2004][229] OR 0.97, 95% CI 0.76-1.24 [Shaw	<u>Small-for-gestational age:</u> aHR= 0.93-0.96 by duration of use, NS after adjustment [Bukowski 2009 Coh][282] aOR= 0.40, 95% CI 0.22- 0.72 [Timmermans 2009 Coh][283] <u>Low birth weight:</u> aOR= 0.43, 95% CI 0.28-0.69 [Timmermans 2009 Coh][283] <u>Orofacial clefts:</u> CL/P OR= 0.82 (p=0.02), CPO OR= 0.95 NS, OFC OR= 1.18 NS [Johnson 2008 MA][193] CL/P OR= 0.54 comparing quintiles of dietary intake [van Rooij 2004[235], as quoted in Johnson 2008 MA][193] CL/P OR= 1.36, CPO OR= 0.37 comparing quantiles of dietary intake [Shaw 2006[234], as quoted in Johnson 2008 MA][193] CL/P OR= 0.64, CPO OR= 0.70 comparing tertiles of dietary intake [Chevrier 2007[232], as quoted in Johnson 2008 MA][193] CL/P OR= 0.80 comparing quantiles of dietary intake [Wilcox 2007[236], as quoted in Johnson 2008 MA][193] CL/P OR= 0.9, CPO OR= 1.0 comparing quantiles of dietary intake [Little 2008[233], as quoted in Johnson 2008 MA][193] Prevalence ratio for cleft lip 0.95 (any fortification), 0.93 with compulsory fortification. For cleft palate 1.01 (any) and 0.92 (compulsory). For orofacial clefts 0.94 (compulsory) [Johnson 2008 MA][193] Orofacial clefts 0/169 folate versus 1/88 control [Kirke 1992 RCT][175] Orofacial clefts 1/593 folate versus 0/602 control [MRC 1991 RCT][177] Prevalence 13/4165 with 2.5 mg folic acid, 7/4128 with 1 mg, 6/2742 with none. [Ulrich 1999 Coh][182]	

Table 7.3.1.3: Summary impact estimates of periconceptual folic acid			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
	2003][230] OR 1.14, 95% CI 0.83-1.57 [Signore 2005][231]	CL/P 2/3017 supplemented versus 2/3431 unsupplemented, OR= 1.14. CPO 1/3018 supplemented versus 1/3432 unsupplemented, OR= 1.14 [Czeizel 1999 Coh][196] High-dose folic acid (~ 6 mg daily) aOR during critical period CL/P= 0.72, CPO= 0.86 [Czeizel 1999 Coh][196] CL/P 9/174 supplemented versus 33/446 unsupplemented OR= 0.64, CPO 6/171 supplemented versus 14/427 unsupplemented OR= 1.58 [Bower 2006 CC][195] CL/P OR= 1.56, CPO OR= 2.07 comparing tertiles of dietary intake [Bower 2006 CC][195] Multivariate relative risk 1.1 for all orofacial clefts, 1.2 for cleft lip, 0.9 for cleft palate with daily use. Multivariate relative risk for unsupplemented by highest quartile dietary intake 0.9, and 0.8 for supplements and highest dietary intake together. [Hayes 1996 CC][197] CL/P 7/940 cases versus 9/940 controls (x^2= 8.23, p= 0.004) [Czeizel 1996 CC][288] CL/P: Prevalence decreased from 9.5/1000 to 9.0/1000. CPO: Prevalence decreased from 6.0/1000 to 5.3/1000 with fortification. [Canfield 2005 Obs][289] Orofacial clefts prevalence decreased from 85.2/100,000 births to 80.2/100,000 births with fortification, Prevalence ratio= 0.94 [Yazdy 2007 Obs][290] <u>Congenital heart defects (CHD):</u> Conotruncal 0/170 folate versus 0/88 control. [Kirke 1992 RCT][175] Conotruncal 1/593 folate versus 1/602 control [MRC 1991 RCT][177] Prevalence 15/4165 with 2.5 mg folic acid, 12/4128 with 1 mg, 13/2742 with none [Ulrich 1999 Coh][182] 50/215 supplemented versus 101/514 unsupplemented OR= 1.24 (conotruncal 17/182 supplemented versus 30/443 unsupplemented OR=1.42) [Bower 2006 CC][195]	

Table 7.3.1.3: Summary impact estimates of periconceptual folic acid			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
		OR= 1.23 (conotruncal OR= 1.88) comparing tertiles of dietary intake [Bower 2006 CC][195] Increasing quartiles of total dietary folate aORs for outflow tract defects 0.90, 1.17, 1.18. aORs for TGA 0.65, 0.78, 0.76. For normally-related great vessels, 1.18, 1.59, 1.68. [Scanlon 1998 CC][201] > = 400 mcg supplement (vs <400) aORs for outflow tract defects 0.97, TGAs 1.04, normally-related vessels 0.91 [Scanlon 1998 CC][201] Any CHD OR=0.82 positive control, 0.83 with genetic defects only, 0.74 negative control. Isolated septal defects OR= 0.62, 0.56 with negative control. Conotruncal OR= 0.77, 0.69 with negative control. AVSD OR= 1.42, 1.28 with negative control. Left ventricular outflow defects OR= 1.23, 1.11 with negative control. Right ventricular outflow defect OR= 1.07, 0.96 with negative control. Complex CHD OR= 0.82, 0.74 with negative control. Other CHDs OR= 0.69, 0.62 with negative control. [van Beynum 2010 CC][200] 19/2976 cases versus 19/2976 controls (x^2= 11.91, p= 0.001) [Czeizel 1996 CC][288] TGA: Prevalence decreased from 4.2/1000 to 3.7/1000 with fortification. TOF, VSD and common truncus did not decrease significantly. [Canfield 2005 Obs][289] <u>Urinary tract defects:</u> Prevalence 9/4165 with 2.5 mg folic acid, 4/4128 with 1 mg, 2/2742 with none [Ulrich 1999 Coh][182] 38/203 supplemented versus 79/492 unsupplemented OR= 1.20, (OR= 1.25 comparing tertiles of dietary intake) [Bower 2006 CC][195] Renal agenesis: Prevalence decreased from 3.9/1000 to 3.6/1000 with fortification. Bladder exstrophy did not decrease significantly. Obstructive genitourinary defects: Prevalence increased from 17.3/1000 to 19.3/1000. [Canfield 2005 Obs][289] <u>Limb reduction defects:</u> 0/169 folate versus 0/88 control [Kirke 1992 RCT][175] 1/593 folate versus 0/602 control [MRC 1991 RCT][177]	

Table 7.3.1.3: Summary impact estimates of periconceptual folic acid			
Maternal Outcomes	**Pregnancy/Fetal Outcomes**	**Newborn Outcomes**	**Infant/Child Outcomes**
		Prevalence 1/4165 with 2.5 mg folic acid, 2/4128 with 1 mg, 2/2742 with none [Ulrich 1999 Coh][182] 6/171 supplemented versus 20/433 unsupplemented OR= 0.75 (OR= 1.19 comparing tertiles of dietary intake) [Bower 2006 CC][195] Upper limb: Prevalence decreased from 2.8/1000 to 2.5/1000 with fortification. Lower limb does not decrease significantly. [Canfield 2005 Obs][289] <u>Other major birth effects:</u> 3/169 folate versus 3/88 control [Kirke 1992 RCT][175] 15/593 folate versus 11/602 control [MRC 1991 RCT][177] 27/192 supplemented versus 92/505 unsupplemented OR= 0.74 (OR= 0.80 comparing tertiles of dietary intake) [Bower 2006 CC][195] Overall congenital anomalies prevalence 27.8% with 2.5 mg folic acid, 26.1% with 1 mg, 25.9% with none [Ulrich 1999 Coh-**Did not separate periconception from first trimester**][182] Omphalocele: Prevalence decreased from 1.9/1000 to 1.5/1000 with fortification. Pyloric stenosis: Prevalence decreased from 15.7/1000 to 14.8/1000. Down syndrome: Prevalence increased from 11.1/1000 to 11.8/1000. [Canfield 2005 Obs][289]	

Key:
*NS= Not statistically significant, where results were significant p-values have been indicated

MA= Meta-analysis
SR= Systematic Review
RCT= Randomised Controlled Trial
ROS= Randomised other study
Obs= Observational (Coh= Cohort, CC= Case-control)
Please refer to the 'Characteristics of Included Studies' table for the dose and duration of supplementation and levels of intake. Unless otherwise stated, results are for studies of folate supplementation

- Further ongoing research (Javois 2007)[298] is needed to validate the effect, if any, of periconceptional folic acid/multivitamins on congenital heart defects, orofacial clefts and maternal and pregnancy outcomes.
- Additionally, research is needed to determine the optimal dose of folic acid for fortification of foods, and to demonstrate which interventions to improve the use of folic acid/multivitamin supplements are most effective in women of reproductive age who are at higher risk of birth defects.

5.4. Other micronutrients

Background

While there is conclusive evidence for the role of folic acid in the preconception period to prevent adverse pregnancy outcomes, very few studies have been conducted to assess the role of other micronutrients. Micronutrients are important in the preconception period since they affect fertility and reproductive function, as well as the early stages of gestation during which fetal development occurs, through various biologic pathways.[299]

Scope of Intervention

We reviewed studies where the intake of any nutrient in the pre- or peri-conception period was reported in relation to pregnancy outcomes. Studies where nutrient intake was assessed postpartum as a proxy for women's preconception intake were excluded.

Impact estimates

Few risk-aversion studies were found that assessed maternal periconceptional micronutrient intake. The focus was mainly on B-complex vitamins and other nutrients involved in important biologic pathways (glycemic and methylation). Overall women with adequate micronutrient levels had lower risk of miscarriage and neural tube defects.

Conclusion and Key messages

There is a dearth of evidence to support supplementation of non-folate micronutrients in the preconception period. Larger controlled trials are urgently needed to determine whether supplementation with other micronutrients, particularly other B-complex vitamins, might further reduce the rates of adverse pregnancy outcomes and congenital birth defects.

5.4.1. Iron supplementation

Background

Prevalence of anemia has been reported to be higher in pregnant compared to non-pregnant women.[300] Maternal iron deficiency in the first trimester of pregnancy has been linked with significant reductions in infant size at birth[301-303] and perinatal mortality.[301, 304] The relationship between maternal anemia and preterm delivery has been studied in the past few years with some studies supporting this association[305-308] but not all.[309] Ronnenberg et al.[310] also reported a significant association between preconception

Table 5.4.1. : Summary of impact estimates of other micronutrients		
Maternal	**Pregnancy/Fetal**	**Newborn**
	Women with sufficient vitamin B6 had a lower risk of early pregnancy loss (aOR 0.7, 95% CI 0.4-1.1) than did women with vitamin B6 deficiency [Ronnenberg 2007][314]	Elevated homocysteine (≥12.4 μmol/L) was associated with a nearly 4-fold higher risk of preterm birth (OR: 3.6, 95% CI 1.3-10.0, P < 0.05). The risk of preterm birth was 60% lower among women with vitamin B-12 ≥ 258 pmol/L than among deficient women (OR: 0.4, 95% CI 0.2-0.9, P < 0.05) and was 50% lower among women with vitamin B-6 ≥30 nmol/L than among deficient women (OR: 0.5, 95% CI 0.2-1.2, NS). Folate status was not associated with preterm birth, and homocysteine and B vitamin status were not associated with LBW or SGA status. [Ronnenberg 2002][315]
	The risk of spontaneous abortion was higher among women with suboptimal plasma concentrations of both folate and vitamin B6 (folate less than or equal to 8.4 nmol/L and vitamin B6 less than or equal to 49 nmol/L) OR 4.1, 95% CI 1.2, 14.4). Homocysteine and vitamin B12 status were not associated with spontaneous abortion risk. [Ronnenberg 2002] [315]	OR 0.49 (0.27-0.90) for highest versus lowest quartile of maternal choline intake periconceptionally and risk of NTDs. aOR 0.99 (0.59-1.66) for highest versus lowest quartile of maternal betaine intake periconceptionally and risk of NTDs [Shaw 2004][320] aOR 0.50 (0.34–0.73) for highest versus lowest quartile of maternal methionine intake (3 months preconception) and risk of NTDs. Effect remained when effect of preconception folate considered simultaneously [Shaw 1997][321] Most factors in the glycemic pathway were not associated with NTDs, with the exception of low levels of fructose and glucose that were significantly associated with anencephaly. Some nutrients that contribute to one-carbon metabolism showed lowered risks (folate, riboflavin, vitamins B6 and B12); others did not (choline, methionine, zinc). Antioxidant nutrients tended to be associated with lowered risks (vitamins C, E, A, b-carotene, lutein). [Carmichael 2010][267]
	No significant associations were found between vitamin concentrations and early pregnancy loss or birth weight [de Weerd 2003][316]	Adjusted analyses revealed decreased NTD risks with increased intakes of methionine, lutein, magnesium, zinc, and thiamin for women who did not use vitamin supplements periconceptionally. We observed decreased NTD risks associated with increased intakes of linoleic acid, cysteine, calcium, and zinc for women who used supplements. We also observed increased NTD risks with increased intakes of oleic acid. For users as well as nonusers of vitamin supplements, we observed reduced risks with increased intakes of grains and dairy products. [Shaw 1999][322]
	Vitamin C and total fetal loss: RR 0.79 (0.10-6.15) [Hemmi 2003][317]	NTD risk estimates were lowest for women whose diets were rich in choline, betaine, and methionine. That is, for women whose intake was above the 75th percentile compared with below the 25th percentile for all three nutrients, the odds ratio was 0.17 (95% CI 0.04, 0.76). [Shaw 2004][320]
	Low periconceptional vitamin C intake (< 70 mg/d) and GDM: OR = 3.7, 95% CI 1.7-8.2). For those in lowest versus highest quintile of plasma ascorbic acid, the risk was 12.8 times higher [Zhang	Limb defects are associated with low dietary vitamin B6 [Robitaille 2009][323] NTDs are not associated with dietary intake of myo-inositol [Shaw 2005][324] Increased risks for CHD associated with lower dietary intakes of linoleic acid, total carbohydrate, and fructose for dTGA, whereas decreased risks were observed for lower intakes of total protein and

Table 5.4.1. : Summary of impact estimates of other micronutrients		
Maternal	**Pregnancy/Fetal**	**Newborn**
	2004][318] Women who had total vitamin C intakes of <10th percentile preconceptionally risk of preterm delivery due to PROM RR 2.2 (95% CI 1.1-4.5). [Siega-Riz 2003][319]	methionine for TOF. Lower dietary intake of several micronutrients, namely folate, niacin, riboflavin, and vitamins B12, A, and E, even after simultaneous adjustment for other studied nutrients, were associated with increased risks of dTGA, but not for TOF. These associations were observed among women who did not use vitamin supplements periconceptionally [Shaw 2010][325] 3-fold increase in the risk of NTDs in mothers who had vitamin B-12 status in the lower quartile, regardless of FA fortification [Thompson 2009][326] Congenital diaphragmatic hernia OR of 0.6 (95% CI: 0.3–1.0) was observed for higher intake of choline. Elevated ORs (1.4 to 1.7) were found for lower intakes of choline, cysteine, methionine, and protein. Among women who took vitamin supplements, higher intakes of B vitamins (i.e., folate, vitamin B1, B2, B6, and B12), minerals (i.e., calcium, iron, magnesium, and zinc), and vitamin E were inversely associated with CDH (ORs from 0.7–0.3). Moreover, among women who did not take vitamin supplements, lower intakes of calcium, retinol, selenium, vitamin B12, and vitamin E had positive associations with CDH (ORs from 1.4 to 2.1) [Yang 2008][327] NTDs and Zinc: highes versus lowest quintile of intake OR = 0.65, 95% CI 0.43-0.99 [Velie 1999 CC][328]

moderate maternal anemia (Hb<95 g/L) and fetal growth restriction and reduced birth-weight.

Several studies have looked into addressing anemia during pregnancy in order to reduce the associated adverse outcomes. Multiple trials on iron supplementation during early pregnancy have shown significant reductions in the frequency of infants with low birth-weights.[303, 311, 312] Various modes of iron supplementation have been studied. The trial in Bangladesh[311] compared supplementation with a powdered form of micronutrients and tablets. It showed greater mean haemoglobin among subjects taking the tablet compared to those taking the powdered form. This was attributed to a higher rate of compliance among tablet users. Another trial[313] with doubly fortified sugar (iron plus vitamin A) showed significant increase in iron stores among women of reproductive age in 2 of the 3 fortified communities.

As a complementary strategy to iron supplementation, periconceptional iron plus folic acid (IFA) supplementation has been suggested by Smitasiri et al.[329] to treat underlying anemia, build up iron stores and prevent neural tube defects. This was used in a trial[330] that reported no improvement in anemic status of pregnant women taking IFA as compared to only folic acid, however women who initiated supplementation before conception showed a significantly greater change in maternal hemoglobin from baseline compared with those who initiated supplementation after conception. In nonpregnant women IFA was significantly more effective in reducing anemia frequency and improving iron stores.

Scope of Intervention

We looked at studies addressing the possible association of preconception iron deficiency anemia with MNCH outcomes. Also we focused on trials rectifying the problem if such an association existed. Since not much has been done with regards to only preconception supplementation, we also included supplementation trials in the general adult population as well as supplementation trials with an iron+other nutrient supplementation.

Impact estimates

A single study by Ronnenberg et al. 2004[310] was found on the association of preconception anemia with poor fetal/neonatal effects. This study showed that the risk of low birthweight infants was significantly greater with moderate preconception anemia (OR: 6.5; 95% CI: 1.6-26.7; P=0.009). Moderate anemia before pregnancy was also significantly associated with fetal growth restriction (OR: 4.6; 95% CI: 1.5-13.5; P=0.006).

Conclusion

Iron deficiency anemia among women of reproductive age is a global problem. The situation only worsens during pregnancy leading to known adverse outcomes. Even with intra-pregnancy iron supplementation to correct the iron status, most improvements take long. Hence it is only natural to target iron deficiency in women of reproductive age before they conceive and try to have the greatest effect in reducing pregnancy-related consequences.

Table 5.4.1.1: Summary of impact estimates on Iron

<table>
<tr><th>Intervention</th><th>Pregnancy</th><th>Fetal</th><th>Newborn</th></tr>
<tr><td>Iron fortification (FeNaEDTA to the vitamin A-fortified sugar)</td><td>
<u>Hemoglobin values: g/L [n]</u> [Viteri 1995][313]
<table>
<tr><td></td><td>Basal</td><td>Final</td></tr>
<tr><td>T1</td><td>131+/-12 [20]</td><td>132+/-19 [20]</td></tr>
<tr><td>T2</td><td>127+/-27 [15]</td><td>132+/-15 [15]</td></tr>
<tr><td>T3</td><td>140+/-14 [29]</td><td>144+/-12 [29]</td></tr>
<tr><td>Control</td><td>138+/- 12 [29]</td><td>141+/- 12 [29]</td></tr>
</table>
<u>Serum ferritin (ln ug/L)</u> [Viteri 1995][313]
<table>
<tr><td></td><td>Basal</td><td>Final</td></tr>
<tr><td>T1</td><td>11.93 +/- 3.12</td><td>21.07 +/- 1.84**</td></tr>
<tr><td>T2</td><td>7.38 +/- 2.47</td><td>17.04 +/- 2.05**</td></tr>
<tr><td>T3</td><td>15.28 +/- 2.56</td><td>25.25 +/- 2.43**</td></tr>
<tr><td>Control</td><td>19.88 +/- 2.44</td><td>19.08 +/- 2.04</td></tr>
</table>
</td><td></td><td></td></tr>
<tr><td>Preconception iron status (also present in anemia section)</td><td></td><td></td><td><u>Low birth weight:</u>
Mild (95 </= Hb < 120 g/L) and moderate (Hb < 95 g/L) anemia were significantly associated with lower birth-weight (139 and 192 g, respectively).
Iron-deficiency anemia alone (Hb < 120 g, ferritin < 12 microg/L, no B-vitamin deficiency) was associated with a 242-g decrease in birth-weight.
Both low (<12 microg/L) and high (>/=60 microg/L) ferritin were also significantly associated with lower birth-weight (106 and 123 g, respectively).
The risk of low birth-weight (LBW) was significantly greater among women with moderate anemia compared with non-anemic controls [OR: 6.5; 95% CI: 1.6, 26.7; P = 0.009] [Ronnenberg 2004][310]

<u>Fetal growth restriction</u>:
The risk of fetal growth restriction (FGR) was significantly greater among women with moderate anemia compared with non-anemic controls OR: 4.6; 95% CI: 1.5, 13.5; P = 0.006. [Ronnenberg 2004][310]</td></tr>
</table>

Key messages

- There is a huge dearth of literature on the link between preconception anemia and MNCH outcomes.
- The only relevant study cites a significant association between a haemoglobin of less than 95g/L and low birth weight and fetal growth restriction
- Supplementation and fortification studies show a significant improvement in the iron status among women

5.4.2. Vitamin A Supplementation

Background

Vitamin A deficiency is pervasive and occurs either when there is a limited intake of dairy products, carotene-rich vegetables and fruits or, occasionally, with malabsorption syndromes. Vitamin A deficiency during pregnancy is known to result in night blindness,[331]
increased risk of maternal mortality[332] premature birth, intrauterine growth retardation, low birth weight,[333] and antepartum hemorrhage.[334]

Whereas pregnant women in the West meet their recommended daily need with appropriate consumption during their reproductive years, women in the developing countries need to replenish their sotres. Vitamin A is associated with anemia[335] and Suharno et al.[336] reported that supplementing pregnant women in their second trimester with both vitamin A (2400 mg) and iron daily for 2 months improved hemoglobin concentrations more than when compared to supplementation with iron or vitamin A alone.

Katz et al.[337] reported no association between small weekly doses of vitamin A or beta-carotene given to women before conception, during pregnancy, and through 24 wk postpartum and improvement of fetal or early infant survival in Nepal. A trial in Ghana also found that once a week vitamin A supplementation in women of reproductive age had no favorable effect on their survival or that of their newborns.[338] These findings were in accord with the lack of effect on stillbirth rate and neonatal/infant survival found in Bangladesh.[339] However another trial in Nepal reported that supplementation of women with either vitamin A or beta-carotene at recommended dietary amounts during childbearing years significantly pregnancy-related mortality by 44%.[332]

Scope of Intervention

Our aim was to find evidence on the effect pre pregnancy vitamin A supplementation may have on MNCH outcomes. However, most of the evidence we found was on women of reproductive age with disaggregated data not available for preconception supplementation.

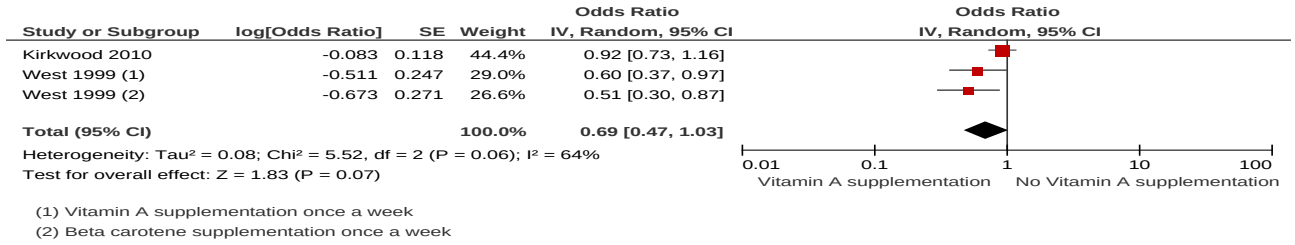
Impact estimates

Due to dearth of selective preconception trials we pooled data from trials amongst women of child-bearing age (including those already pregnant). Our analyses failed to show any significant reduction in neither maternal nor fetal/neonatal mortality (**Figure 5.4.2.1; Figure 5.4.2.2**).

Conclusion

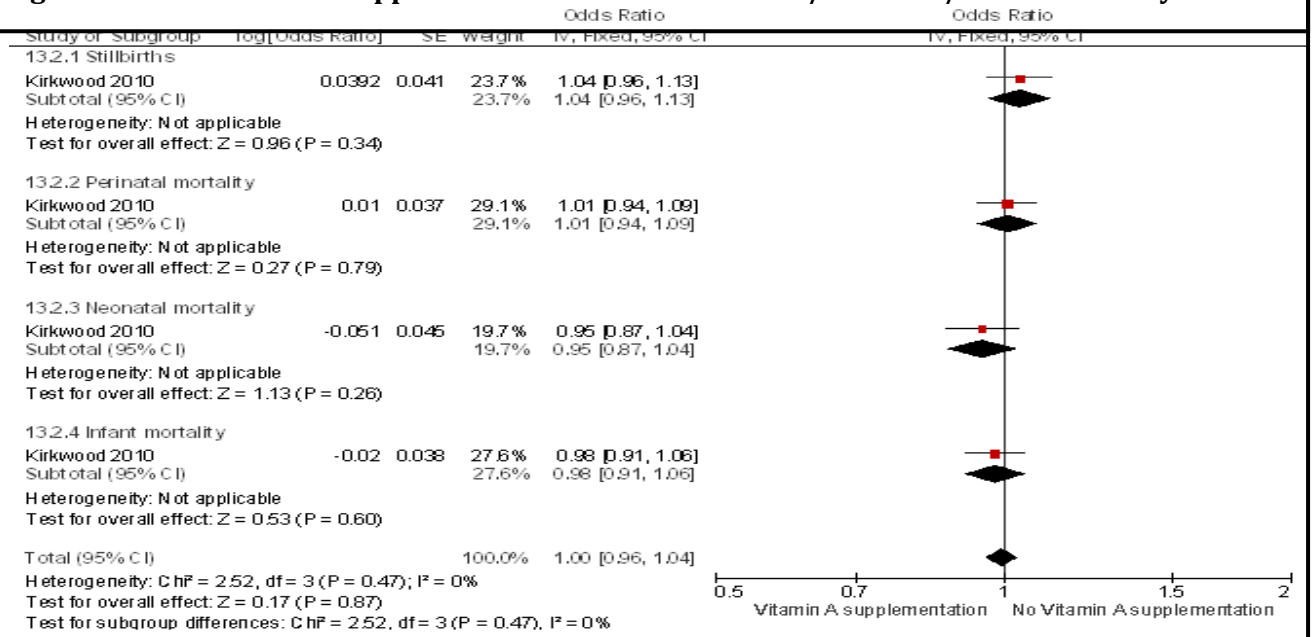
Although limited, the current evidence does not support inclusion of Vitamin A supplementation in women of reproductive age. However the potential benefits may still have been overlooked and larger, more focused trials are needed to evaluate any possible relation of Vitamin A with reducing pregnancy related morbidities and mortalities.

Figure5.4.2.1: Vitamin A Supplementation and odds of maternal mortality



Citation to the included Studies:
Kirkwood 2010[338], West 1999[332]

Figure 5.4.2.2: Vitamin A supplementation and odds of Fetal/Neonatal/Infant mortality



Citation to the included Study:
Kirkwood 2010[338]

Key messages:

- Current evidence does not prove a beneficial effect of Vitamin A supplementation on reducing maternal and/or fetal/neonatal mortality.
- Current evidence mainly comes from trials amongst women of reproductive years (whether currently pregnant or not) where the results cannot be disaggregated to clearly ascertain the role of preconception vitamin A supplementation.
- Future trials need to center on how pre-pregnancy provision of vitamin A supplements could possibly lower adverse pregnancy related outcomes.

Table 5.4.2: Summary impact estimates for Vitamin A			
Maternal	**Pregnancy**	**Newborn**	**Infant**
Maternal mortality: 39 601 pregnancies and 138 pregnancy-related deaths in the vitamin A supplementation group (348 deaths per 100 000 pregnancies) compared with 39 234 pregnancies and 148 pregnancy related deaths in the placebo group (377 per 100 000 pregnancies); adjusted OR 0·92, 95% CI 0·73–1·17; p=0·51. 1326 women died in 292 560 woman-years in the vitamin A supplementation group (453 deaths per 100 000 years) compared with 1298 deaths in 289 310 woman-years in the placebo group (449 per 100 000 years); adjusted rate ratio 1·01, 0·93–1·09; p=0·85 [Kirkwood 2010][338] Mortality related to pregnancy in the placebo, vitamin A, and â carotene groups was 704, 426, and 361 deaths per 100 000 pregnancies, yielding RR (95% CI) of 0.60 (0.37 to 0.97) and 0.51 (0.30 to 0.86). This represented reductions of 40% (P < 0.04) and 49% (P < 0.01) among those who received vitamin A and â carotene. Combined, vitamin A or â carotene lowered mortality by 44% (0.56 (0.37 to 0.84), P < 0.005) and reduced the maternal mortality ratio from 645 to 385 deaths per 100 000 live births, or by 40% (P < 0.02). [West 1999][332]	**Stillbirths**: Adjusted OR for stillbirths (per 1000 births) –(95% CI) Placebo 1.00 vs. Vit A supplementation 1.04 (0.96–.13) [Kirkwood 2010][338]	**Perinatal mortality:** Adjusted OR for perinatal mortality - (95% CI) Placebo 1.00 vs. Vit A supplementation 1.01 (0.94–1.08)(p value 0.85) [Kirkwood 2010][338] **Neonatal mortality:** Adjusted OR for neonatal mortality - (95% CI) Placebo 1.00 vs. Vit A supplementation 0.95 (0.87–1.04) (p value 0.27) [Kirkwood 2010][338]	**Infant mortality:** Adjusted rate ratio for infant mortality - (95% CI) placebo 1.00 vs. Vit A supplementation 0.98 (0.91–1.05) (p value 0.58) [Kirkwood 2010][338]

5.4.3. Iodine supplementation

Background

Iodine deficiency is a universal health problem. It is thought to be the most common preventable cause of mental retardation. The iodine requirement during pregnancy is sharply elevated. Iodine stores to draw from, progressive pathologic changes goiter and hypothyroidism can occur that can adversely affect maternal and fetal health.[340] Severe iodine deficiency during pregnancy causes maternal and fetal hypothyroxinemia[341] which leads to irreversible brain damage with mental retardation and neurologic abnormalities.[342]

There are two main approaches to giving supplementary iodine: either on a daily basis, typically using potassium iodide, or on an annual basis, using a slowly released iodine preparation such as iodised oil. In a trial in PNG,[343] the incidence of cretinism was significantly reduced in offsprings of women given oil-based iodine injections [RR 0.27; 95% CI: 0.12-0.60]. Another trial[344] of intra-pregnancy iodized oil injections, in a severely iodine deficient area, showed a lower occurrence of children with low psychomotor scores. A similar result was reported in a study[345] in China with oral iodized oil given before the third trimester of pregnancy. Other studies on supplementation of women of child-bearing age have also suggested modest cognitive benefits for infants and children of maternal iodine treatment.[346-348] These studies had their own limitations and possible effect of confounders.[349] Other trials of iodine supplementation in pregnant women[350-353] have also shown, via indirect measures, that supplementation is generally effective in leading to an improved thyroid status in both the mother and the neonate; although no direct MNCH outcome was studied.

Scope of intervention

Iodine supplementation during the preconception period and its effects of preventing MNCH outcomes, related to iodine deficiency, has not been studied sufficiently. Therefore we used evidence from intra-pregnancy supplementation trials and intend to extrapolate their findings to our study period.

Impact estimates

A recent Cochrane review by Mahomed et al. 2007[354] aimed to assess the effects of iodine supplementation before or during pregnancy in areas of iodine deficiency. However they only found 3 relevant trials which were conducted in pregnant women and no relevant preconception supplementation trial. Their results showed that supplementation during pregnancy with injectable iodized oil led to a significant 20% reduction in deaths during infancy and early childhood. They also showed that supplementation led to significant decrements in cretinism diagnosed at 4 years of age (RR 0.27; 95% CI: 0.12-0.60) as well as that diagnosed at 10-16 years of age (RR 0.17; 95% CI: 0.05-0.58). Supplementation in severely deficient mothers also led to positive increments in birth-weight of the newborns.

Table 5.4.3: Summary impact estimates for Iodine

Maternal	Pregnancy	Newborn	Infant
	Lipiodol given 1-3 months preconception normalized thyroid function in mother and newborn, increased placental and birth weight, decreased rates of prematurity,	The results showed that if the iodine supplement was given before conception the nervous form of endemic cretinism was prevented. [Pharoah 1987][343]	

	stillbirths and abortion [Chaouki 1994]		

Conclusion

Although providing adequate iodine in mid-to-late pregnancy improves infant cognitive development, there are greater benefits when iodine is given before or early in pregnancy.[349] Trials of supplementation during pregnancy have led to improved maternal and fetal outcomes. These findings can be extrapolated to say that preconception supplementation and attainment of a steady-state of iodine stores before planning a pregnancy would successfully avert the grave consequences associated with iodine deficiency. Hence we suggest that iodine supplementation trials be implemented on an international level as a under the auspices of respective governments.

Key messages

- Trials on pre-pregnancy supplementation with iodine and their effects on preventing unfavorable pregnancy related outcomes are unavailable.
- Evidence from trials conducted during pregnancy more than highlights the importance of addressing the deficiency states before conceiving, to have the greatest impact in reducing both maternal and fetal/neonatal effects of hypothhyroxemia.
- Future research should aim at the best way of implementing iodine supplementation programs for the general population, especially targeting women of reproductive ages.

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Section VI

Diagnosis and treatment of chronic diseases

6.1. Diabetes

Background

Diabetes continues to be an ever-increasing global problem. The prevalence of Type 2 continues to increase worldwide,[1, 2] especially in the developing countries.[3, 4] This in turn means more women of reproductive age in developing countries have diabetes, hence a greater number of pregnancies are complicated by the condition[5, 6] putting both the mother and the fetus at an increased risk of morbidity and mortality.[7] Diabetes in pregnancy is associated with elevated rates of miscarriage,[8] pre-eclampsia,[9, 10] preterm labor and caesarean sections[11, 12] and higher rates of fetal malformation[11, 13-15] neural tube defect, urinary tract disorder, macrosomia,[16, 17] birth injury,[12, 15, 18] and perinatal mortality.[19, 20] Optimal glycemic control during pregnancy may reduce these diabetes-related-risks but what is now considered a more effective time to intervene is that before pregnancy. Systematic reviews done on the effectiveness of preconception care in diabetic women show improving trends in MNCH outcomes.[11, 21, 22]

Scope of intervention

Studies have shown that infants of women with pre-existent insulin dependent diabetes mellitus have a 10-fold greater risk of a congenital malformation and a fivefold greater risk of being stillborn than infants in the general population.[23] Significant associations between pre-gestational diabetes and perinatal mortality and congenital malformations, as well as other neonatal and maternal morbidities, were also found in other studies.[24-29] Preconception diabetic care is a multidisciplinary approach with the goal of care being to obtain the lowest possible hemoglobin A1C without significant episodes of hypoglycemia. Adequate glycaemic control in this period is the key to reducing the occurrence of the above mentioned adverse MNCH outcomes. A recent review showed that for each 1-SD unit increase in periconceptional GHb, the associated risk of a congenital malformation increased by an odds ratio of 1.2 (95% CI 1.1–1.4).[30] According to the ADA attainment of an HbA1C level of less than 1% above normal reduces the rate of malformations and spontaneous abortions to no diabetes rates. However a study in the Netherlands stated that despite planned pregnancies (with achievement of good glycemic controls), maternal and neonatal complications were still elevated.[31] The content for preconception care (**Table 6.1.1**) broadly includes educating the patient with regards to the disease and its interplay with pregnancy; educating the patient about self-management skills; physician-directed assessment and care of the disease and complications; counseling about diet, exercise and reproductive advice.

Table 6.1.1: Content of preconception care for women with pregestational diabetes

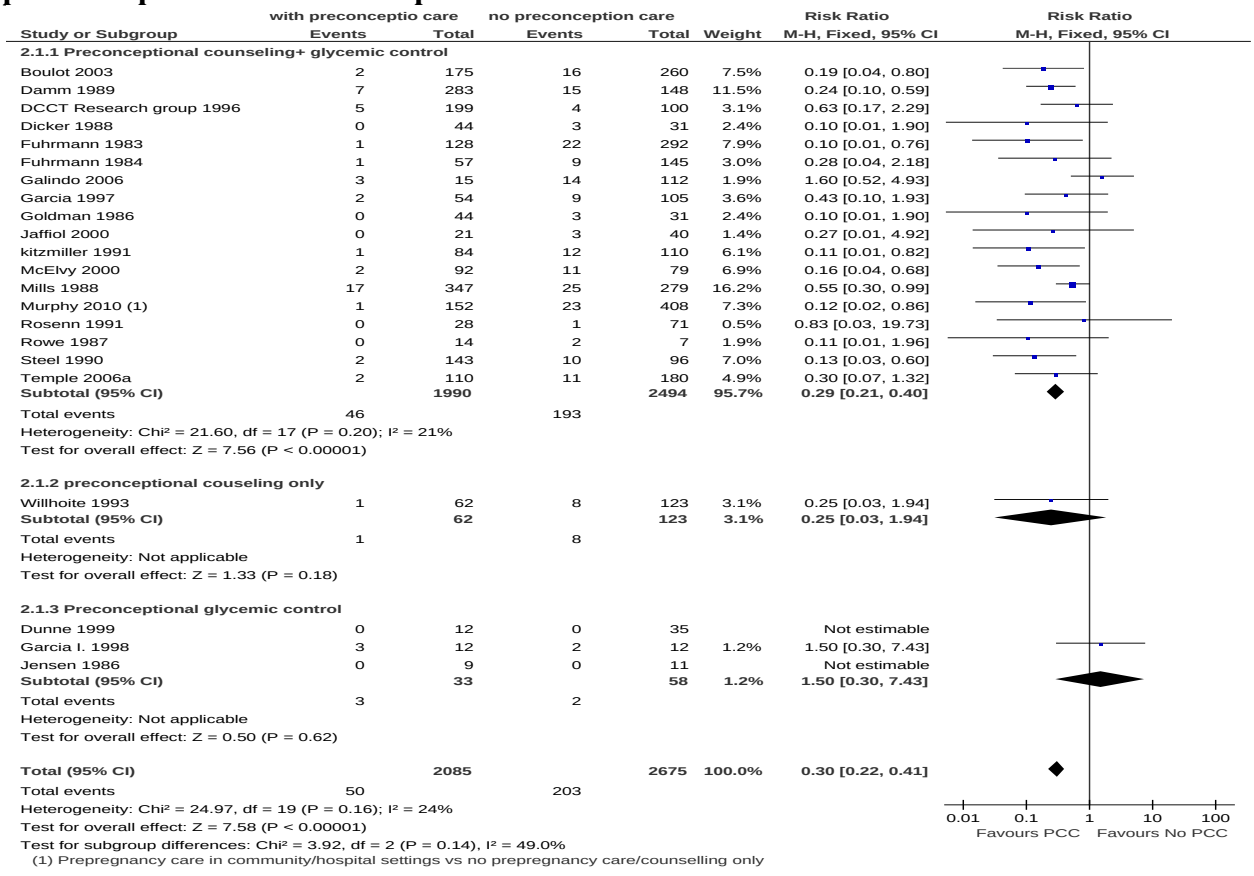
- Educate about the importance of strict glycemic controls with an HbA1C level of less than 6-7%
- Educate and emphasize self-management skills with preset monitoring targets
- Counsel about the elevated risks of maternal complications (Pre-eclampsia, preterm labor, post-partum hemorrhage) and fetal complications (miscarriage, perinatal mortality, congenital malformations, macrosomia) with poor glycemic control
- Counsel about diet (as per protocol for diabetes). Emphasize the importance of healthy physical activity and weight management.

- Counsel about the risks attached to unplanned pregnancies and advise use of good contraception until good metabolic control is achieved.
- Commence preconception folic acid supplementation (5mg/day)
- Review current medication list for diabetes and switch from Oral hypoglycemics to insulin to achieve target blood glucose levels before conception. Review other medications as well.
- Evaluate and treat diabetic complications

Impact estimates

We found 23 studies relevant to our intervention under review that looked at various outcomes related to pre gestational diabetes. These studies were mostly cohorts looking at the effectiveness of preconception care for diabetic mothers in reducing adverse pregnancy related effects and only one trial. Meta-analysis of 21 studies showed that preconception care was able to significantly reduce the occurrence of congenital malformations (RR 0.30; 95% CI: 0.22-0.41) (**Figure 6.1.1; Figure 6.1.2**). This finding is in line with the results of a review by Ray et al.[11]

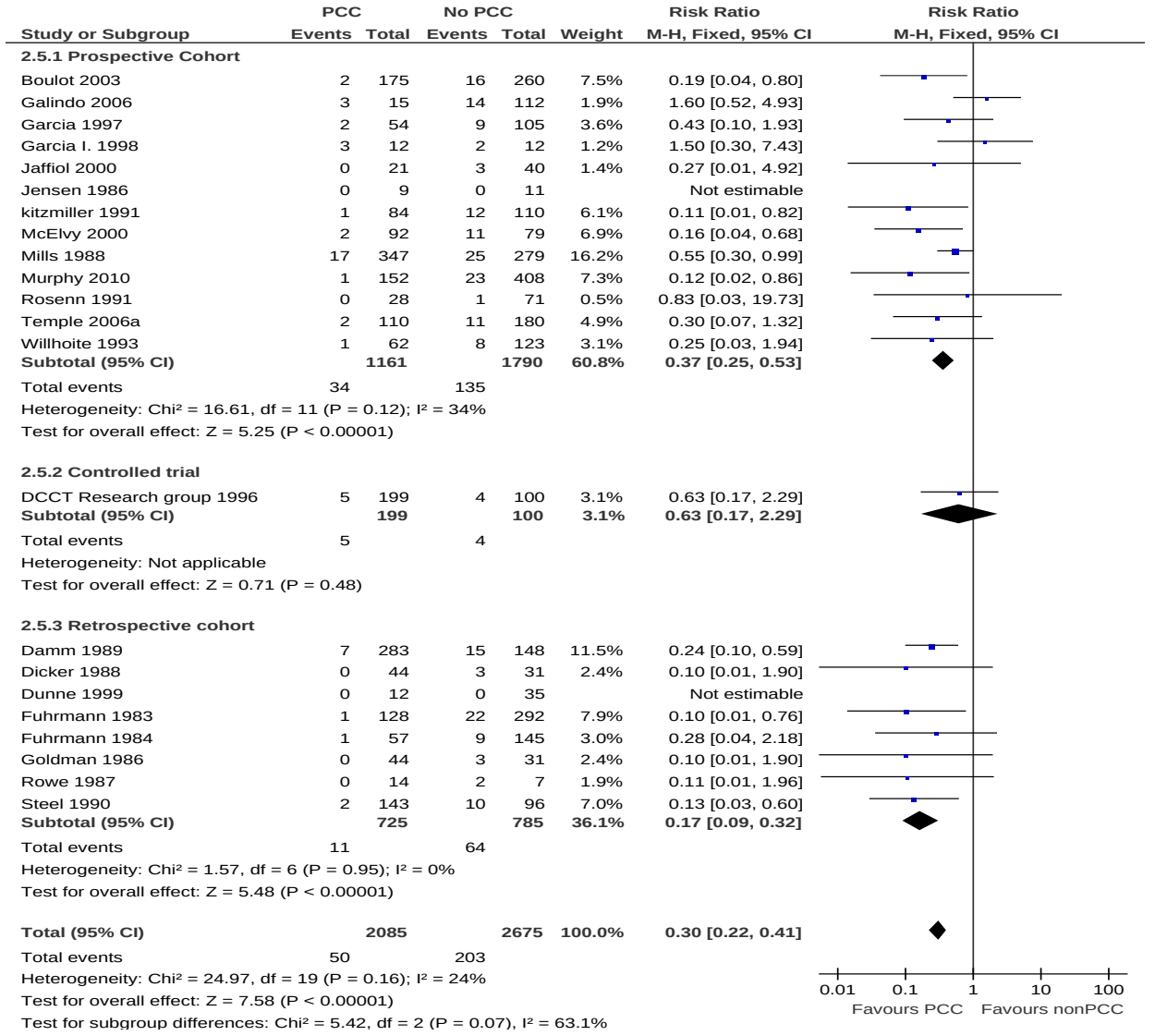
Figure 6.1.1: congenital malformations in preconception care versus non preconception care with respect to intervention



Citations to the included studies:

Boulot 2003[32], Damm 1989[33], DCCT research Group 1996[20], Dicker 1988[34], Fuhrmann 1983[35], Fuhrman 1984[36], Galindo 2006[37], Garcia 1997[38], Goldman 1986[39], Jaffiol 2000[40], kitzmiller 1991[41], McElvy 2000[42], Mills 1988[43] Rosenn 1991[44], Rowe 1987[45], Steel 1990[46], Temple 2006[47], Willhoite 1993[48], Dunne 1999[49], Garcia I. 1998[50], Jensen 1986[51], Murphy 2010[52]

Figure 6.1.2: congenital malformations in preconception care versus non preconception care with respect to study design

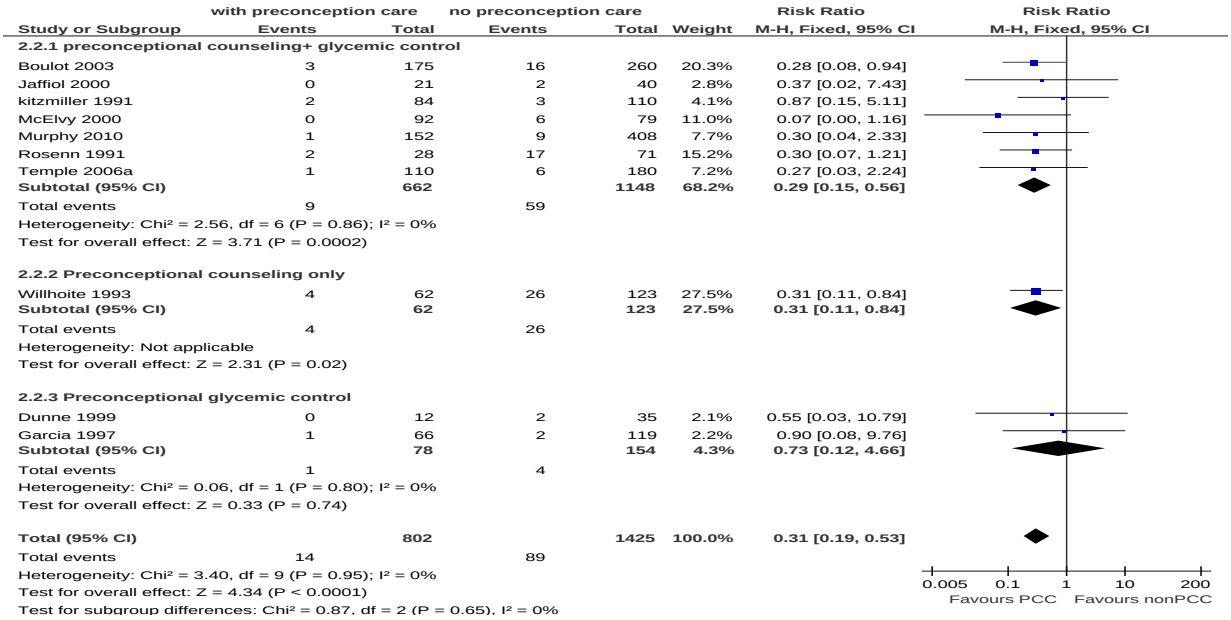


Citations to the included studies:
Boulot 2003[32], Galindo 2006[37], Garcia 1997[38] , Garcia I. 1998[50], Jaffiol 2000[40], Jensen 1986[51], kitzmiller 1991[41], Mcelvy 2000[42], Mills 1988[43], Rosenn 1991[44], Temple 2006[47], Willhoite 1993[48], DCCT research Group 1996[20], Damm 1989[33], Dicker 1988[34], Dunne 1999[49], Fuhrmann 1983[35], Fuhrman 1984[36], Goldman 1986[39], Rowe 1987[45], Steel 1990[46], Murphy 2010[52]

Disaggregating the data to observe what effect preconception counseling plus strict metabolic control had, showed a 71% reduction in the rate of congenital anomalies when compared to mothers receiving standard antenatal care. Prospective cohorts were better at citing this positive association.

Pooled data for the effect of preconception care on the risk of perinatal mortality was also significant (RR 0.31; 95% CI: 0.19-0.53) with counseling plus strict glycaemic control leading to a 71% reduction in the events in this group compared to the standard antenatal care group. (**Figure 6.1.3; Figure 6.1.4**). These figures are comparable to those of a recent review[21] with the differences being attributed to inclusion of studies with a low to moderate level of bias by them.

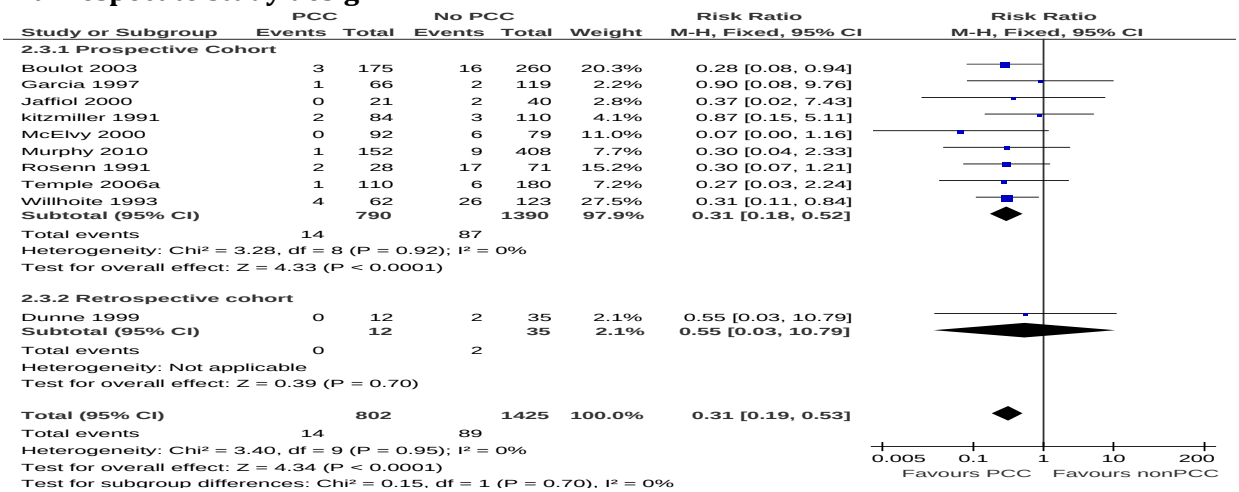
Figure 6.1.3: Perinatal mortality in preconception care versus non preconception care with respect to intervention



Citations to the included studies:

Boulot 2003[32], Jaffiol 2000[40], kitzmiller 1991[41], Mcelvy 2000[42], Rosenn 1991[44], Temple 2006[47], Willhoite 1993[48], Dunne 1999[49], Garcia 1997[38], Murphy 2010[52]

Figure 6.1.4: Perinatal mortality in preconception care versus non preconception care with respect to study design



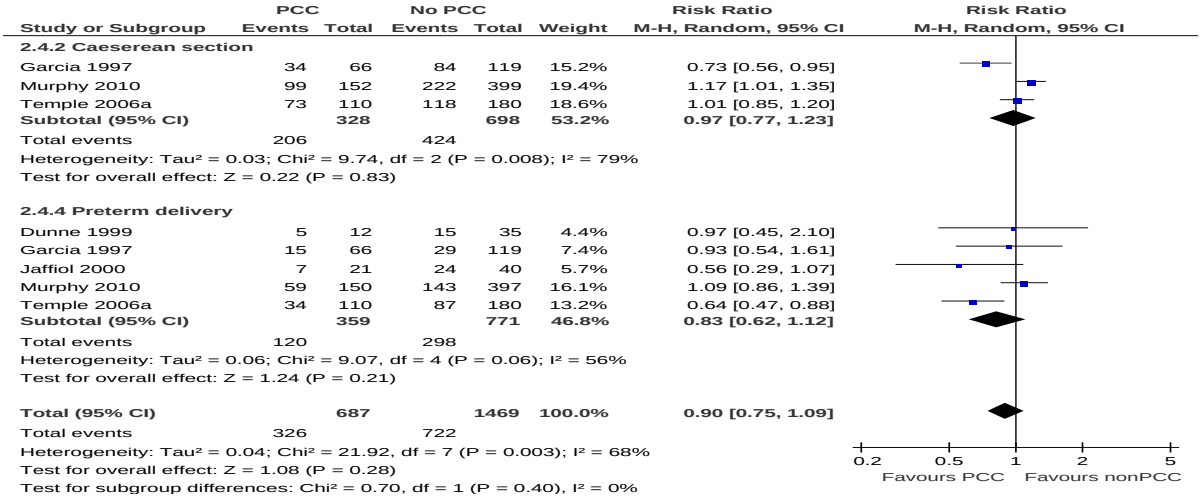
Citations to the included studies:

Boulot 2003[32], Garcia 1997[38], Jaffiol 2000[40], kitzmiller 1991[41], Mcelvy 2000[42], Rosenn 1991[44], Temple 2006[47], Willhoite 1993[48], Dunne 1999[49], Murphy 2010[52]

When looking at pregnancy complications, the meta-analysis supported the effectiveness of preconception care in reducing the rate of preterm delivery (RR 0.83; 95% CI: 0.62-1.12) and of caesarean sections (RR 0.97; 95% CI: 0.77-1.23) but both results were non-significant (**Figure6.1.5**). Results for other fetal/neonatal outcomes were also non-significant (**Figure 6.1.6**). Preconception care led to a non-significant 12% reduction in macrosomia (**Figure 6.1.7**). Our data revealed that preconception care was valuable in significantly dropping the level of HbA1C during the first trimester of pregnancy (**Figure 6.1.8; Figure 6.1.9**). As hyperglycemia during the period of organogenesis leads to an increased risk of congenital malformations, this achievement of better glycaemic control in the 1st trimester may explain the concurrent reduction of anomalies as well as subsequent perinatal death. A single study

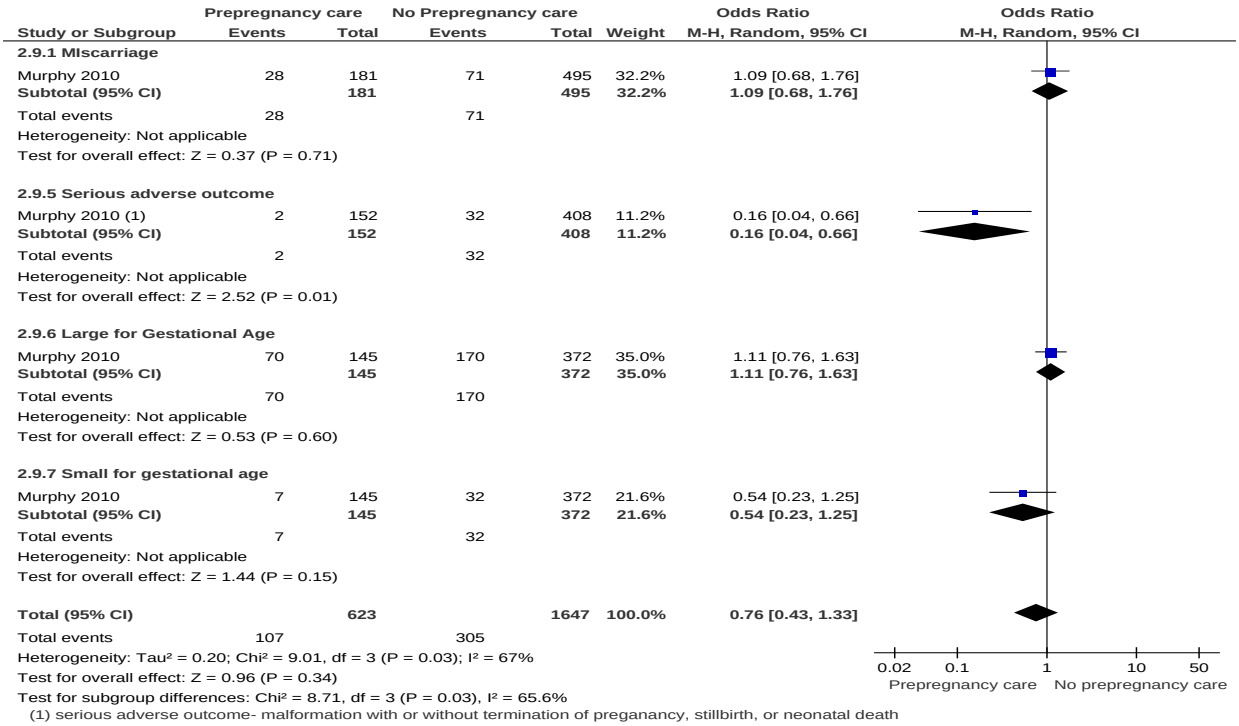
by Heller 2010[53] showed a weak non-significant effect of preconception insulin in reducing the 1st trimester HbA1C as compared to commencement of insulin in early pregnancy (**Figure 6.1.10**).

Figure 6.1.5: Pregnancyoutcomes in preconception care versus non preconception care



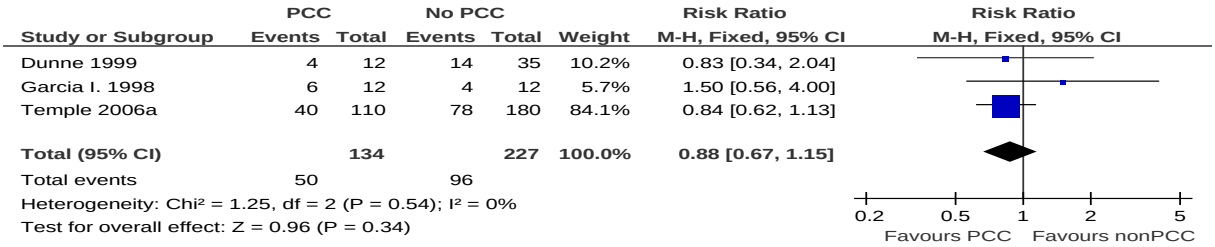
Citations to the included studies:
Garcia 1997[38], Dunne 1999[49], Garcia 1997[38], Jaffiol 2000[40], Temple 2006[47], Murphy 2010[52]

Figure 6.1.6: Fetal/Neonatal outcomes in preconception care versus non preconception care



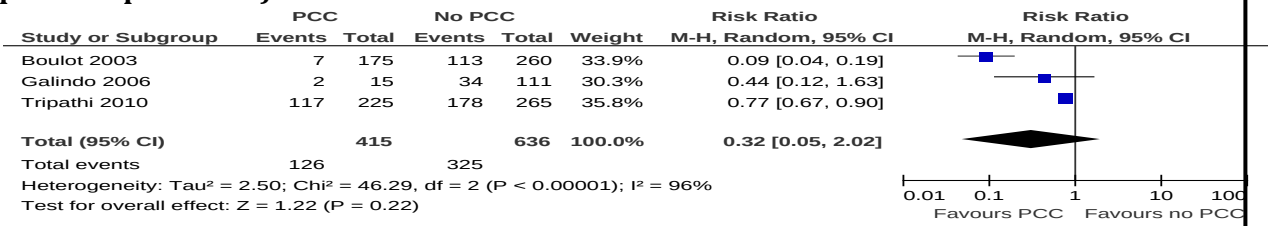
Citations to the included studies:
Murphy 2010[52]

Figure 6.1.7: Macrosomia in preconception care versus non preconception care



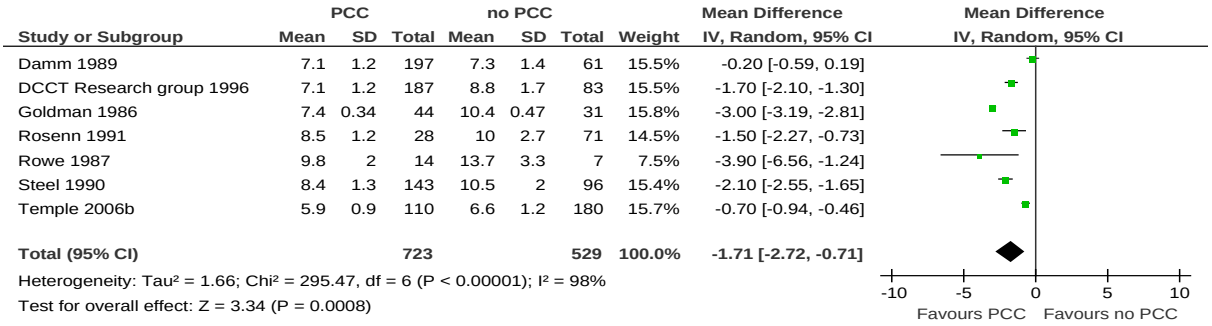
Citations to the included studies:
Dunne 1999[49], Garcia I. 1998[50], Temple 2006a[47]

Figure 6.1.8: maternal HbA1C > 7-8% in 1st trimester (preconception care versus non preconception care)



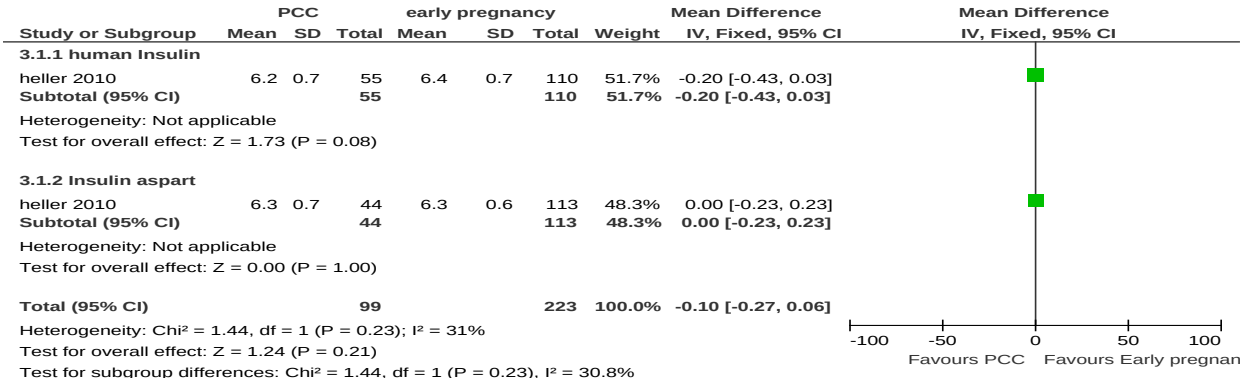
Citations to the included studies:
Boulot 2003[32], Galindo 2006[37], Tripathi 2010[54]

Figure 6.1.9: Mean maternal HbA1C in 1st trimester (preconception care versus no preconception care)



Citations to the included studies:
Damm 1989[33], DCCT research Group 1996[20], Goldman 1986[39], Rosenn 1991[44],Rowe 1987[45], Steel 1990[46], Temple 2006b[55]

Figure 6.1.10: Mean HbA1C level in 1st trimester: Human insulin versus Insulin aspart (preconception care vs. early pregnancy)



Citations to the included studies:
Heller 2010[53]

Table 6.1.2: Summary of impact estimates for diabetes				
Maternal	**Pregnancy**	**Newborn**	**Infant**	**Others**
Maternal mortality **HbA1C 1st trimester levels:** among pregnancies with fair control, the rate of preconception care was higher than in the poor control group (17.3% vs. 5.5%). HbA1C > 7%: 2/15 PCC vs. 34/111 non PCC. (RR 0.44 [0.12, 1.63]) [Galindo 2006][37] HbA1C > 8%: 7/175 PCC vs. 113/260 non PCC (RR 0.09 [0.04, 0.19]) [boulot 2003][32] Preconception counseling was associated with better glycemic control 3 months preconception (OR 1.91, 95% CI 1.10 –3.04) and in the first trimester (2.05, 1.39 –3.03) [Tripathi 2010][54] pooled difference in mean HbA1C -2.3% (95% CI -2.1- -2.4) [ray 2001][11] **Maternal hypoglycemia:**	**Preterm birth**: RR 0.97 [0.45, 2.10] [Dunne 1999][49] RR 0.93 [0.54, 1.61] [Garcia 1997][38] RR 0.56 [0.29, 1.07] [Jaffiol 2000][40] RR 0.64 [0.47, 0.88] [Temple 2006a][47] **Pre-eclampsia:** There was no difference in rates of pre-eclampsia (13.1 versus 12.6%) between women who did and who did not attend pre-pregnancy care. [Temple 2006b][55] **Cesarean section**: RR 0.73 [0.56, 0.95] [Garcia 1997][38] The rate of cesarean delivery was significantly different (P = 0.005) in PPG I vs. PPG III [McELvy 2000][42]	**Congenital malformations:** Major anomalies rate in PCC (2.1%) vs. non PCC (6.5%). (Pooled RR 0.36 95% CI 0.22-0.59) [Ray 2001 SR – NC][11] pooled RR for major n minor anomalies in PCC vs. non PCC 0.32 (0.17-0.59) [Ray 2001 SR – NC][11] PCC 1/84 vs. 12/110 non PCC. RR 0.11 [0.01, 0.82] [Kitzmiller 1991- PC][41] 1/62 PCC vs. 8/123 non PCC. RR 0.25 [0.03, 1.94] [Willhoite 1993- PC][48] 0/28 PCC vs. 1/171 non PCC. RR 0.83 [0.03, 19.73] [Rosenn 1991- PC][44] 0/44 PCC vs. 3/31 non PCC. RR 0.10 [0.01, 1.90]. [Goldman 1986 - RC][39] 2/175 PCC vs. 16/260 non PCC [RR 0.19 [0.04, 0.81]. [Boulot 2003-PC][32] 0/21 PCC vs. 3/40 non PCC. RR 0.27 [0.01, 4.92] [Jaffiol 2000 – PC][40] Rate was significantly lower in the PPC group 1.0% than the NPPC group 8.2%, (p < 0.01). RR 0.24 [0.10, 0.59] [Damm 1989 – PC][33] 5/199 PCC vs. 4/100 non PCC. RR 0.63 [0.17, 2.29] [DCCT 1996- RCT][20] 0/44 PCC vs. 3/31 non PCC. RR 0.10 [0.01, 1.90] [Dicker 1988- PC][34] 3/15 PCC vs. 14/112 non PCC. RR 1.60 [0.52, 4.93] [Galindo 2006 – PC][37] 2/92 PCC vs. 11/79 non PCC. RR 0.16 [0.04, 0.68] [McElvy 2000- PC][42] 17/347 PCC vs. 25/279 non PCC (RR 0.55 [0.30, 0.99]) [Mills 1988][43] 0/28 PCC vs. 1/71 non PCC (RR 0.83 [0.03, 19.73]) [Rosenn 1991][44] 2/110 PCC vs. 11/180 non PCC (RR 0.30 [0.07, 1.32]) [Temple 2006a][47] 1/57 PCC vs. 9/145 non PCC (RR 0.28 [0.04, 2.18]) [Fuhrman 1984][36]		**Behaiour change:** Teens that received the program significantly improved in knowledge (CD 42.7%, *P* _ 0.001; book 45.3%, *P* _ 0.001; control 12.6%, *P* _ 0.38) and sustained effects at the 3-month follow-up (post-test 2) (CD *P* _ 0.96; book *P* _ 0.71). There were significant group-by-time Effects for beliefs (benefits and barriers) [benefits *F* (2, 40.1) _ 3.48, *P* _ 0.040; barriers *F* (2, 40) _ 4.82, *P* _ 0.013]. At 3 months, those who received the CD had significantly decreased

Table 6.1.2: Summary of impact estimates for diabetes				
Maternal	**Pregnancy**	**Newborn**	**Infant**	**Others**
In the period of embryogenesis and organogenesis, about 42% of subjects recorded no hypoglycemic episodes, 35% recorded one to two episodes per week, and 23% experienced several episodes per week. [kitzmiller 1991][41] In the first half of pregnancy, the estimated risk of severe hypoglycemia was 70% higher in subjects randomly assigned in early pregnancy versus those randomly assigned preconception (RR 1.70 [95% CI 0.91–3.18], P = 0.097). [Heller 2010][53] During the first half of pregnancy, the RR of severe hypoglycemia in women randomly assigned in early pregnancy/preconception was 1.70 (95% CI 0.91–3.18, P= 0.097) [Heller 2010][53] In women with preconception, severe	The caesarian section rate was high and similar between groups, 75% (group 1-PCC) vs. 74.2% (group 2- non PCC) [Dunne 1999][49] Pregnancy planning rates improved significantly for Type 1 DM (62.5% planned versus 18.9% in original study p = 0.01), and did not change for Type 2 DM. Caesarean section (LSCS) rate was high in the original study, particularly in Type 1 DM (77%), and was lower after review (47.6% in Type 1 DM p < 0.05 compared to original study, and 44.4% in Type2 DM, p = ns). Planning was associated with lower HbA1c before and during pregnancy (6.0 +/- 1.4% versus 8.1 +/- 1.8% (p = 0.0035), and 5.5 +/- 1 versus	2/143 PCC vs. 10/96 non PCC (RR 0.13 [0.03, 0.60]) [Steel 1990][46] 0/14 PCC vs. 2/7 non PCC (RR 0.11 [0.01, 1.96]) [Rowe 1987][45] No significant difference in congenital malformation [Jensen 1986][51] PCC group had significantly lower rate of congenital malformations 1.1% compared to the NPCC group 7.0% (p < 0.01) [Fuhrmann 1983, 1984][35] Congenital abnormalities in the PCC group were 3/12 compared to 2/12 in the NPCC group. [Garcia.I 1998][50] **<u>Perinatal mortality:</u>** 4/62 PCC vs. 26/123 non PCC RR 0.31 [0.11, 0.84] [Willhoite 1993-PC][48] 3/175 PCC vs. 16/260 non PCC [RR 0.28 [0.08, 0.94] [Boulot 2003 -PC][32] 1/66 PCC vs. 2/119 non PCC (RR 0.90 [0.08, 9.76]) [Garcia 1997][38] 0/21 PCC vs. 2/40 non PCC (RR 0.37 [0.02, 7.43]) [Jaffiol 200][40] 2/84 PCC vs. 3/110 non PCC (RR 0.87 [0.15, 5.11]) [Kitzmiller 1991][41] 0/92 PCC vs. 6/79 non PCC (RR 0.07 [0.00, 1.16]) [McElvy 2000][42] 2/28 PCC vs. 17/71 non PCC (RR 0.30 [0.07, 1.21]) [Rosenn 1991][44] 1/110 PCC vs. 6/180 non PCC (RR 0.27 [0.03, 2.24]) [Temple 2006a][47] 4/62 PCC vs. 26/123 non PCC (RR 0.31 [0.11, 0.84]) [Willhoite 1993][48] 0/12 PCC vs. 2/35 non PCC (RR 0.55 [0.03, 10.79]) [Dunne 1999 RC][49] **<u>Macrosomia:</u>**		(_20.5%, *P* _ 0.04) perceptions of barriers, those that received the book had significantly increased (21.8% *P* _ 0.03) perceptions of barriers, and control subjects had no significant change (*P*_0.90). Intention to seek PC and use effective family planning had a significant time effect [*F* (1,37) _ 5.75, *P* _ 0.022] from baseline to post-test 1. Only those who received the book showed a significant decrease from post-test 1 to post-test 2 (_13.0%, *P* _ 0.02); those who received the CD and control

Table 6.1.2: Summary of impact estimates for diabetes				
Maternal	**Pregnancy**	**Newborn**	**Infant**	**Others**
hypoglycemia rates occurring before and during the first and second halves of pregnancy and postpartum for Insulin Aspart versus human insulin were 0.9 versus 2.4, 0.9 versus 2.4, 0.3 versus 1.2, and 0.2 versus 2.2 episodes per patient per year, respectively (NS). [Heller 2010][53] HbA1c was significantly lower in the first trimester in the PCC group compared to the NPCC group , (p < 0.01) [Garcia .I 1998][50]	6.5 +/- 1.5% (p < 0.001)), greater gestational age at delivery (38.2 versus 36.2 weeks p = 0.0318) and lower rate of LSCS (31.6% versus 72.7% (p = 0.0295)). [Gunton 2002][56]	4/12 PCC vs. 14/35 non PCC (RR 0.83 [0.34, 2.04]) [Dunne 1999 – RC][49] PCC 6/12 neonates were macrosomic while 4/12 were macrosomic in the NPCC group. [Garcia .I 1998][50] **<u>Adverse pregnancy outcomes:</u>** Despite fewer malformations (4.3 vs. 7.3%; *P*=0.04) during the prepregnancy care program, overall differences in perinatal mortality (1.8 vs. 3.7%; *P* = 0.07) and adverse outcome (6.0 vs. 9.2%; *P* = 0.07) were not significant. Rates of adverse outcomes were unchanged (6.5%) in type 1 diabetes. In type 2 diabetes, there were reductions both in adverse outcomes (5.3 vs. 16.4%; *P*=0.0008) and in malformations (4.5 vs. 12.3%; *P* = 0.009). Independent predictors of serious adverse pregnancy outcome (major congenital malformation, stillbirth, or neonatal death) in pregnancies complicated by type 1 and type 2 diabetes: Prepregnancy care 0.20 (0.05–0.89) 0.03. perinatal mortality during 1999–2004 compared with during the 2006–2009 regional prepregnancy care program 20/535 (3.7) vs 10/562 (1.8) 0.07. congenital malformation during 1999–2004 compared with during the 2006–2009 regional prepregnancy care program 39/535 (7.3) 24/562 (4.3) 0.04 [Murphy 2010][52]		subjects sustained their modest increases. [Charron-Prochownik 2008][57]

PC – prospective cohort RCT – randomized controlled trial SR – systematic review SR-NC – Non Cochrane systematic review
RC – retrospective cohort

Grade table

We conducted quality assessment for studies addressing 2 of the major outcomes associated with the pre pregnancy diabetes, namely congenital malformations and 0perinatal death.

For the former we used a total of 20 observational studies, all conducted in developed nations. With the RR ranging from 0.11-1.60 the final RR was 0.32 and hence it was concluded that the effect of preconception care on congenital malformations was large. There were inconsistencies between the studies but most studies had results going in the same direction of a positive effect of the intervention on the outcome. Range of control group risk was from 1.4-28.6%. The quality of evidence was given as 'moderate' by the software.

Preconception prevention and management of diabetes for Congenital malformation

Patient or population: patients with Congenital malformation
Settings: France, Spain, Germany, Denmark, UK, USA, Israel, andScotland
Intervention: Preconception prevention and management of diabetes

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Corresponding risk Control	Preconception prevention and management of diabetes	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Congenital malformation Follow-up: mean 11 months	**Study population**		RR 0.32 (0.23 to 0.43)	4200 (20 studies)	⊕⊕⊕⊖ **moderate**[1,2,3]	
	79 per 1000	**25 per 1000** (18 to 34)				
	Low risk population					
	14 per 1000	**4 per 1000** (3 to 6)				
	High risk population					
	286 per 1000	**92 per 1000** (66 to 123)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Relative risk varied from 0.11 to 1.60
[2] RR=0.32
[3] Confounders were not adjusted and regression analysis was not used

For perinatal mortality we used 9 studies. All 9 were observational studies carried out in Europe and America. The final estimate of effect was quoted as RR 0.31 95% CI (0.18-0.54) and thus PCC had a large effect on perinatal mortality. The range of control group risk was given as 1.67-21.1. There were no reported inconsistencies or indirectness of results. Publication bias was not evident. Overall the quality of evidence was shown to be high.

Preconception diabetic care for reducing perinatal mortality

Patient or population: patients with reducing perinatal mortality
Settings: France, Spain, UK, and USA
Intervention: Preconception diabetic care

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Corresponding risk Control	Preconception diabetic care	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Perinatal mortality Diabetic care Follow-up: mean 6.6 years	**Study population**		RR 0.31 (0.18 to 0.54)	1667 (9 studies)	⊕⊕⊕⊕ **high**[1,2]	
	79 per 1000	**24 per 1000** (14 to 43)				
	Low risk population					
	17 per 1000	**5 per 1000** (3 to 9)				
	High risk population					
	211 per 1000	**65 per 1000** (38 to 114)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] RR=0.31
[2] Confounders were not adjusted using regression

Conclusion

Preconception care (diet and exercise counseling, family planning and a stringent glycaemic control) for women with preexisting Diabetes is effective in addressing the ever-increasing rates of adverse fetal consequences (congenital malformation, perinatal mortality) as well as serious maternal outcomes (preterm labor, level of maternal HbA1c in the first trimester of pregnancy). The problem however lies in the fact that a substantial number of women with diabetes do not access such preconception care interventions and continue to have unplanned pregnancies with deleterious MNCH results. Since less than 30% of those with diabetes present for preconception care, every office visit ofevery female diabetic adolescent or woman of childbearingage should be regarded as a preconception care visit.

Also with more women having children in their later years, screening for type 2 diabetes among women of childbearing age becomes more important.

Future research needs to aim at evaluating the effectiveness of preconception care on the incidence of other MNCH outcomes like caesarean sections, spontaneous abortions, via proper trials. What it needs more, however, is to find ways of successfully integrating preconception careinto the routine care of all women of reproductive age suffering from diabetes.

Key messages

- High level evidence was found for the positive effect of preconception care on reduction of perinatal mortality. The level of evidence of data for the effect of preconception care on the occurrence of congenital anomalies was moderate. Preconception care was found to have a large effect on reduction of both the outcomes.
- Preconception care of women with diabetes led to an overall 70% reduction in congenital malformations as compared to children born to women receiving standard antenatal care.
- Preconception care led to a 69% reduction in the occurrence of perinatal mortality associated with preexisting diabetes.
- Better glycaemic control as evidenced by an improved HbA1C in the 1st trimester following preconception care led to significant reductions in the above outcomes.
- Preconception care led to a non-significant 17% decrease in preterm births and a 3% reduction in the rate of C-sections. Pooled data for other fetal/neonatal outcomes did not reach a level of significance either.
- Future research needs to address the gap between provision and availability of preconception care intervention by diabetic women of reproductive age to see similar positive effects in entire populations.

6.2. Epilepsy management

Background

Women with epilepsy during their child-bearing years not only face the possible risk for adverse pregnancy outcome as a result of the teratogenic effects of antiepileptic drugs upon the developing fetus[58, 59] but also the potential effect of maternal seizures on the developing fetus.[60-62] Most women with epilepsy have no change in seizure frequency during pregnancy but about 15- 33% have more seizures during pregnancy.[63] This may

be due to a change in the pharmacokinetics of the anti-epileptic drugs[64] or due to the hormonal changes occurring in pregnancy.[65]

Unplanned pregnancies rates in women are high but these may be even higher in women with epilepsy because antiepileptic drugs interfere with hormonal contraception.[66] The rates of congenital malformations range from 2.3-18.6% in infants of women with epilepsy versus 2- 3% in the general population.[67] Different drugs lead to different types and different rates of anomalies, with the highest rates being associated with valproate.[68, 69]

Scope of intervention

Preconception care of women with epilepsy includes a careful revision of each case to ascertain the diagnosis, the need for continued AED therapy, selection of suitable drugs with optimization of the dosage and prescription of folic acid. Most studies have shown that the risk of malformations in fetus is expected to be low with monotherapy, use of a relatively lower dose, adequate spacing out of daily doses and preconception use of folic acid.[70] have recommended that valproate not be used as a first-line drug in women of childbearing potential as it is associated with an increased risk of impaired cognitive function at 3 years of age. An audit of the preconception counseling of women with epilepsy showed that this intervention may lead to a reduction of major fetal abnormalities.[71]

A recent review, to determine the effectiveness of preconception counseling in women suffering from epilepsy, found no high-quality studies that optimized pregnancy outcomes among these women.[72] Such counseling would not only entail a review of the current status of the disease and its treatment modalities but also provide family planning options along with commencement of folic acid prior to conception among other things. While on the one hand there is extensive support for the pre-conception counseling of all women, of child-bearing years, suffering from epilepsy on the other hand there is a dearth of evidence evaluating the efficiency of such an intervention in dealing with adverse pregnancy outcomes of the disease and its treatment.

Table 6.2.1 - Content of preconception care for Women with epilepsy

- Careful revision of each case to ascertain the diagnosis.
- Counseling about the increased risk of seizures during pregnancy.
- Counseling about the fetal risks associated with the disease as well as the medications.
- Converting a poly-therapy anticonvulsant regimen to a monotherapy anticonvulsant regimen and subsequently evaluating for control of the disease process before any planned conception.
- Counseling about effective contraception and about potential interaction between certain AED and hormonal contraceptives leading to a failure in contraception.
- Folic acid supplementation

Impact estimates

Many studies looking at the effect of preconception counselling in women with chronic disorders versus healthy women, have also looked into women with epilepsy but there comparison group was not relevant to us hence these studies were not included. The only study[71] assessing the effectiveness of preconception counselling in women with epilepsy reported that none of the 85 women who were counseled before pregnancy had an abnormal foetus in the subsequent pregnancy as compared to almost 19% of the women who did not receive any preconception counseling (as they were already

pregnant) who had an abnormal fetus (with 3 pregnancy terminations). One patient in the counselled group had an early miscarriage, followed by a normal subsequent pregnancy, and 1 had a preterm birth compared to 3 preterm births in the control group. They also showed that post-counseling 71% of WWE used a single drug and none used >2 drugs as compared to 32% and 20% respectively in the control group. Most of the counselled women used carbamezapine/lamotrigine compared to the control WWE, 41% of whom used valproate.

A recent survey[73] reported that women with epilepsy are not getting the advice they need on issues relating to contraception and pregnancy. This point was also conformed in another study[74] which showed that physicians managing WWE did not place adequate emphasis on preconception care.

Conclusion

Preconception management is the cornerstone for epilepsy care in WWE. . What is recommended is a multidisciplinary approach, involving the patient's primary care physician, an obstetrician who specializes in high-risk pregnancies, and a neurologist. WWE should be reviewed before planning a pregnancy in order to optimize therapy before conception. Ideally changes in antiepileptic drug therapy should be made at least 6 months before planned conception, if possible. All WWE should be persuaded to begin folic acid supplementation (≥0.4 mg/day) during reproductive years and continue throughout pregnancy. The current evidence for preconception counseling is encouraging but not conclusive and requires further thorough investigation. Effective elements of counseling or mode of delivery need to be identified via future research. Trials should be conducted to evaluate the value of counseling or other behavioral interventions in the preconception period in reducing clinically relevant outcomes.

Key messages

- Preconception care for WWE entails re-evaluation of disease status and control, review of current therapy and appropriate changes to doses and regimens and folic acid supplementation well before planning a pregnancy.
- Current evidence for effectiveness of PCC is encouraging but inconclusive.
- Future research should look for effective elements of counseling or mode of delivery.

Table 6.2.2: Summary of impact estimates for epilepsy

Maternal /Paternal	Pregnancy	Newborn	Infant	Others
Antiepileptic taken: The proportion of women in the un-counseled group taking more than one anticonvulsant was higher than in the preconception group. The type of anticonvulsant taken pre-conceptually was also different although the main difference was in the counseled group taking much less valproate and more lamotrigine. No patients in the counseled group were taking a combination of carbamazepine and valproate, which may be particularly	**Premature Birth:** One patient in the counseled group had an early miscarriage, but a normal subsequent pregnancy and 1 had a preterm birth compared to 3 preterm births in the already pregnant group. [Betts 1999][71]	**Fetal Abnormalities:** No women who had counseling had an abnormal fetus in the subsequent pregnancy. Eleven of the 59 women already pregnant at referral had an abnormal fetus (major anomalies only) three of which were terminated. [Betts 1999][71]		

teratogenic. None of the counseled women took more than 2 drugs compared to 20% in the already pregnant women. [Betts 1999][71]				

6.3. Management of Phenylketonuria

Background

Increasing numbers of treated individuals with inherited metabolic diseases are surviving childhood, forming relationships and considering their reproductive options.[75]

With dietary interventions having allowed women suffering from PKU to lead an essentially normal life, more women with phenylketonuria are becoming pregnant and need appropriate management as poor disease control is associated with a multitude of fetal consequences like facial dysmorphism, microcephaly, developmental delay, learning difficulties and congenital heart disease.[75, 76]

Scope of intervention

We intended to accumulate evidence from current literature on the effect of maternal phenylketonuria on the pregnancy outcome, specifically of preconception levels of phenylalanine. Also we looked for any preconception intervention which worked in lowering the MNCH risks associated with poorly controlled phenyalanine levels.

Preconception care (**Table 6.3.1**) consists of counseling regarding the fetal risks (facial malformations, growth deficits, micorcephaly) associated with the disease, commencement of a phenylalanine restricted diet, attaining safe phenylalanine levels (100[67] –360[66] µmol/L or <6mg/dL[77, 78] atleast 3 months before conception; and maintaining them throughout gestation.When counseling patients great importance has to be put on the need for effective contraception till such safe levels are reached.

6.3.1 - Content for preconception care of women with PKU

- Educate about the pregnancy-related risks associated with the disease
- Counsel about the importance of achieving low phenylalanine levels during child-bearing years
- Promote a low Phenylalanine diet in the reproductive years.
- Attaining safe Phe levels atleast 3 months before a planned conception- <6 mg/dL, and maintaining throughout pregnancy
- Counsel about importance of contraception

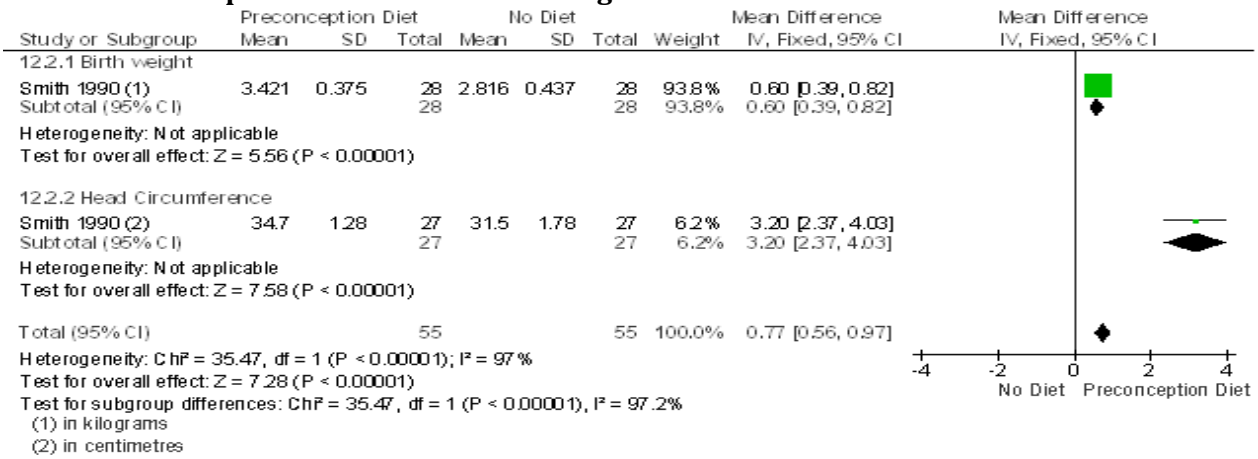
Impact estimates

Rouse et al.[76] in a cohort of women with blood Phenylalanine levels >240umol/L found that mean phenylalanine levels at 4 to 8 weeks gestation predicted congenital heart defect ($P < 0.0001$). They also found that facial abnormalities were significantly related to the time of maternal Phenylalanine control and each abnormality increased in frequency as Phenylalanine control was delayed. The percentage of offspring with >3 dysmorphic features (49% overall) was related to time of maternal Phenylalanine control ($P=0.002$), increasing from 19% in offspring of mothers in control before pregnancy to 62% when control was not achieved before 20 weeks' gestational age. None of the IUGR infants were born to mothers who achieved Phenylalanine control before 10 weeks as compared to 31% in those mothers achieving control between 30

and 40 weeks gestation (p < 0.001). The frequency of offspring with microcephaly was significantly related to time of maternal Phenlalanine control (P=0.001): 8% in the offspring of women in control before conception as compared to 67% in offspring of mothers not in control by 30 weeks' gestational age.In women who were preconceptionally treated with good control, microcephaly occurred in only 3.6% of the pregnancies.[79]

From current literature we were able to analyze the effect of a preconception dietary intervention on the growth of the fetus. Our analysis showed that a strict preconception diet was significantly associated with an increment in mean birth weight compared to no dietary restrictions (MD 0.60; 95% CI: 0.39-0.82). The association was also significant for an increase in head circumference (MD 3.20; 95% CI: 2.37-4.03). Improved infant growth markers were also associated with following a strict preconception diet in other studies (**Figure 8.3.1**).[80, 81]

Figure 6.3.1: Mean Birth-weight and Head circumference in Phenylketonuric mothers on a Strict Preconception diet vs. those following no diet



Citations to the included studies:
Smith 1990[82]

Koch et al.[80] also reported that a preconception diet led to a 1st trimester PHe level of 500umol/L compared to 641 umol/L in those on a postconception diet. Maillott et al.[83] also reported a significant decrease in 1st trimester mean PHe level in those on a preconception diet versus a post-conception diet [248.8 +/-86.6 compared with 493.6 +/- 289.4 mol/L; P < 0.0001].

Conclusion

Given the complications of the maternal PKU syndrome, a systematic approach to those intending to get pregnant is required. Our analysis revealed a significant positive effect of strict dietary control in the preconception period and improved growth parameters in the newborn. Studies have also reported a decrement in other fetal risks associated with the disease after attainment of an adequate control of phenylalanine levels in the 1st trimester, brought about by following a stringent dietary plan before pregnancy. There is evidence that a preconception phenylalanine-restricted diet works, however what is needed now is to finalize a preconception protocol for women with PKU and implement it on a larger scale for better coverage.

Table 6.3.2: Summary of impact estimates for PKU				
Maternal /Paternal	**Pregnancy**	**Newborn**	**Infant**	**Others**
	PHe levels: PKU 1st trimester PHe level: Diet started preconception (n=10) = 500. diet started in 1st trimester (n=30) = 641 diet not followed (n=1) =1296 [Koch 1990][80] Mean blood Phe levels during pregnancy; diet begun preconception vs. post conception (203.5 +/- 58 compared with 269 +/-115 mol/L, respectively; P < 0.0003) [Maillot 2008][83] During the first trimester (248.8 +/-86.6 compared with 493.6 +/- 289.4 mol/L; P < 0.0001). [Maillot 2008][83] **Pregnancy complications:** If creatinine is <125umol/L there is a 85–95% pregnancy success rate, although 25% will develop maternal complications such as pre-eclampsia. Whereas, with creatinine >250umol/L, pregnancy success rate is only 20–30%, 85% develop maternal complications, 60% of babies are growth restricted, and 70% preterm. . [Germain 2006][84]	**Growth parameters:** normal birth weights and head circumferences in 17 infants born to mothers who by the time of conception received a strict low phenylalanine diet and had blood phenylalanine concentrations below 0.6 mmol/L. [Drogari 1987][81] *Diet initiated*preconception: n=10 length 48.9 (44%) weight 3151 (47%) head circumference 32.9 (28%) Trimester 1: n=27 length 48.5 (61%) weight 2926 (44%) head circumference 33.0 (31%) Control n=27 length 51.5 (86) Weight 3610 (88) Head Circumference 35.5 (83) [Koch 1990][80] **Facial dysmorphology:** percentage of offspring with more than three dysmorphic features (49% overall) was related to time of maternal Phe control (P = .002), increasing from 19% in offspring of mothers in control before pregnancy to 62% when control was not achieved before 20 weeks' gestational^^ [Rouse 2004][76] **Postnatal Growth restriction:** Ranged from 6% in offspring of women in control before conception to 67% of offspring of women who did not achieve control before 30 weeks' gestational age. ^^ [Rouse 2004][76] **Microcephaly**: 8% in the offspring of women with mild HPA and those in control before conception, 18% of those in control by 10 weeks, 45% of those	**Cognitive Development:** The data for offspring from 26 maternal PKU pregnancies treated prior to conception indicate that the cognitive development of these children is within the normal range (IQ/DQ 85-119). [Guttler 1990][85] Data show that the effect of preconceptional dietary treatment was children with a normal performance, contrary to their older siblings born following untreated pregnancies. The outcomes of the pregnancies were healthy children who have developed normally. Their IQs are 105 and 119 at ten and four years of age, respectively and their head circumferences are normal. [Guttler 1990][85]	

Table 6.3.2: Summary of impact estimates for PKU				
Maternal /Paternal	**Pregnancy**	**Newborn**	**Infant**	**Others**
		in control between 10 and 20 weeks, 40% of those in control between 20 and 30 weeks, and 67% in offspring of mothers not in control by 30 weeks' gestational age^^ [Rouse 2004][76] **<u>CHD</u>**: None of the women in control before conception had an offspring with CHD, three in control between 0 and 10 weeks had an offspring with CHD (4% of mothers in this group), 11 in controls between 10 and 20 weeks had an offspring with CHD (14%) and 18 in control after 20 weeks had an offspring with CHD (13%). ^^ [Rouse 2004][76]		

Key messages

- Strict dietary control before conception has a strong association with improved growth parameters (birth weight, head circumference).
- Strict preconception phenylalanine restricted diet leads to an improved mean PHe level in the 1st trimester, the period of organogenesis.
- Research into better preconception care plans for women with PKU and more effective implementation of these plans is needed.

6.4. Addressing thyroid disorders preconceptionaly

Background

Women of child bearing age may suffer from hypo- or hyper-function of the thyroid gland, more often than not due to an autoimmune process. Hypothyroidism during pregnancy is known to lead to adverse maternal (gestational hypertension and pre-eclampsia,[86] abruption placenta, postpartum hemorrhage, abortion[87] and preterm delivery),[88, 89] fetal (congenital anomalies, growth retardation, fetal distress,[90] perinatal death)[88] and neonatal consequences (cognitive disorders).[91]

Literature on the association between thyroid disease during pregnancy and preterm delivery is most abundant, with most attributed to autoimmune thyroid disease.[92-95] In a study by Casey et al[87] preterm delivery was significantly increased in women with subclinical hypothyroidism (TSH at or above the 97.5th percentile, normal free T4) compared with controls. Studies show a higher incidence of very preterm deliveries and threatened preterm deliveries in women with thyroid dysfunction compared to controls[96] with one cohort that showed a significant, almost 3-fold increased incidence of hypothyroidism in the very preterm delivery group compared with controls.[97] Browne et al (2009)[98] found modest statistically significant associations between maternal report of thyroid disease and an increased risk of selected birth defects (left ventricular outflow tract obstruction, hydrocephaly, anorectal atresia, and hypospadias). A positive association between maternal thyroid disease and birth defects was also reported by Ferencz et al (1997).[99]

Hypothyroid women adequately treated with levothyroxine during pregnancy have a lower rate of preterm deliveries.[100] Vaquero et al.[101] found that thyroid replacement therapy was more effective in preventing a new miscarriage associated with thyroid dysfunction than immunoglobulins. A review by Reid et al.[102] on interventions for management of hypothyroidism during pregnancy identified one trial[94] on the effectiveness of levothyroxine treatment in reducing maternal as well as fetal morbidity. It showed a significant 72% decrease in preterm birth (RR 0.28; 95% CI: 0.10-0.80), along with non-significant reductions in pre-eclampsia (RR 0.61; 95% CI: 0.11-3.48), early 1st trimester miscarriage (RR 0.25; 95% CI: 0.06-1.15), hypertension (RR 0.65; 95% CI: 0.22-1.92), placental abruption (RR 0.30; 95% CI: 0.01-7.29).

The prevalence of hyperthyroidism in pregnant women ranges from 0.05-0.2% with more than 90% attributed to Grave's. Among the most frequent complications are the hypertensive disorders of pregnancy. Also reported are spontaneous abortion and preterm delivery.[103] Pregnancy can be complicated with preterm delivery, preeclampsia, heart failure, thyroid storm, fetal growth retardation and intrauterine

fetal death and neonatal thyroid dysfunction.[104] Also treatment may be complicated with fetal hypothyroidism and congenital anomalies.[105]

Thyroid status at the time of conception plays an important role in the occurrence of these pregnancy related outcomes. According to the study by Abalovich et al.[100] none of the women who were euthyroid at the time of conception experienced preterm deliveries.

Scope of intervention

While literature on the effect of thyroid status on maternal, fetal and neonatal effects is abundant, much work still needs to be done with regards to the effect of preconceptional thyroid status on these outcomes. Many recommend attainment of a TSH <2.5 mU/L before the start of pregnancy. Since purely preconception literature was unavailable we looked at the effect of peri-conceptional interventions addressing adverse pregnancy related outcomes and even those studying the effect of the disease and treatment on MNCH outcomes. Content of preconception care for women with thyroid disorders consists of a thorough assessment of the disease status, advice on the achievement of a euthyroid status well before conception, counseling about the pregnancy-related risks associated with thyroid dysfunction (gestational hypertensive disorders, preterm birth, congenital anomalies, cognitive disorders, neonatal death). Medications need to be adjusted in order to have optimal thyroid function and the importance of useful contraception should be stressed upon till such a time.

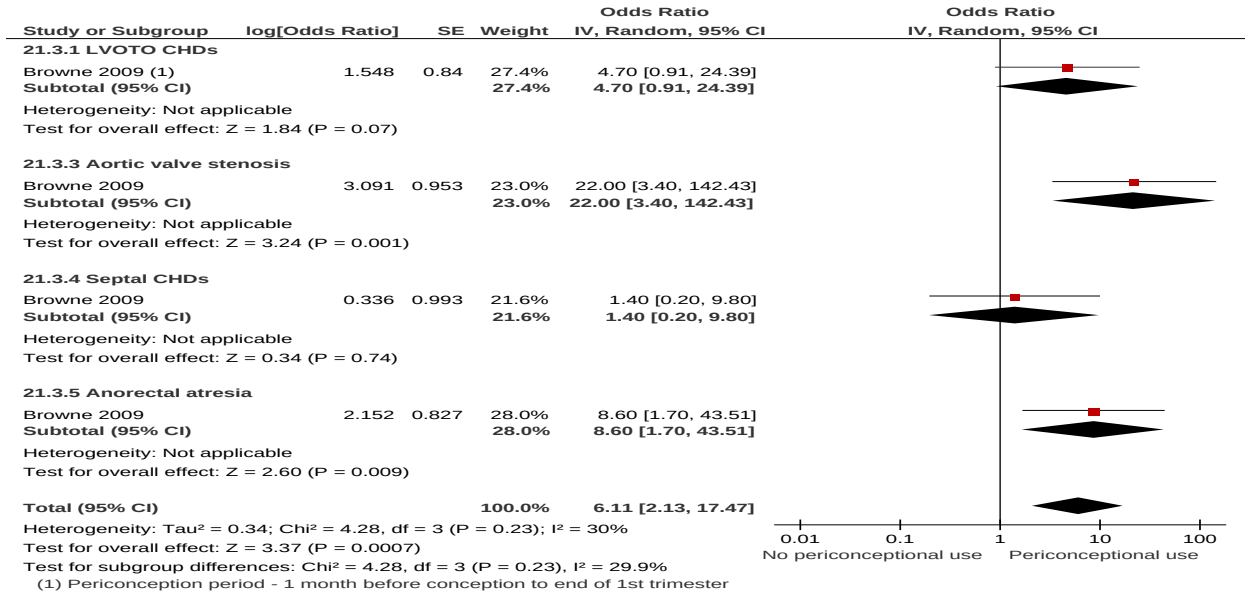
Impact estimates

Thyroid status at the time of conception plays an important role in the occurrence of these pregnancy related outcomes. According to the study by Abalovich et al.[87] none of the women who were euthyroid at the time of conception experienced preterm deliveries. Very little literature was available on preconception disease status and itsoutcomes or on preconception drug regimens and their effects. A narrative by Mestman et al.[106, 107] underscores the importance of pre-pregnancy counseling for hyperthyroid women and the use of contraception until achievement of a euthyroid status before conceiving. Earl et al.[108] found no interventions for the prevention and treatment of hyperthyroidism during pregnancy.

There result for usage of antithyroid drugs (ATD) was inconclusive due to the small potential risk of adverse fetal effects of methimazole and maternal effects of propylthiouracil. Another study reports that both ATDs are equally effective and safe in the treatment of hyperthyroidism in pregnancy.[109] Periconception use of ATD was however; shown to significantly increase the rates of selected birth defects (Browne 2009) (**Figure 6.4.1**).

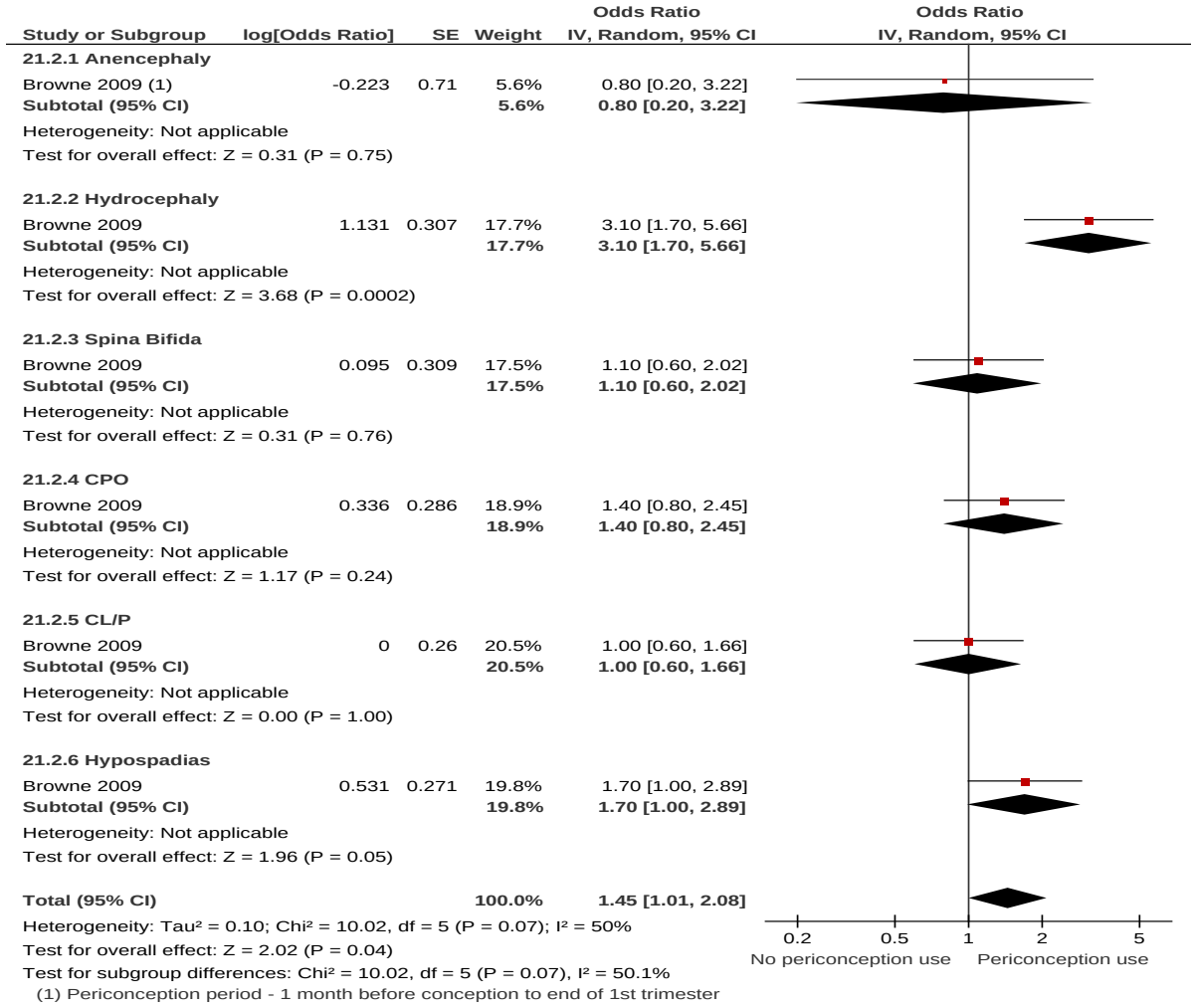
Browne et al (2009) also reported estimates on association of periconception thyroxine and selected birth defects which were similar to estimates for any thyroid disease. Rotondi et al.[110] conducted a trial on the preconception adjustment of levothyroxine and found that it may lead to adequate thyroid function in the 1st trimester; however they did not look at any MNCH outcome (**Figure 6.4.2**). Results suggest that in hypothyroid women anticipating pregnancy (with serum TSH in the lower quartile of normal range), the pre-conception adjustment of L-T4 doses may result in adequate maternal thyroid function up to the first post-conception evaluation.[110]

Figure 6.4.1: Periconception use of anti-thyroid medications and Birth defects



Citation of included study:
Browne 2009[98]

Figure 6.4.2: Periconception use of thyroxine and Birth defects



Citations to the included study:
Browne 2009[98]

Table 6.4.1: Summary of impact estimates for thyroid dysfunction				
Maternal /Paternal	**Pregnancy**	**Newborn**	**Infant**	**Others**
	Miscarriage: In the thyroid supplementation group (66 mg of thyroid extract, started before conception and continued until the 20th week) among patients with thyroid antibodies, 13 out of 16 pregnancies (81.2%) ended in live birth. Only one pregnancy loss occurred among patients with a mild underlying thyroid pathology treated with thyroid replacement therapy. [Vaquero 2000][101]			

Conclusion

There was an absolute dearth of evidence from the preconception period. However, logic dictates that ensuring maternal biochemical euthyroidism in the first trimester, when the fetus is dependent on maternal thyroxine, might optimize fetal outcome. To achieve this target those already suffering from thyroid dysfunction need to be re-evaluated before they plan to conceive, their treatment regimens need to be re-adjusted and they need to be counseled about the probable risks to both lives that an unachieved euthyroid status may lead to. Future research not only needs to find the missing link between thyroid function before conception and a fall in associated MNCH morbidities, it also needs to focus on how to achieve this in women with thyroid disorders who want to conceive.

Key messages

- Thyroid dysfunction during pregnancy leads to a multitude of maternal and fetal consequences.
- Current literature says attainment of a euthyroid status during the 1st trimester is essential for reducing thyroid related morbidity
- Trials need to be conducted on the effectiveness of comparable treatment modalities when given in the preconception period.

6.5. Systemic Lupus Erythromatoses (SLE) and other connective tissue diseases

Background

Systemic lupus erythematosus (SLE) predominantly affects women in the childbearing age group, and thus the effect of pregnancy on the disease and vice versa is an important consideration in the management of these patients. Despite all the advances in understanding the disease pathology and management options pregnancy in lupus is still considered to be a high-risk pregnancy.[111] There is a higher rate of foetal loss, pre-term delivery and intrauterine growth restriction in lupus pregnancies.[111-113] Pre-existing hypertension or renal dysfunction further increases the risk of pre-eclampsia and pregnancy-induced hypertension.[113-115] Several studies have found the frequency of fetal loss to vary between 11-24%.[112, 116-119] While some studies advocate that active disease increases the risk of fetal loss,[117, 120, 121] other studies show no statistically significant difference between pregnancies in women with active lupus and those in women with inactive lupus.[122, 123]

Active disease at conception is a known predictor of poor outcome.[115, 122, 124] A flare during the year prior to conception pointed to increased risks of a flare again during pregnancy.[125, 126]

Scope of intervention

SLE is a prime example of an autoimmune disorder. We decided to use this disease to study the possible effects of autoimmunity on MNCH outcomes. We also intended to look at the effects of treatment modalities for SLE and how, if any available intervention (like counseling, behavioural programs) targeting such women improved the pregnancy outcomes.

The content of preconception care for women with autoimmune disorders, and SLE per say are enlisted in table **6.5.1.**

6.5.1 - Content of preconception care for women with SLE

- Counsel about risks associated with active disease at conception (preterm birth, fetal loss, disease flare-up, pre-eclampsia)
- Counsel about the importance of optimal disease control before pregnancy and encourage planning a pregnancy when the disease is in a quiescent stage for atleast 6 months, especially in the case of pre-existing lupus nephritis
- Counsel about the teratogenic potential of medications and switch to a safer regimen

Impact estimates

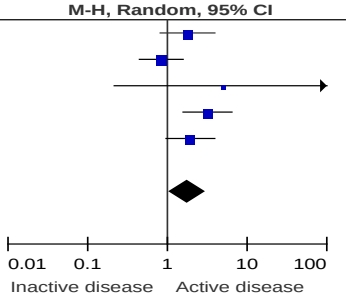
We found a number of observational studies looking at the effect of active disease in the preconception period on pregnancy related outcomes. Our analysis showed that preconception active SLE was associated with multiple maternal and fetal/neonatal outcomes. An active disease increased the risks of gestational flares by 77% (p=0.04) (**Figure 6.5.1).** There was an over three-fold increase in the risk of developing pregnancy induced hypertension if the disease was active (specifically with nephritis) before pregnancy (p=0.002); no association was found with risk of preeclampsia. There was also a significant rise in the preterm deliveries if the disease was not in remission before conception (RR 1.71;95% CI: 1.18-2.48); this risk was further increased by 13% if the woman suffered from active nephritis pre-pregnancy.

Figure 6.5.1 - Preconception disease activity and disease flares during pregnancy

	Active disease		Inactive disease			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Carmona 1999 (1)	5	10	12	43	22.1%	1.79 [0.82, 3.92]	
Carmona 2005 (2)	12	41	15	43	26.4%	0.84 [0.45, 1.57]	
Chandran 2005	1	18	0	31	2.8%	5.05 [0.22, 117.89]	
Imbasciati 2009	26	57	8	56	24.3%	3.19 [1.58, 6.44]	
Podjanee 2007	6	11	14	50	24.4%	1.95 [0.97, 3.92]	
Total (95% CI)		**137**		**223**	**100.0%**	**1.77 [1.02, 3.07]**	
Total events	50		49				

Heterogeneity: Tau² = 0.19; Chi² = 8.67, df = 4 (P = 0.07); I² = 54%

Test for overall effect: Z = 2.05 (P = 0.04)



(1) Nephritis

(2) Nephritis

Citation to the included studies:
Carmona 1999[127], Carmona 2005[128], Chandran 2005[129], imbasciati 2009[130], podjanee 2007[131]

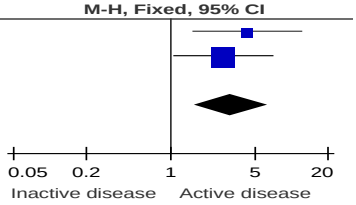
Coming to adverse SLE related fetal/neonatal outcomes, it was seen that a positive disease activity in the preconception period significantly increased perinatal mortality

by twice as much (RR 2.42; 95% CI: 1.06, 5.51) (**Figure 6.5.2; Figure 6.5.3; Figure 8.5.4; Figure 6.5.5)**. No association was seen with either spontaneous abortions (**Figure 6.5.6)** or restricted fetal growth (**Figure 6.5.7)**. Our results confirmed the findings of Smyth et al.[132]

Figure 6.5.2 - Preconception disease activity and hypertension during pregnancy

Study or Subgroup	Active disease Events	Total	Inactive disease Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Carmona 1999 (1)	5	10	5	43	27.9%	4.30 [1.53, 12.06]
Carmona 2005 (2)	13	41	5	43	72.1%	2.73 [1.07, 6.97]
Total (95% CI)		**51**		**86**	**100.0%**	**3.17 [1.55, 6.45]**
Total events	18		10			

Heterogeneity: Chi² = 0.44, df = 1 (P = 0.51); I² = 0%
Test for overall effect: Z = 3.17 (P = 0.002)



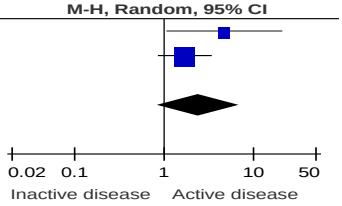
(1) nephritis
(2) nephritis

Citation to the included studies:
Carmona 1999[127], Carmona 2005[128]

Figure 6.5.3 - Preconception disease activity and preeclampsia during pregnancy

Study or Subgroup	Active disease Events	Total	Inactive disease Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Carmona 2005	9	41	2	43	32.8%	4.72 [1.08, 20.55]
Podjanee 2007	6	11	16	50	67.2%	1.70 [0.87, 3.34]
Total (95% CI)		**52**		**93**	**100.0%**	**2.38 [0.83, 6.79]**
Total events	15		18			

Heterogeneity: Tau² = 0.31; Chi² = 1.90, df = 1 (P = 0.17); I² = 47%
Test for overall effect: Z = 1.62 (P = 0.10)

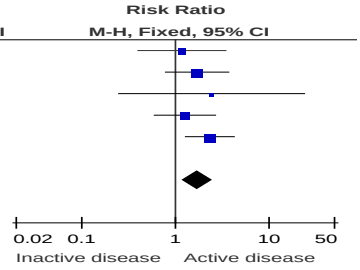


Citation to the included studies:
Carmona 2005[128], Podjanee 2007[131]

Figure 6.5.4 - Preconception disease activity and preterm delivery

Study or Subgroup	Active disease Events	Total	Inactive disease Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Carmona 1999 (1)	3	10	11	43	15.5%	1.17 [0.40, 3.44]
Carmona 2005 (2)	13	41	8	43	29.1%	1.70 [0.79, 3.68]
Georgiou 2000	1	8	2	39	2.5%	2.44 [0.25, 23.75]
Podjanee 2007	5	11	18	50	24.2%	1.26 [0.60, 2.66]
Wagner 2009 (3)	12	23	15	67	28.6%	2.33 [1.29, 4.22]
Total (95% CI)		**93**		**242**	**100.0%**	**1.71 [1.18, 2.48]**
Total events	34		54			

Heterogeneity: Chi² = 2.25, df = 4 (P = 0.69); I² = 0%
Test for overall effect: Z = 2.85 (P = 0.004)



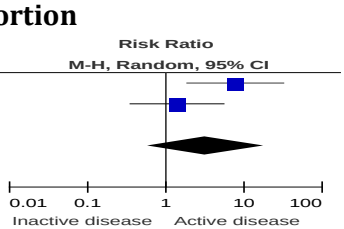
(1) Nephritis
(2) Nephritis
(3) Nephritis

Citation to the included studies:
Carmona 1999[127], Carmona 2005[128], Georgiou 2000[121], podjanee 2007[131], Wagner 2009[133].

Figure 6.5.6- Preconception disease activity and spontaneous abortion

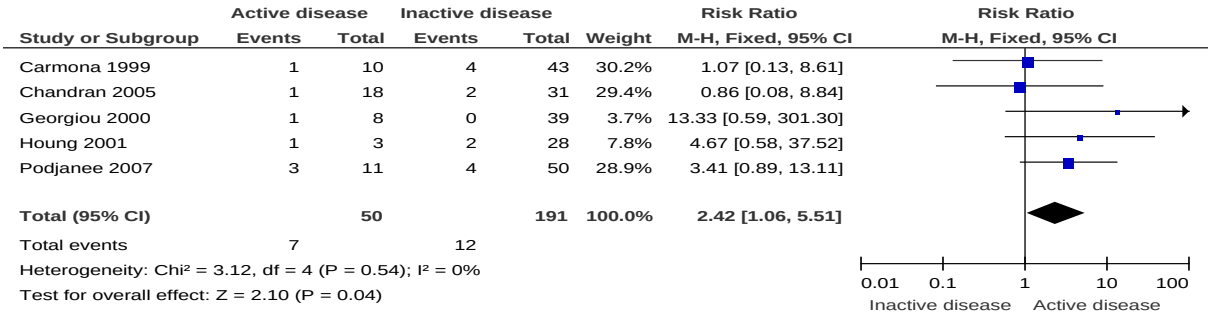
Study or Subgroup	Active disease Events	Total	Inactive disease Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Chandran 2005	9	18	2	31	49.5%	7.75 [1.88, 31.99]
Georgiou 2000	2	8	7	39	50.5%	1.39 [0.35, 5.51]
Total (95% CI)		**26**		**70**	**100.0%**	**3.26 [0.58, 18.14]**
Total events	11		9			

Heterogeneity: Tau² = 1.03; Chi² = 3.02, df = 1 (P = 0.08); I² = 67%
Test for overall effect: Z = 1.35 (P = 0.18)



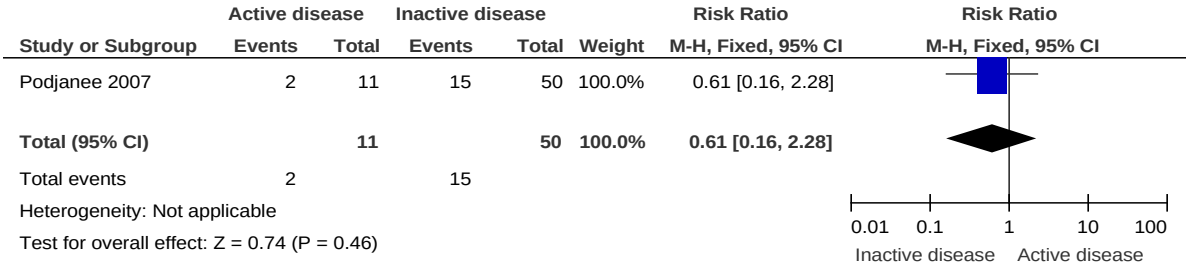
Citation to the included studies:
Chandran 2005[129], Georgiou 2000[121]

Figure 6.5.5. Preconception disease activity and perinatal mortality



Citation to the included studies:
Carmona 1999[127], Chandran 2005[129], Georgiou 2000[121], Huong 2001[115], podjanee 2007[131]

Figure 6.5.7- Preconception disease activity and fetal growth restriction



Citation to the included studies:
Podjanee 2007[131]

Conclusion

Pregnancy is safe in most lupus patients who conceive while the disease is inactive; however pregnancy statistically increases SLE activity. Active SLE prior to pregnancy is associated with a less favorable maternal and fetal outcome and conception should hence be avoided, if possible. Our analysis showed that an active disease status in the preconception period significantly increased the risks of gestational flares by 77%, pregnancy –induced hypertension by over 3 folds, preterm deliveries by twice as much and perinatal mortality by over two-folds. No association was found with preeclampsia, fetal growth restriction or spontaneous abortions. These findings highlight the importance of a preconception intervention to address the reproductive issues in women suffering from SLE.

Table 6.5.2: Summary of impact estimates for SLE and other connective tissue diseases

	Maternal /Paternal	Pregnancy	Newborn	Infant	Others
SLE	**Maternal morbidity:** A comparison between the maternal outcome of pregnancies in lupus anticoagulant positive and negative women showed no significant difference in the incidence of any complication. [Daskalakis 1998][134] **Pre-pregnancy**	**Stillbirths/ spontaneous abortion:** Intrauterine fetal death occurred four times more often in women where the disease was active at the time of conception than in women where it was inactive. [Skomsvoll 2007][135] Stillbirth was associated with previous lupus nephropathy ($p < 0.05$) and hypertension at conception ($p<0.001$). [Cortes 2002][122] Active disease vs inactive disease at conception: spontaneous abortion – 2/8 vs 7/39. Stillbirth 1/8 [Georgiou	**AntiPhospholipid detection and fetal outcomes:** APA noted at any time before pregnancy increased the low birth-weight rate (75%) six fold and the perinatal loss (33.3%) more than tenfold but did not affect the rate of spontaneous abortions. Any kind		

Table 6.5.2: Summary of impact estimates for SLE and other connective tissue diseases					
	Maternal /Paternal	**Pregnancy**	**Newborn**	**Infant**	**Others**
	<u>renal impairment and deterioration of renal disease</u> – If creatinine is <125umol/L at conception then in only 2% will renal function deteriorate during pregnancy, with no significant progression to end-stage renal failure or deterioration post-partum. At the other end of the spectrum, if creatinine is >170umol/L at conception, then in 65–75% renal function will worsen during pregnancy, 50–60% will have further deterioration post-partum and 33–40% will develop end-stage renal failure. [Germain 2006][84]	2000][121] **<u>Deliveries</u>**: Term deliveries- active disease vs inactive disease (1/8 vs 35/38) Preterm deliveries – 1/8 vs 2/39 [Georgiou 2000][121] **<u>Disease exacerbation:</u>** clinical exacerbation of lupus disease was observed in 11 (66%) of 15 cases where SLE was clinically active at the time of conception, and in only one (9%) of 11 cases where SLE nephritis was in stable clinical remission for at least five months before conception. The data indicate that successful outcome of pregnancy may be expected even in the more severe forms of lupus nephritis if gestation begins after a sustained, complete clinical remission. [Jungers 1982][136] Among 18 pregnancies in patients with lupus nephritis, 50% of patients with active disease at conception flared during pregnancy but for those with inactive disease, only 20% had flares. [Houser 1980][137] Of the 25 pregnancies with active renal disease at conception, 48% had flares of nephritis. This percentage was higher than that of pregnancies with inactive renal disease at the time of conception (32%) [Hayslett 1980][138] The rate of disease flares during lupus pregnancies was reported to be 62% and 7.4%, respectively, for those with active and inactive nephritis at conception. [Bobrie 1987][139] SLE lupus nephropathy at conception vs. no nephropathy; Flare 5 (30%) vs. 12 (24%) Hypertension 5 (50%) vs. 5 (11.6%) p=0.01 Preterm delivery 3 (30%) vs. 11 (25.5%). [Carmona 1999][127] Active SLE at conception- n=4, abortions 0, stillbirths 0, prematurity 2, term newborn 2. [Cavallasca 2008][140]	of hemocytopenias without APA, noted before pregnancy did not worsen the fetal outcome in SLE. [Pajor 1998][141] **<u>Birth weight:</u>** No differences in birth weight were found between patients with active disease at conception (2363±900 versus 2842±888 in inactive disease). [Carmona 1999][127] SLE lupus nephropathy at conception vs. no nephropathy; Gestational age at delivery 35.9+/-3.7 vs. 37.3+/-4.2 p=0.04 Neonatal birth weight 2441+/- 967 vs. 3229+/-1747 N.S. Perinatal mortality 1 (10%) vs. 4 (9.3%). [Carmona 1999][127] Active SLE at conception- n=4, low birth weight 1. [Cavallasca 2008][140] Mortality: 18 women with active SLE at conception vs. 31 with inactive disease- Neonatal death 0 vs. 1, Live birth 5 vs. 19. Only active disease adversely affected the outcome (13/18 versus 4/23, P<0.05). [Chandran 2005][129]		

Table 6.5.2: Summary of impact estimates for SLE and other connective tissue diseases					
	Maternal /Paternal	**Pregnancy**	**Newborn**	**Infant**	**Others**
		18 women with active SLE at conception vs. 31 with inactive disease- Induced abortions 3 vs. 8, Spontaneous Abortions 9 vs. 2, Stillbirth 1 vs. 1. [Chandran 2005][129] Variables significantly associated with flares during pregnancy were increased number of flares before gestation ($p < 0.05$), and previous treatment with chloroquine ($p < 0.05$). Flares during pregnancy were more common in women with active disease at conception, although this was not significant [Cortes 2002][122] **Pregnancy complications:** If creatinine is <125umol/L there is a 85–95% pregnancy success rate, although 25% will develop maternal complications such as pre-eclampsia. Whereas, with creatinine 250umol/L, pregnancy success rate is only 20–30%, 85% develop maternal complications, 60% of babies are growth restricted, and 70% preterm. [Germain 2006][84]	Over half (57 per cent) of the foetuses born to lupus anticoagulant-positive mothers died, compared with only 10 (23 per cent) born to mothers who were lupus anticoagulant negative ($p = 0.013$). Differences were even more marked in comparing perinatal mortality: nine (43 per cent) in the positive group compared with three (7 per cent) in the negative group ($p = 0.0015$). [Daskalakis 1998][134]		
Marfan's	Significant risks in undergoing pregnancy if the aortic diameter is 2 4.0 cm or if there has been a steady increase in the aortic root dimension over preceding visits. Women with Marfan's syndrome are at significant **risk** of aortic dissection in pregnancy even in the absence of preconceptional cardiovascular abnormality. [Lipscomb 1997][142]				

Key messages

- Evidence supports timing of pregnancy relative to SLE activity. Active disease at conception was associated with hypertension and pre-eclampsia
- Active nephritis per say, was associated with maternal hypertension and premature birth.

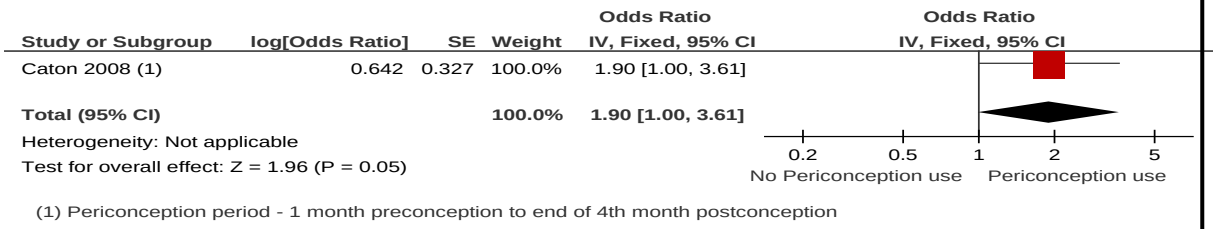
- No relevant literature addressing interventions for reducing SLE-related pregnancy outcomes were found.

6.6. Other chronic conditions

Chronic Hypertension and heart disease – pregnancies complicated by chronic hypertension are associated with increased risk of hypertensive disorders of pregnancy and other organ dysfunctions as well as increased fetal risks of preterm birth, intrauterine growth retardation, fetal loss, hypospadias and abruption placenta.[143]

Romunstad et al (2007)[144] found a significant association between prepregnancy systolic as well as diastolic blood pressure and low birth weight. Magnussen et al (2007)[145] found systolic blood pressures of greater than 130 mmHg to increase the risk of pre-eclampsia by more than 7 times. Because there is an increasing burden of unplanned pregnancies, fetal exposure to antihypertensive medications might occur before a woman knows she is pregnant. Caton et al (2008)[143] studied the effect of periconception use of anti-hypertensives and found a positive association with the occurrence of hypospadias (**Figure 6.6.1**), with a non-significant increase with exposures only to antiadrenergic agents at any time between 1 month preconception and the fourth month of pregnancy.

Figure 6.6.1: Periconception use of antihypertensives and risk of Hypospadias



(1) Periconception period - 1 month preconception to end of 4th month postconception

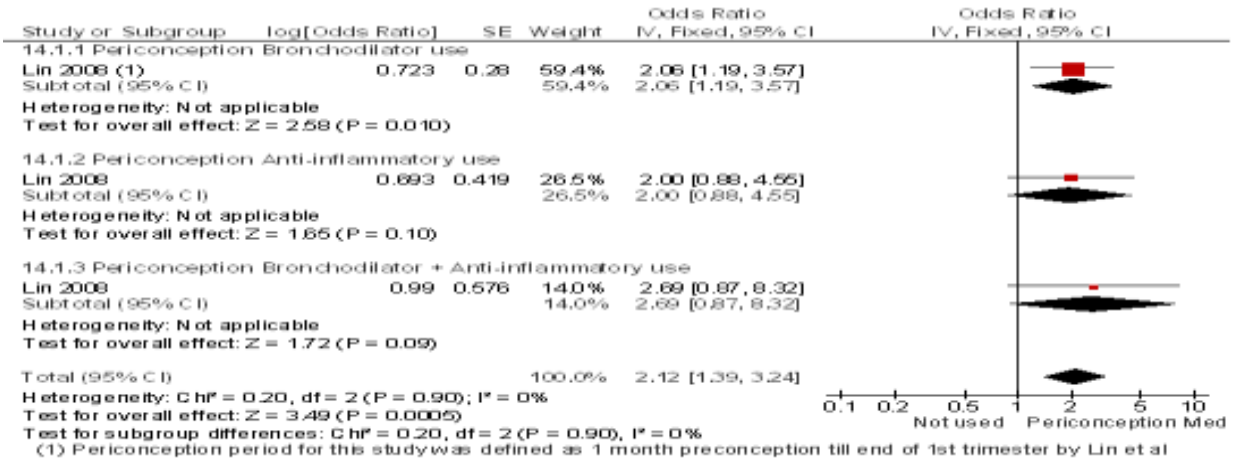
Citation of included study:
Caton 2008[143]

Approximately 1% of pregnancies are complicated by cardiac disease. As more affected women are surviving into reproductive age, congenital heart disease in pregnancy is increasingly common. Pregnancy in such patients leads to an increased morbidity and mortality due to decompensation of the cardiac condition. Cohort studies demonstrate improved maternal and fetal outcomes when cyanotic heart disease[146] and symptomatic obstructive lesions are corrected prior to pregnancy.[147]

Asthma - research demonstrates that asthma in women with severe asthma prior to pregnancy is more likely to worsen during pregnancy. This reinforces the importance of adequate asthma control prior to conception[148] Asthma that is not adequately controlled during pregnancy can result in serious Maternal complications (preeclampsia, hypertension, and hyperemesis gravidarum)[149] as well as increased Fetal complications (stillbirth and infant death, neonatal hypoxia, intrauterine growth retardation, premature birth, and low birthweight).[150] It is observed that the dangers of uncontrolled asthma are greater than the risks of indispensable asthma medications. Whereas oral corticosteroid use in the first trimester has been associated with reduced birthweight, an increased risk of preeclampsia, and an increased risk of oral clefts.[151, 152] Observational cohort data does not link maternal exposure to inhaled beta agonists, cromolyn, inhaled corticosteroids, or oral theophylline to an increased risk of preeclampsia, congenital anomalies, preterm birth, or low-birthweight infants.[153] Patients using an inhaled corticosteroid before pregnancy did not have an increase in

adverse pregnancy outcomes relative to the group that was not using them.[154] Analysis showed that periconception use of asthma medications was significantly linked to a greater risk of gastroschisis (OR 2.12; 95% CI: 1.39-3.24) especially the use of bronchodilators which significantly doubles the risk (**Figure 8.6.2**).

Figure 6.6.2: Use of bronchodilators in the periconception period and odds of Gastroschisis in newborns



Citations to the included study:
Lin 2008[155]

Chronic renal disease- Adverse pregnancy outcomes associated with maternal renal disease include preeclampsia, anemia, chronic hypertension, cesarean delivery, preterm delivery, fetal growth restriction, and increased fetal loss and stillbirth.[156, 157] Renal hypertension is associated with a 10-fold increase in fetal loss compared to women with spontaneously or therapeutically normal blood pressures.[158]

Headache – frequent prepregnancy headaches were found to be statistically significantly associated with poor mental health in the first 3 months of gestation as well as with antepartum depression.[159]

Table 6.6.1 – Content of care for other chronic diseases (Menard 2009)[160]

Chronic Hypertension and heart disease

- counsel about the risk of fetal (preterm birth, IUGR, fetal loss, hypospadias) and maternal (hypertensive disorders of pregnancy) adverse outcomes associated with pregnancy
- Assess for complications and manage appropriately.
- counsel to achieve optimum control of the cardiac disease prior to conception
- Counsel about conditions in which pregnancy is contraindicated (EF<40%, prior cardiac event, left outflow tract obstruction, arrhythmias, ventricular dysfunction, cyanosis).
- Genetic counselling of those with congenital cardiac disease
- Counsel about the risks associated with anti-hypertensives like ACE-i and ARB and stop these medications prior to pregnancy.
- Those with pre-existing cardiac disease who are on anticoagulants should be changed to a less teratogenic anticoagulant prior to conception.
- Counsel about the importance of effective contraception among those on anti-hypertensives not planning a pregnancy. Offer a suitable contraceptive method to achieve optimum timing of the pregnancy in those with cardiac disease.

Asthma

- Counsel about the potential for their asthma control to worsen with pregnancy and the importance of achieving asthma control prior to a pregnancy through appropriate medical management and avoidance of triggers.

- Women of reproductive age with asthma should be treated with pharmacologic step therapy for their chronic asthma based on the ACAAI-ACOG recommendations
- Those with poor control of their asthma should be encouraged to use effective birth control until symptom control is achieved.

Chronic Renal disease

- Counsel women about the risks of adverse maternal and fetal outcomes related to pregnancy.
- Counsel about achieving normal blood pressures before conception
- Counsel about the adverse fetal effects of ACE-i and ARB and offer contraception
- Discontinue ACE-i/ARB regimen before planning a pregnancy
- Encourage effective contraception use while optimal disease control is not achieved

Multiple Sclerosis

- Women of reproductive age diagnosed with MS should know that there is a significant decrease in relapse rate during pregnancy, followed by a significant increase after delivery. Caesarean sections, abortions, prematurity and low birth weight seem to occur in a slightly higher frequency among women with MS, however, these outcomes are a result of multiple etiological factors, and the risk is not significantly higer. Neonatal deaths and malformation rates have not been found to be higher in women with MS (Finkelsztejn 2011)[161]

Table 6.6.1: Summary of impact estimates of other chronic conditions

Condition	Maternal	Pregnancy	Newborn	Infant	Others
Prepregnancy headache	**Pregnancy symptoms**: Frequent prepregnancy headache was found to have a direct association with pregnancy symptoms only. Multivariate analysis of the association between frequent prepregnancy headache and use of different drugs showed that frequent prepregnancy headache was directly associated only with the more frequent use of headache medications in the frequent prepregnancy headache group. Frequent prepregnancy headache was statistically significantly associated with poor mental health in the first trimester and increased depression during pregnancy but not with fatigue. [Arooma 1996][159]				

Heart disease	**Maternal mortality:** Patients with the following conditions carry a maternal mortality of more than 25% and therefore should be advised against pregnancy • Primary and secondary pulmonary hypertension • Peripartum cardiomyopathy (PPCMP) with persistent reduced ejection fraction • Marfan's syndrome with aortic root dilatation • Complicated coarctation of aorta [Hameed 2007][162] Prognostic indicators to predict cardiac events in pregnancy, ie, heart failure, arrhythmia, stroke, death: • New York Heart Association (NYHA) Functional Class II (or cyanosis) • Outlet obstruction of the left heart • Prior cardiac event (heart failure, arrhythmia, stroke) • Ejection fraction <40% The risk of a cardiac event with 0, 1, and >1 prognostic indicators were estimated to be 5, 27, and 75%, respectively. [Siu 1997][164]	**Fetal risks:** increased risk of spontaneous abortion, cardiac anomaly (4-14%) in the presence of maternal congenital heart disease (CHD), preterm labor, low birth weight, and intrauterine growth restriction (IUGR). [hameed 2007][162] **Preeclampsia:** The odds ratio of developing preeclampsia for women with baseline systolic blood pressures greater than 130 mm Hg (highest fifth) was 7.3 (95% CI 3.1 to 17.2) compared with women with systolic blood pressures less than 11mmHg (lowest fifth). [Magnussen 2007][145] Risk factors significantly associated with increased risk of pre-eclampsia: nulliparity (RR 2.38; 95% CI .28–2.49); multiple pregnancy (RR 2.10; 95% CI 1.90–2.32); history of chronic hypertension (RR 1.99; 95% CI 1.78–2.22) [Conde-Aguedelo 2000][163]	**Birth-weight**: after additional adjustment for pre-pregnancy BMI, the associations of high maternal systolic blood pressure (>129mmHg) with low birth weight for gestational age were further strengthened (z score -0.16; -0.26, -0.06). Prepregnancy diastolic blood pressure showed similar associations (z scores-0.07; -0.17, 0.03) Triglyceride levels were positively associated with birth weight for gestational age (z-score: 0.07; -0.05, 0.17). The crude analysis of total cholesterol showed a positive association with birth weight for gestational age (z-score: 0.09; -0.01, 0.20). [Romundstad 2007][165]		

Multiple sclerosis	**Post-partum relapse:** Women with greater disease activity in the year before pregnancy and during pregnancy have a higher risk of relapse in the postpartum 3 months. There was a 1.7-fold increased risk with each relapse experienced during the pre-pregnancy year and 1.8-fold increased risk for each relapse during pregnancy (P < 0.002 and 0.02 respectively). Patients who had a higher Disability Status Scale at pregnancy onset were also more likely to have a post-partum relapse (odds ratio = 1.3, P = 0.04). [Vukusic 2004][166]				

6.7. Medication Use

Background

Medication usage among pregnant women and women of reproductive age is common. It has been estimates that more than 80% of pregnant women take OTC or prescription drugs during pregnancy.[167] National surveys among women of reproductive age document that chronic conditions often requires the ongoing administration of medications for maintenance are not uncommon among women of reproductive age.[168] As maternal age and body mass index increase, it is likely that an even greater proportion of women who are planning a pregnancy or who could become pregnant will have chronic diseases that necessitate prescription medications.

Scope of intervention

Our aim was to look for studies assessing interventions dealing with the repercussions of various medications being frequently used by women. Regularmedications being used by women suffering from chronic diseases are covered in the sections of their respective disorders. We also looked at studies particularly addressing the deleterious effects of such medication, on the health of both the mother and the fetus, when taken in the period before conception.

Impact estimates

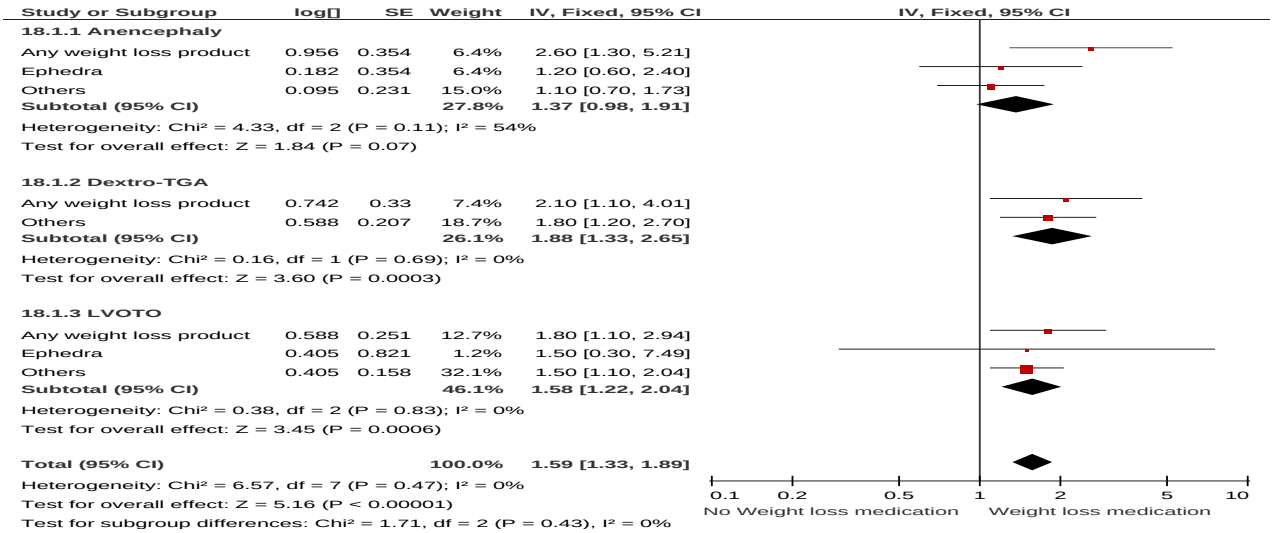
We found studies assessing the effect of use of weight-loss drugs and oral contraceptives.

Weight loss drugs

Analysis of the effect of periconception use of weight-loss drugs showed a significant association with overall higher rates of congenital anomalies (OR 1.59; 95% CI: 1.33-1.89). This association was stronger for congenital heart defects with an 88% increase in incidence of Dextro-TGA and a 58% increase in the incidence of LVOTO (OR 1.88; 95% CI: 1.33-2.65); (OR 1.58; 95% CI: 1.22-2.04) respectively. Bitsko et al.[169] reported

the association with 'Aortic Stenosis' to be highest among the LVOTO defects (OR 1.2; 95% CI: 0.5-3.1) (**Figure 6.7.1**).

Figure 6.7.1 Odds of Congenital malformations in newborns of mothers using weight loss products in the periconception period.

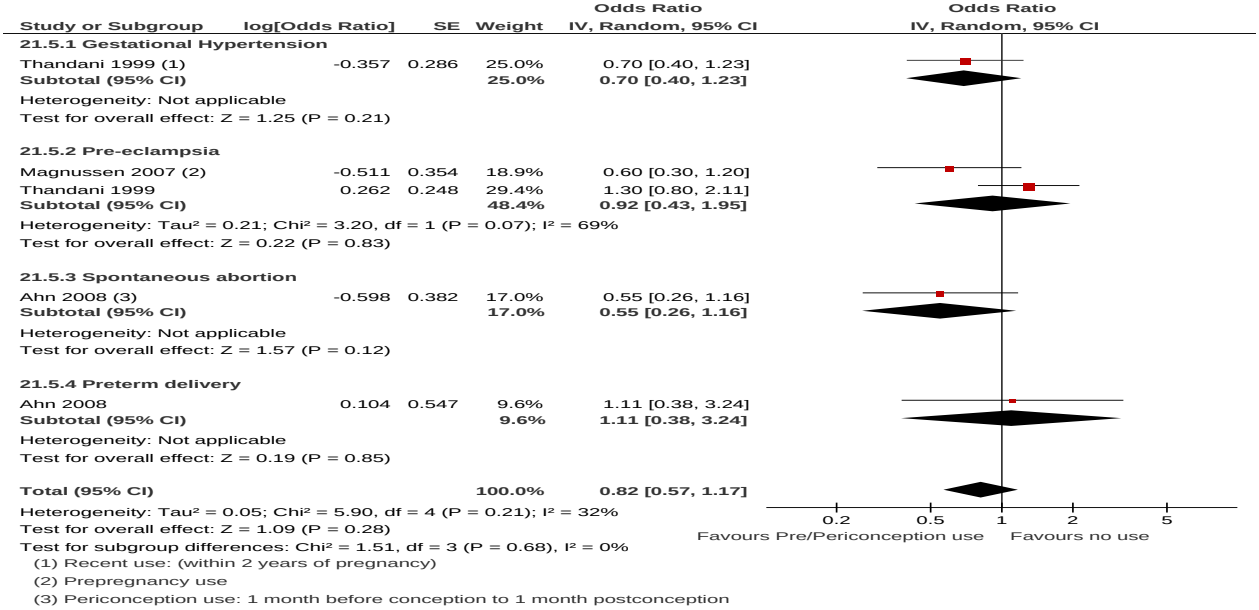


Periconception period: defined as 1 month before conception to end of 1st trimester by Bitsko et al.
Citation to the included studies
Bitsko 2008[169]

Oral contraceptive pills

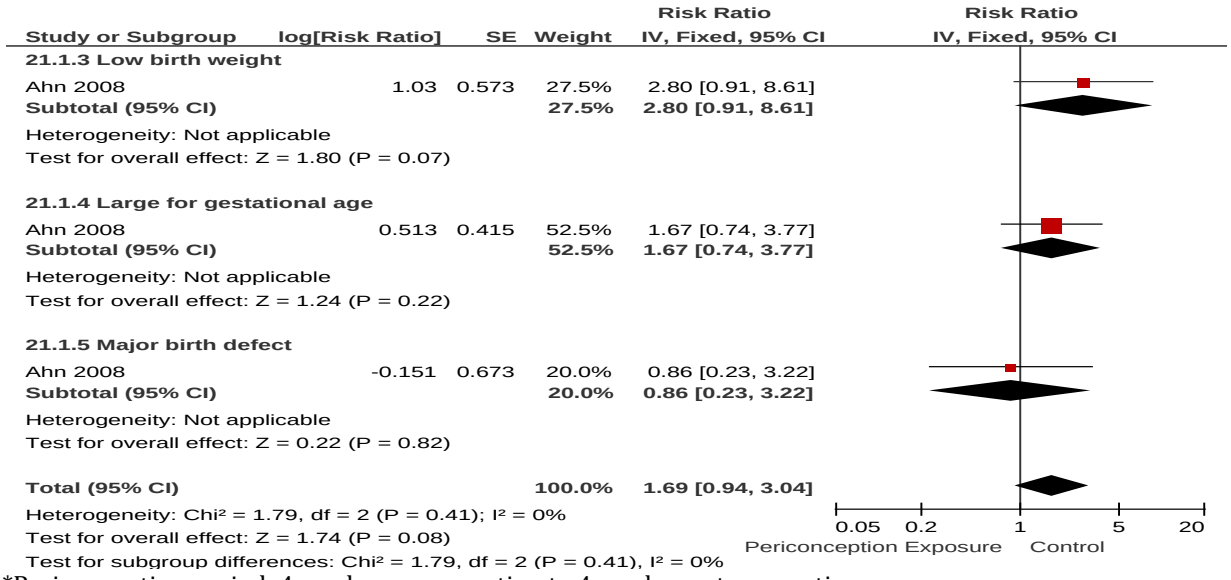
No significant association was found between pre/peri-conception use of oral contraceptives and gestational hypertension, pre-eclampsia, preterm delivery, spontaneous abortion (**Figure 6.7.2**), LGA, major birth defect or LBW (**Figure 6.7.3**); however periconception use of oral contraceptive pills (OCP) lead to an almost three-fold increase in the risk of Down's in infants (**Figure 6.7.4**).

Figure 6.7.2: Pregnancy outcomes of Pre/Periconception use of oral contraceptives



Citation of included study:
Ahn 2008[170], Magnussen 2007[145], Thandani 1999[171]

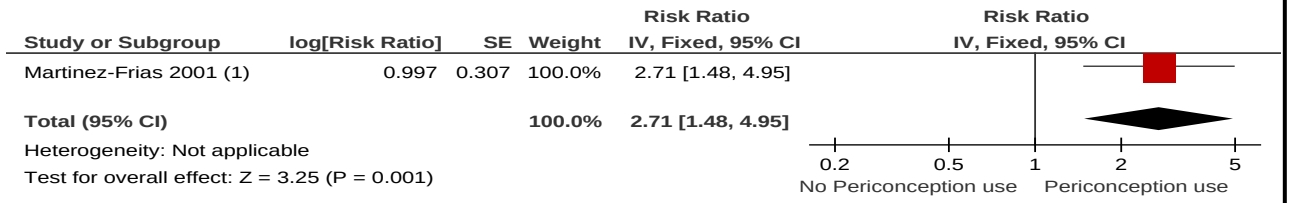
Figure 6.7.3: Fetal outcomes of Periconception use of oral contraceptives



*Periconception period: 4 weeks preconception to 4 weeks post-conception

Citation of included study: Ahn 2008[170]

Figure 8.7.4: Periconception use of oral contraceptives and risk of Down's syndrome



(1) Periconception use (stopped after conception) by mothers younger than 35 years of age

Citation of included study:
Martinez-Frias 2001[172]

Vasoactive substances

Werler et al.[173] reported aspirin use in the periconception period to lead to a significantly greater risk of amniotic bands (OR 2.5; 95% CI: 1.4-4.6); vasoconstrictor and decongestant use led to a higher incidence of transverse limb defects (TLD) (OR 1.4; 95% CI: 1.1-2.0); (OR 1.7; 95% CI: 1.2-2.3) respectively.

Conclusion

Several drugs have been contraindicated during pregnancy for their adverse effects on maternal and fetal outcomes. Our review of the literature found important evidence pertaining to the periconception use of certain drugs used regularly for chronic disorders or other purposes. Anti-asthmatics, especially bronchodilator use, in the periconception period led to a more than two-fold increase in the incidence of gastroschisis. Weight-loss drugs led to a 58% increase in the risk of congenital malformations, especially congenital heart defects. OCPs led to a non-significant increase in various pregnancy and fetal outcomes. Vasoactive substances, like aspirin, decongestants and vasoconstrictors were associated with limb defects.

Key messages

- Periconception use of bronchodilators leads to a significant doubling of the rate of gastroschisis, especially the use of bronchodilators.

Table 6.7.2: Summary of impact estimates for medications					
Interventions	**Maternal**	**Pregnancy**	**Newborn**	**Infant**	**Others**
Bronchodilators			**Gastroschisis:** Maternal bronchodilator use had a statistically significant elevated risk of gastroschisis (adjusted (OR) = 2.06, 95 percent CI: 1.19, 3.59). Lin 2008[155] Anti-inflammatory use showed an increased but not statistically significant association with gastroschisis (adjusted OR = 2.00, 95 percent CI: 0.88, 4.51). Lin 2008[155] Women who used both anti-inflammatories and bronchodilators had the highest risk, although not statistically significant (adjusted OR = 2.69, 95 percent CI: 0.87, 8.28). Lin 2008[155]		
OCPs (periconception)		**Gestational age:** The median gestational age at delivery was 39.1 (27.0–41.0) weeks in the exposed group and 39.3 (27.4–42.0) weeks in the control group (P = 0.19). [Ahn 2008][170] (1 month preconception to 1 month post-conception) **Pre-eclampsia:** Women who used oral contraceptives at baseline had nearly half the risk of pre-eclampsia of never or previous users (adjusted odds ratio 0.6, 95% confidence interval 0.3 to 1.0), but duration of use was not associated with risk of pre-eclampsia. [Magnussen 2007][145] Compared with never users and past users, multivariate relative risk among recent users (within 2 yrs of pregnancy) for the development of preeclampsia was 1.3 (95% CI, 0.8-2.4). Recent use of OCPs (8 or more years) predisposes to a 2.1 (95% CI, 1.1-4.2)	**Low birth weight:** In the exposed group, 7.1% of babies were born with low birth weight versus 2.6% in the control group (P = 0.068). [Ahn 2008][170] **Down's syndrome:** Periconceptional use vs no use by mothers < 35 yr of age RR 2.71 (1.48, 4.95). Stopped 1 month before conception vs no use RR 1.06 (0.76, 1.47) Stopped 2 months before conception vs no use RR 1.12 (0.78, 1.61) Stopped > 3 months before conception vs no use RR 1.18 (0.95, 1.45). [Martinez-Frias 2001][172]		

Table 6.7.2: Summary of impact estimates for medications					
Interventions	**Maternal**	**Pregnancy**	**Newborn**	**Infant**	**Others**
		risk for preeclampsia. [Thandani 1999][171] **<u>Gestational hypertension</u>**: Compared with never users and past users, multivariate relative risk among recent users (within 2 yrs of pregnancy) for the development of gestational hypertension was 0.7 (95% CI, 0.4-1.0). Recent use of oral contraceptives (8 or more years) predisposes to a 0.6 (95% CI, 0.3-1.2) risk for gestational hypertension. [Thandani 1999][171]			
Weight loss products (e.g. ephedra)			**<u>Malformations:</u>** Use of any weight loss product was associated with anencephaly (aOR 2.6; 95% CI: 1.3–5.3), dextro-transposition of the great arteries (aOR 2.1; 95% CI: 1.1–4.3), and aortic stenosis (aOR 3.4; 95% CI: 1.5–7.9). Use of products containing ephedra showed an increased aOR with anencephaly (aOR 2.8; 95% CI: 1.0–7.3). Other weight loss products were associated with dextro-transposition of the great arteries (aOR 1.8; 95% CI: 1.2–2.7), and aortic stenosis (aOR 2.1; 95% CI: 1.3–3.5). [Bitsko 2008][169]		
Anti-hypertensive medications			**<u>Birth defects:</u>** Observed slight to moderate elevations in the risk of severe hypospadias for maternal untreated hypertension (adjusted OR 2.1; 95% CI: 1.6‑2.9) and antihypertensive medication use during 1 month preconception through pregnancy month 4 (adjusted OR 1.4; 95% CI: 0.7‑2.9). [Caton 2008][@143]		
Thyroxin	**<u>Dose adjustment:</u>** In at least 9 of these 34 pregnancies (26%), the women were having dose	**<u>Thyroid function:</u>** Results suggest that in hypothyroid women anticipating pregnancy (with serum TSH in the lower quartile of normal range), the pre-conception adjustment of L-T4 doses may result in adequate maternal thyroid function	**<u>Birth defects:</u>** OR of 1.7 (1.0-2.7) for periconceptional thyroxine use and hypospadias. CPO OR 1.4 (0.8-2.3) CLP OR 1.0 (0.6-1.6) Hydrocephaly – OR 3.1 (1.7-5.8)		

Table 6.7.2: Summary of impact estimates for medications					
Interventions	**Maternal**	**Pregnancy**	**Newborn**	**Infant**	**Others**
	adjustments prior to (as well as during) pregnancy compared with none in the group not needing alteration in pregnancy (P < 0.001). [Kothari 2008][174]	up to the first post-conception evaluation. post-conception serum FT4 levels showed significantly higher rates of FT4 serum levels below the 25th centile of the normal range (0% vs. 36.4% for partially suppressive and replacement doses of L-T4 respectively; P, 0.05). [Rotunda 2004][110]	Anencephaly – OR 0.8 (0.2-2.3) Spina bifida – OR 1.1 (0.6-2.1) [Browne 2009]^^[98] CHDs: (periconceptional thyroxine use) Conotruncal-OR 1.0 (0.6-1.7) LVOTO- OR 1.3 (0.8-2.1) RVOTO - 1.0 (0.6-1.8) Septal – OR 1.1 (0.8-1.6) [Browne 2009]^^[98]		
Anti thyroid medications			Maternal exposure to antithyroid medication was rare; estimates could be calculated for only a few defect groups. Elevated ORs were observed for each of the case groups and were statistically significant for aortic valve stenosis (22.0; 95% CI, 3.4–114.0) and anorectal atresia (8.6; 95% CI, 1.7–40.2), but were based on only four exposed cases for each of these birth defects. [browne 2009]^^[98]		
Vasoactive substances			**Limb defects:** Maternal cigarette smoking and aspirin use each increased the risk of Amnoitic Bands (AB-L), but not Terminal Tranverse Limbs Deficiency (TLD); while decongestants and possibly antihypertensive medications increased the risk of TLD, but not AB-L. OR for isolated AB-L and vasoconstrictor use 0.9 (0.5, 1.7), aspirin use 2.5 (1.4, 4.6). OR for isolated TLD and vasoconstrictor use 1.4 (1.1, 2.0), decongestant use 1.7 (1.2, 2.3), aspirin use 1.3 (0.8, 2.2), vasodilator use 1.5 (0.6, 3.8). [Werler 2009][173] (periconceptional period defined as 2 weeks before the last menstrual period and ending 14 weeks after the last menstrual period)		
Any medication other than OCPs, including iron			**Orofacial defects:** Maternal use: CL/P risk OR (95%CI)1.7 (1.1–2.4), CPO risk OR (95%CI) 1.9 (1.0–3.3)* Paternal use: CL/P risk OR (95%CI) 1.4 (0.8–2.3) , CPO		

Table 6.7.2: Summary of impact estimates for medications					
Interventions	**Maternal**	**Pregnancy**	**Newborn**	**Infant**	**Others**
supplements			risk OR (95%CI) 0.5 (0.2–0.6)[#] Both Parents use: CL/P risk OR (95%CI) , 8.0 (1.8–35.5) , CPO risk OR (95%CI) 3.7 (0.5–27.2). [Krapels 2006][175]		

*Periconception period- 3 months before conception to 3 months after
[#] Periconception period- 3 months before conception to 2 weeks after
^^Periconception period- 1 month before conception to 3 months after
[@]Periconception period- 1 month before conception to 4 months after

Table 6.7.3: Summary of impact estimates for SLE				
Maternal /Paternal	**Pregnancy**	**Newborn**	**Infant**	**Others**
Maternal morbidity: A comparison between the maternal outcome of pregnancies in lupus anticoagulant positive and negative women showed no significant difference in the incidence of any complication. [Daskalakis 1998][134]	**Stillbirths/ spontaneous abortion:** Intrauterine fetal death occurred four times more often in women where the disease was active at the time of conception than in women where it was inactive. [Skomsvoll 2007][135] Stillbirth was associated with previous lupus nephropathy ($p < 0.05$) and hypertension at conception ($p<0.001$). [Cortes 2002][122] Active disease vs inactive disease at conception: spontaneous abortion – 2/8 vs 7/39. Stillbirth 1/8 [Georgiou 2000][121] **Deliveries**: Term deliveries- active disease vs inactive disease (1/8 vs 35/38) Preterm deliveries – 1/8 vs 2/39 [Georgiou 2000][121] **Disease exacerbation:** clinical exacerbation of lupus disease was observed in 11 (66%) of 15 cases where SLE was clinically active at the time of conception, and in only one (9%) of 11 cases where SLE nephritis was in stable clinical remission for at least five months before conception. The data indicate that successful outcome of pregnancy may be expected even in the more severe forms of lupus nephritis if gestation begins after a	**AntiPhospholipid detection and fetal outcomes:** APA noted at any time before pregnancy increased the low birth-weight rate (75%) six fold and the perinatal loss (33.3%) more than tenfold but did not affect the rate of spontaneous abortions. Any kind of hemocytopenias without APA, noted before pregnancy did not worsen the fetal outcome in SLE. [Pajor 1998][141] **Birth weight:** No differences in birth weight were found between patients with active disease at conception (2363±900 versus 2842±888 in inactive disease). [Carmona 1999][127] SLE lupus nephropathy at conception vs. no nephropathy;		

Table 6.7.3: Summary of impact estimates for SLE				
Maternal /Paternal	**Pregnancy**	**Newborn**	**Infant**	**Others**
	sustained, complete clinical remission. [Jungers 1982][136] Among 18 pregnancies in patients with lupus nephritis, 50% of patients with active disease at conception flared during pregnancy but for those with inactive disease, only 20% had flares. [Houser 1980][137] Of the 25 pregnancies with active renal disease at conception, 48% had flares of nephritis. This percentage was higher than that of pregnancies with inactive renal disease at the time of conception (32%) [Hayslett 1980][138] The rate of disease flares during lupus pregnancies was reported to be 62% and 7.4%, respectively, for those with active and inactive nephritis at conception. [Bobrie 1987][139] SLE lupus nephropathy at conception vs. no nephropathy; Flare 5 (30%) vs. 12 (24%) Hypertension 5 (50%) vs. 5 (11.6%) p=0.01 Preterm delivery 3 (30%) vs. 11 (25.5%). [Carmona 1999][127] Active SLE at conception- n=4, abortions 0, stillbirths 0, prematurity 2, term newborn 2. [Cavallasca 2008][140] 18 women with active SLE at conception vs. 31 with inactive disease- Induced abortions 3 vs. 8, Spontaneous Abortions 9 vs. 2, Stillbirth 1 vs. 1. [Chandran 2005][129] Variables significantly associated with flares during pregnancy were increased number of flares before gestation ($p < 0.05$), and previous treatment with chloroquine ($p < 0.05$). Flares during pregnancy were more common in women with active disease at conception, although this was not significant [Cortes 2002][122]	Gestational age at delivery 35.9+/-3.7 vs. 37.3+/-4.2 p=0.04 Neonatal birth weight 2441+/-967 vs. 3229+/-1747 N.S. Perinatal mortality 1 (10%) vs. 4 (9.3%). [Carmona 1999][127] Active SLE at conception- n=4, low birth weight 1. [Cavallasca 2008][140] Mortality: 18 women with active SLE at conception vs. 31 with inactive disease- Neonatal death 0 vs. 1, Live birth 5 vs. 19. Only active disease adversely affected the outcome (13/18 versus 4/23, $P<0.05$). [Chandran 2005][129] Over half (57 per cent) of the foetuses born to lupus anticoagulant-positive mothers died, compared with only 10 (23 per cent) born to mothers who were lupus anticoagulant negative ($p = 0.013$). Differences were even more marked in comparing perinatal mortality: nine (43 per cent) in the positive group compared with three (7 per cent) in the negative group ($p = 0.0015$). [Daskalakis 1998][134]		

- Periconception use of any weight loss drug was significantly associated with an increased incidence of congenital anomalies in the fetus, especially heart defects.
- Periconception use of oral contraceptives led to no significant increase in spontaneous abortions or any fetal outcomes.
- Periconception use of vasoactive substances was linked to limb defects in the fetus.

Table 6.7.1: Summary of impact estimates for chronic diseases

Maternal /Paternal	Pregnancy	Newborn	Infant	Others
Any illness, including common cold		**Orofacial defects:** Maternal illness: CL/P risk OR (95%CI) 1.7 (1.2–2.5), CPO risk OR (95%CI) 1.5 (0.8–2.6). [Krapels 2006]*[175]		

*Periconception period- 3 months before conception to 3 months after

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Section VII

7. Mental health

Background

With the current prevalence of psychiatric illnesses, there is a significant risk of women's antenatal and postpartum periods being made difficult with the onset or recurrence of a psychiatric illness.

Evidence suggests that depression and anxiety during pregnancy and postpartum severely impact family life, the mother-infant relationship, and the future mental health of the child.[1-4] A large meta-analysis stated that up to 18% of women experience depressed mood during pregnancy.[5] A Brazilian study noted that common mental disorders, in general, were autonomously related with LBW and PTD in pregnant teenagers.[6] however, an earlier study had found no relationship between depression and pregnancy outcomes for teens but found an association with poor outcomes in adults.[7] Maternal antenatal depression generally has been highly correlated with PTD.[8-10] Similarly, depression also appears to be a significant risk factor for LBW.[9, 11, 12] Depression also has noteworthy associations with miscarriage, antepartum hemorrhage, greater uterine artery resistance and a higher risk of operative deliveries.[11] Additional risks are associated with the medications being used to treat depression. A retrospective study of depressed women treated with SSRIs or untreated found in utero exposure to SSRIs linked with earlier gestational age and lower birth rate;the exposed group also had higher rates of neonatal respiratory distress syndrome, jaundice, and feeding problems. [13, 14]. Other studies also suggest first trimester exposure to SSRIs increasing the risks of PTD and restricted fetal growth.[15, 16]

Bipolar Disorder (BD) is a severe recurrent illness that is associated with high rates of morbidity and mortality in the absence of adequate treatment. Manic episodes may be associated with increased risky behaviors such as sexual activity or substance use, which could affect health during pregnancy as well as lead to a significant risk of unintended pregnancies.[17] Patients with bipolar disorder have a very high risk of comorbid alcohol or substance abuse disorders – reaching up to 60% in some studies - which could have direct adverse impacts on fetal outcomes[18, 19] Bipolar disorder itself has also been found to be associated with placental abnormalities and antepartum hemorrhages but not stillbirths, fetal anomalies, birthweight or gestational age.[20] Bipolar disorder is especially challenging during the reproductive years, as related outcomes consist of potential fetal teratogenic risk from medications to control the condition, and high risk of recurrence if treatment is discontinued suddenly.[21] Recurrence risk was 2.3 times greater after discontinuing mood stabilizer treatment and women who discontinued the mood stabilizer abruptly had a 50% risk of recurrence within 2 weeks versus 22 weeks in women who gradually tapered their mood stabilizer treatment.[22]

Cognitive-behaviour therapy-based intervention provided to pregnant women, by community workers, was shown to effectively reduce depression by 77% 3 months post-intervention (aOR 0·22; 95% CI: 0·14-0·36) and this effect was still significant at the 1-year follow-up (aOR 0·23; 95% CI: 0·15-0·36).[23]

Scope of intervention

We wanted to assess the effect pre-existent psychiatric conditions in women in the preconception period on maternal and fetal morbidity and mortality. Included were more prevalent conditions like mood disorders as well as conditions like schizophrenia. We looked primarily at the risks and benefits, to the mother as well as her unborn child, of continuing or changing or even discontinuing the psychotropic regimens for the above mentioned disorders.

The content of preconception care for psychiatric conditions is enlisted in table 11.1.

Table 7.1- Content of preconception care for psychiatric conditions

- Screen women in their child-bearing years for mood disorders and identify those at risk
- Counsel women with pre-existing depression and anxiety disorders about the potential risks of an untreated illness and the negative family outcomes.
- Counsel women with psychiatric disorders to achieve a euthymic state before conception
- Counsel women of the increased risk of relapse on discontinuing their antidepressants and anxiolytics
- Inform about the risks and benefits of various treatment options prior to conception and during pregnancy
- Counsel women with bipolar disorder of the considerable risk of a relapse during pregnancy.
- Counsel women with BD about the fetal risks associated with mood stabilizers (cardiac malformations) and anticonvulsants (birth defects) and the importance of discontinuing them before conception. Change medications before conception to reduce exposure of the fetus to multiple meds
- Educate women with BD about the importance of strict contraception during bipolar episodes.
- Counsel women with schizophrenia about the negative maternal and fetal outcomes associated with the disease.
- Devise a plan for relapse prevention and management of the illness before the patient attempts conception.

Impact estimates

While the effect of psychiatric conditions and their relative treatment during pregnancy has been widely studied, there is a serious lack of evidence of how prepregnancy disease and psychotropic drugs may affect pregnancy. From the evidence we gathered from existing literature that pre-pregnancy depression is significantly related to preterm births (OR 1.04; 95% CI: 1.02-1.07)[24] and adolescent depression per say was significantly associated with an increased risk of miscarriages (aOR 2.25; 95% CI: 1.12-4.50).[25] After adjusting for confounding factors, adolescent depression was not significantly associated with induced abortion (aOR 1.42; 95% CI: 0.79-2.57).[25]

When assessing for maternal morbidity, adolescent depression was positively associated with suffering from intimate partner violence (aOR 3.47; 95% CI: 1.11-10.84) but not STDs (aOR 1.50; 95% CI: 0.83-2.72).[25] Silverman et al.[26] concluded that a pre-existing psychiatric condition was one of the best predictors of development of post-partum depression. Literature also showed that a pre-pregnancy psychotic or bipolar illness substantially increased the risk of a postpartum psychotic or bipolar event.[27]

Our search for the effect of maternal bereavement on neonatal/infant health revealed that loss of a close relative in the 7-12 months before conception did not increase the risks of autism, epilepsy or febrile seizures in the infant. However, loss of a child or spouse in the 6 months preceding conception was positively associated with ADHD in the male child, childhood obesity and congenital malformation.

Inteventions specifically targeting women of reproductive age suffering from a psychiatric condition show that group-counseling[28] and interventions leading to empowerment of women have reported lowering of depression in these women but the results so far have not been significant (**Figure 7.1.1**) (**Figure 7.1.2**). Interventions teaching coping skills or based on stepwise facilitation seem to significantly lower depression levels and these lowered levels were persistent at the 1-yr follow-up.[29] However, morbidities associated with depressions are higher. (**Figure 7.1.3**).

Interventions addressing psychiatric conditions are enlisted with a brief description in **table7.1.2**.

Table 7.1.2 - Intervention studies addressing mental illnesses

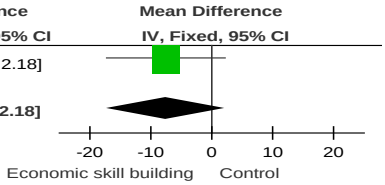
Study/yr	Intervention	Results
[Rychtarik 2005][29]	Coping-Skills training and 12 step facilitation: Compared the immediate and long-term efficacy of an empirically based coping skills training (CST) program and a theoretically distinct professionally administered 12-step, Al-Anon facilitation condition for women whose partners have alcoholism. Participants in the CST condition learned to conceptualize their distress from within a family stress and coping perspective. Participants in the TSF condition learned to view their problem as one of codependence; the 12 steps of Al-Anon then served as a blueprint to facilitate codependence recovery.	At the end of the treatment or delay period, depression was significantly less in Coping Skills Training (CST) and 12-step facilitation (TSF) relative to Delayed Treatment Control (DTC). Depression at the 12-month follow-up continued to be significantly lower than at pretreatment, $F(1, 35) = 74.37$, $p < .0001$, $PV = .28$.
[Tripathy 2010][28]	Every group met monthly for a total of 20 meetings, and a local woman, selected on the basis of criteria identified by the community, facilitated the meetings. Groups used methods such as picture-card games, role play, and story-telling to help discussions about the causes and effects of typical problems in mothers and infants, and devised strategies for prevention, homecare support, and consultations.	Did not note a significant effect on maternal depression overall, but the reduction in moderate depression was 57% in year 3 (0·43, 0·23–0·80)**
[Hirani 2010][30]	The interventions of economic skill-building and counseling were delivered through the trained community health workers for 8 weeks, one session per week. The economic skill-building intervention included skills for employment attainment and retention such as, effective communication, balancing personal and work life and time management, conflict resolution, dealing with abuse and harassment, enhancing self efficacy, effective parenting, and personal hygiene and grooming.	Among the first 24 women who completed the intervention, women who received economic skill-building reported lower depression scores although the differences were not statistically significant.

Women with serious mental illnesses are at a greater risk of having had >1 sexual partner or having been raped and are hence more likely to have unplanned, unwanted pregnancies.[31] There support system has been reported to be generally lacking.[32] They have a greater possibility of engaging in risky behavior during pregnancy (substance abuse, suicide attempts) or of being abused.[33] All this makes it imperative for their physicians to not only screen vigorously for such cases but also to provide comprehensive family planning and contraceptive counseling as well as attach them to relevant support systems.

Figure 7.1.1: Economic skill building and depression prevalence

Study or Subgroup	Economic Skill building Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Hirani	20.1	11.3	9	27.63	9.1	8	100.0%	-7.53 [-17.24, 2.18]
Total (95% CI)			**9**			**8**	**100.0%**	**-7.53 [-17.24, 2.18]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.52 (P = 0.13)

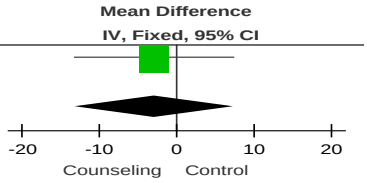


Citation to included studies:
Hirani 2010[30]

Figure 7.1.2: Counselling and depression prevalence

Study or Subgroup	Counseling Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Hirani	24.71	10.9	7	27.63	9.1	8	100.0%	-2.92 [-13.17, 7.33]
Total (95% CI)			**7**			**8**	**100.0%**	**-2.92 [-13.17, 7.33]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.56 (P = 0.58)

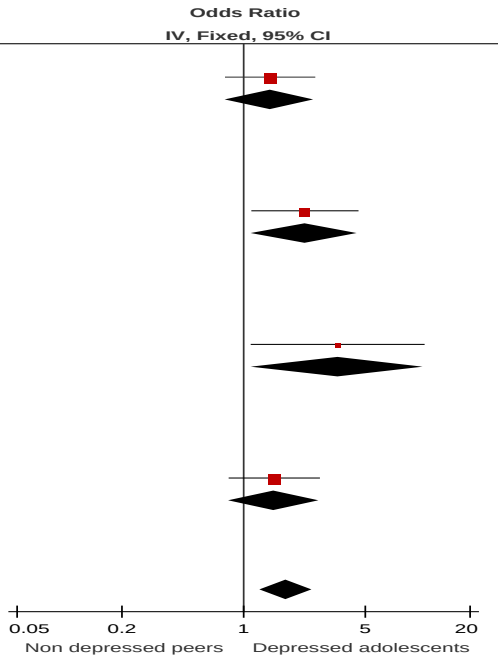


Citation to included studies:
Hirani 2010[30]

Figure 7.1.3: Morbidities associated with depression in adolescents

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
11.3.1 Induced abortion				
Jonsson 2010	0.351	0.299	33.9%	1.42 [0.79, 2.55]
Subtotal (95% CI)			**33.9%**	**1.42 [0.79, 2.55]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.17 (P = 0.24)				
11.3.2 Miscarriage				
Jonsson 2010	0.811	0.356	23.9%	2.25 [1.12, 4.52]
Subtotal (95% CI)			**23.9%**	**2.25 [1.12, 4.52]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 2.28 (P = 0.02)				
11.3.3 Intimate Partner Violence				
Jonsson 2010	1.244	0.581	9.0%	3.47 [1.11, 10.83]
Subtotal (95% CI)			**9.0%**	**3.47 [1.11, 10.83]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 2.14 (P = 0.03)				
11.3.4 STD (ever)				
Jonsson 2010	0.405	0.302	33.2%	1.50 [0.83, 2.71]
Subtotal (95% CI)			**33.2%**	**1.50 [0.83, 2.71]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.34 (P = 0.18)				
Total (95% CI)			**100.0%**	**1.75 [1.24, 2.46]**

Heterogeneity: Chi² = 2.64, df = 3 (P = 0.45); I² = 0%
Test for overall effect: Z = 3.21 (P = 0.001)
Test for subgroup differences: Chi² = 2.64, df = 3 (P = 0.45), I² = 0%



Citation to included studies:
Jonsson 2010[25]

Table 7.1.3: Impact estimates of Mental health

Maternal	Pregnancy	Newborn	Infant/Child	Others
STD: The association between adolescent depression in females and subsequent sexually transmitted disease was attenuated by adjustment for background variables.^^ [Jonson 2010][25] Adolescents with high psychological distress, relative to those with low psychological distress, were more likely to have a biologically confirmed STI (adjusted odd ratio (AOR) = 1.40, 95% CI 1.01–1.94). [Seth 2009][#34] **Postnatal Depression:** Symptoms associated with postpartum depression (PPD) were best predicted by a pre-pregnancy history of physical or sexual abuse, a history of psychiatric problems, or psychiatric diagnosis at the time of first prenatal visit.**[Silverman 2010][26] Of the 46 who tried to conceive, 69% (20 of 29) became pregnant within 12 months. The other 37% (17 of 46) chose to avoid pregnancy, including one who sought to adopt a child. The most commonly reported reasons to avoid pregnancy were fear of adverse effects of medicines on fetal development (56%, 10 of 18) and fear of illness recurrence if maintenance treatment were discontinued (50%, nine of 18). Fewer women expressed concerns about potential genetic transmission of bipolar disorder to offspring (22%, four of 18), reluctance to repeat previous pregnancy-associated illness (17%, three of 18), and fear that recurring mania or depression would adversely affect a fetus or existing children (17%, three of 18). [Vaguer 2002][21]	**Preterm birth**: Pre-pregnancy depressive mood was significantly associated with preterm birth (OR 1.04, 95% CI 1.02, 1.07 [Gavin 2009][24] Pre-pregnancy depressive mood was predictive of preterm birth among black women (OR 1.05, 95% CI 1.02 1.12) but not white women (OR 1.00, 95% CI 0.95, 1.06). [Gavin 2009][24] **Miscarriage:** The association between adolescent depression in females and subsequent miscarriage was not attenuated by adjustment for background variables.^^ [Jonson 2010][25] **Induced abortion:** The association between adolescent depression in females and subsequent induced abortion was attenuated by adjustment for background variables.^^ [Jonsson 2010][25] **Recurrence**: Rates of recurrence during the first 40 weeks after lithium discontinuation were similar for pregnant and non-pregnant women but then sharply increased postpartum. Postpartum recurrences		**Bereavement:** aHR 0.95 (95% CI 0.59–1.52) for mother losing a close relative 7-12 months preconception and child autism, aHR 0.88 (0.54–1.34) for 0-6 months preconception [Li 2009 Coh][37] Incidence rate ratio 1.02 (95% CI 0.90-1.17) for mother losing a close relative up to 1 year preconception and child developing epilepsy in first decades of life [Li 2008 Coh][38] aHR 1.03 (95% CI 0.93–1.15) for mother losing a close relative 7-12 months preconception and childhood febrile seizures, aHR 1.01 (0.92–1.12) for 1-6 months preconception, slightly stronger effect for recent loss of a child [Li 2009 Coh][39] aHR 1.47 (1.00–2.16, p<0.05) for maternal loss of a child/spouse 0-6 months preconception	**Intervention**: Did not note a significant effect on maternal depression overall, but the reduction in moderate depression was 57% in year 3 (0·43, 0·23–0·80)**[Tripathy 2010][28] Among the first 24 women who completed the intervention, women who received economic skill-building reported lower depression scores although the differences were not statistically significant. [Hirani 2010][30] **Intimate Partner Violence:** Adolescent depression was still a significant predictor of intimate partner violence after adjustment for background variables.^^ [Jonsson 2010][25] **Risky sexual practices**: Adolescents with high psychological distress, relative to those with low psychological distress, were more likely to use condoms inconsistently in the past 2 months (AOR = 1.50, 95% CI 1.02–2.21), not use condoms

Table 7.1.3: Impact estimates of Mental health				
Maternal	**Pregnancy**	**Newborn**	**Infant/Child**	**Others**
Women who perceived that pregnancy had a positive influence on their illness course and overall well-being (47%, 16 of 34); those who reported negative effects (53%, 18 of 34). [Vaguer 2002][21]	were 2.9 times more frequent than recurrences in non-pregnant women during weeks 41-64 (70% versus 24%). Depressive or dysphoric-mixed episodes were more prevalent in pregnant than non-pregnant women (63% versus 38% of recurrences). [Viguera 2001][35] Having a postpartum mood episode after a first pregnancy significantly increased the risk of a postpartum episode after subsequent deliveries (p = .02). [Freeman 2002][36]		and male offspring ADHD [Li 2010 Coh][40] OR 3.31 (95%CI 1.71–6.42) for maternal loss of a close relative 0-6 months preconception and childhood overweight [Li 2010 Coh][41] AOR 1.31 (95%CI 1.01-1.69) for death of child 0-6 months preconception and congenital malformations. [Hansen 2000 Coh][42]	during their last casual sexual encounter (AOR = 1.89, 95% CI 1.08–3.30), have sex while high on alcohol or drugs in the past 2 months (AOR = 1.47, 95% CI 1.07–2.02), have male sexual partners with concurrent female sexual partners (AOR = 1.98, 95% CI 1.36–2.90), have low condom use self-efficacy (AOR = 1.54, 95% CI 1.15–2.07), partner sexual communication self-efficacy (AOR = 1.77, 95% CI 1.31–2.39), refusal self-efficacy (AOR = 2.05, 95% CI 1.52–2.77) and be more fearful of communicating with their partners (AOR = 1.98, 95% CI 1.47–2.67). [Seth 2009][#34]

**Pregnant women

^^formerly depressed adolescents and their non-depressed peers at age 30 years

#adolescents

Conclusion

Mental health conditions are prevalent among women of reproductive age and a substantial proportion goes untreated. Due attention may be being paid to screening for and treating psychosocial issues during pregnancy and post-partum but non-pregnant women are being neglected in this regard. There is a deficiency of evidence associating the status of disease and treatment in the preconception period with adverse MNCH effects. This explains the lack of literature on effective interventions targeting such women, implementation of which would be a task of its own. Interventions already proved efficacious in pregnancy should also be evaluated for women before pregnancy.

Key messages

- A substantial proportion of mental health conditions in women of child-bearing age remain undiagnosed.
- Adolescent depression significantly increases: the risk of miscarriages by more than two folds; the risk of IPV by more than three-folds.
- Current interventions have not yielded significant impacts on lowering depression in non-pregnant women.
- MNCH effects of preconception disease status and treatment of other psychiatric conditions still needs to be explored.

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Section VIII

8. Intimate partner violence

Background

Irrespective of their demographics, women around the globe have been subjected to intimate partner violence (IPV). IPV against women is a major public health concern as it adversely affects both the physical, mental and reproductive health of a woman and that of the newborn. physical abuse by a partner at some point in life was reported by 13–61% of women of 49 years of age and sexual violence by a partner was reported by 6–59% of them.[1] A literature review by Sharps et al.[2] show that 3-19% of pregnant women are battered. Violence during pregnancy has been associated with poor health outcomes including increased risk of preterm labor,[3] antepartum hemorrhage,[4] LBW infants,[3] fetal loss,[5-7] sexually transmitted diseases[8] and post-partum depression.[9] Coker et al.[10] reported that women who 'ever experienced' IPV were more than twice as likely to suffer from various kinds of physical and mental health problems. Having experienced IPV is associated with a higher occurrence of unwanted pregnancies,[11-13] gynecologic morbidity[14-16] and involvement in risky sexual behaviours.[14, 16, 17] Silverman et al.[18] reported that women reporting intimate partner violence in the year prior to pregnancy had a greater risk of preterm delivery, LBW and newborn requiring ICU care when compared to those women not reporting IPV. Data suggests that intensive advocacy interventions may improve the quality of life where as brief advocacy interventions improve safe behaviors.[19] Coker et al.[20] reported that of the women experiencing physical or sexual IPV, 53% sought community-based or professional services for IPV; women with higher education levels and those experiencing more severe violence were most likely to seek services. This illustrates the importance of having interventions which would also aim at improving literacy in women and lead to empowerment of these women.

Evidence is promising of the effectiveness of several strategies for the prevention of intimate partner and sexual violence, particularly the use of microfinance with gender equality training[21] and of programmes that promote communication and relationship skills within communities ('Stepping Stones').[22]

Scope of intervention

Evidence dictates that IPV is a widespread problem and its repercussions, a serious health burden. We know that IPV during pregnancy maybe catastrophic for the mother and her unborn child. Given that pre-pregnancy violence continues well into pregnancy as well as post-partum, even if at a lower rate,[9, 23] it is imperative to intervene before conception in order to improve overall IPV-related-MNCH outcomes including promotion of safer sexual behaviors. For outcomes where pre-pregnancy exposure data was not looked at, we took exposure to IPV in women in general.

The content of preconception care for women suffering from intimate partner violence includes firstly identifying such women, which can be effectively done by asking all

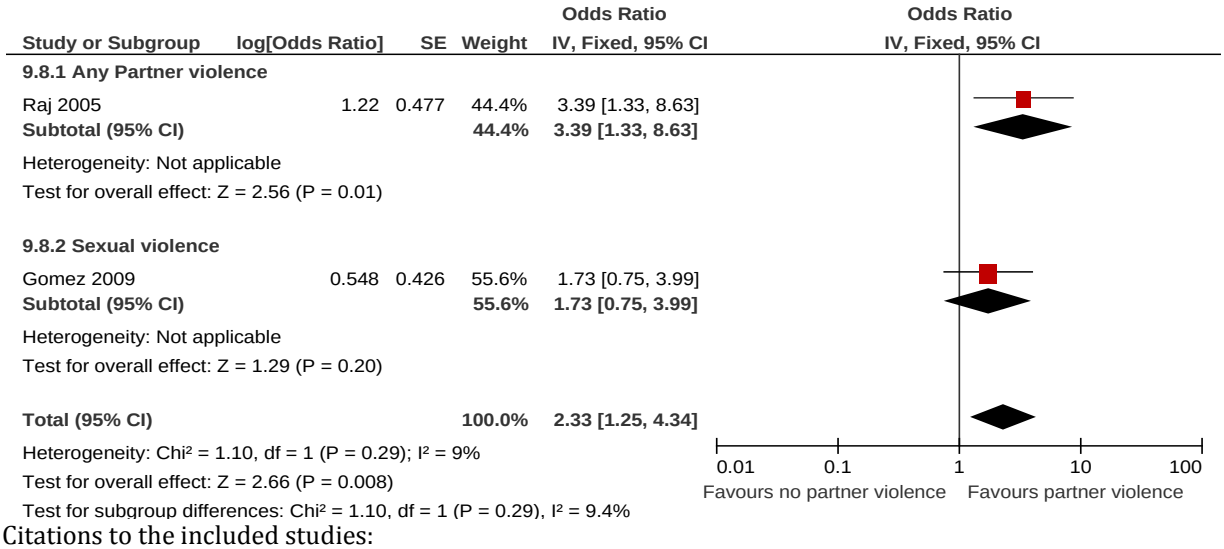
women about their experiences of violence from any source, at any point in life. Their condition needs to be evaluated and their injuries treated. Women suffering from IPV need to be informed about the significant harm to the mother, the fetus,and the newborn infant that such abuse can potentially cause and hence of the crucial role of contraceptives. They need be counseled for the psychological trauma that they've suffered from. And finally they need to be referred to an agency/support group that specializes in dealing with such cases.

*Sexual violence specifically in adolescents is dealt with in the section on ***'Adolescents'***.

Impact estimates

Most of the studies we reviewed for effect of IPV exposure were in women in the general population. These studies were mostly risk aversion studies. From our analysis we found that intimate partner violence positively led to unintended pregnancies; this finding was significant (OR 2.33; 95% CI: 1.25-4.34) (**Figure 8.1.1**).

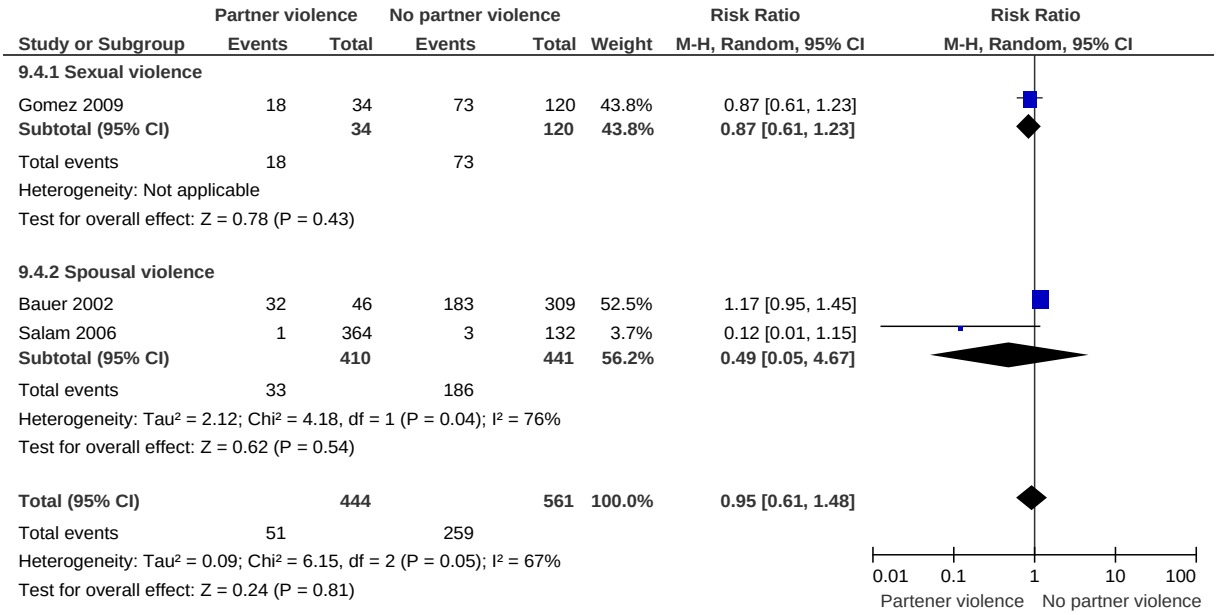
Figure 8.1.1: Intimate partner violence and risk of unintended pregnancies (in women who have undergone IPV in the last 1 year



Citations to the included studies:
Raj 2005[24], Gomez 2009[25]

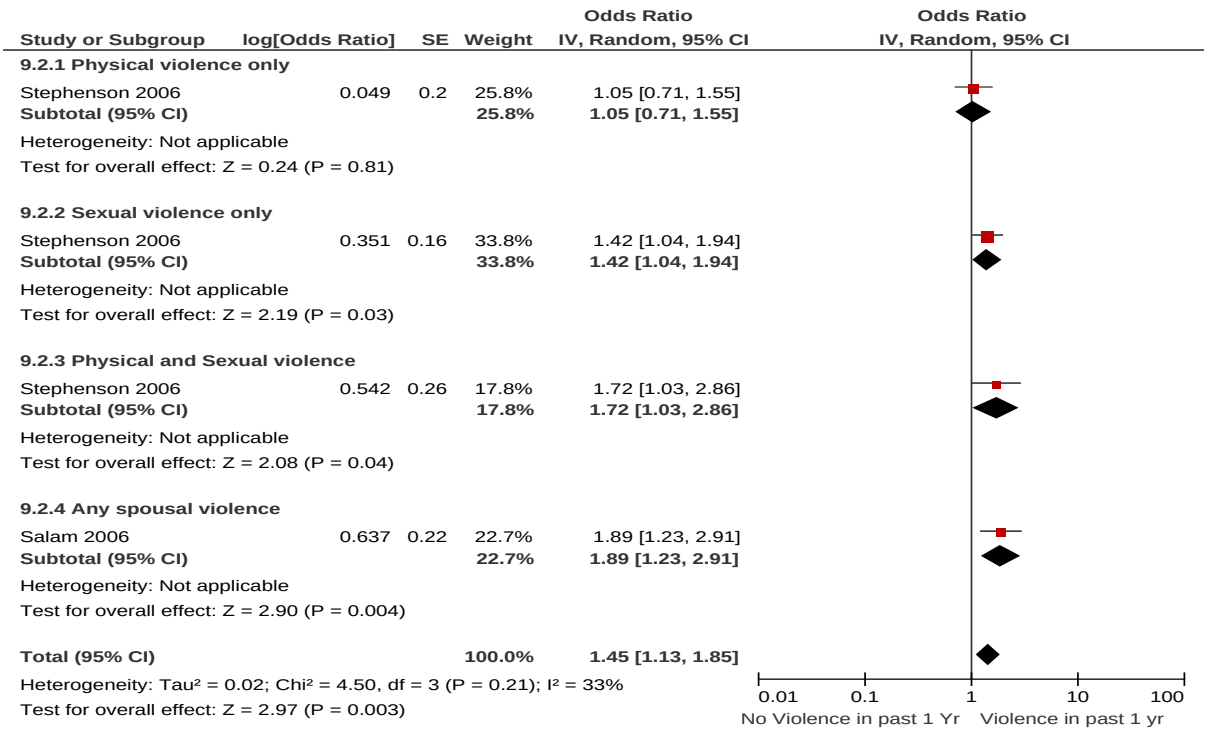
Results from another study did not report an association (OR 0.65; 95% CI: 0.37-1.14).[8] We found no association between IPV and condom use in women (**Figure 8.1.2**). A significant increase in gynecologic morbidities was reported in women suffering from IPV (OR 1.45; 95% CI: 1.13-1.85) (**Figure 8.1.3**) and rates of STIs were non-significantly raised by more than 2 folds in these women (**Figure 8.1.4**). Gynecologic morbidity increased significantly with any spousal abuse (OR 1.89; 95% CI: 1.23-2.91); combined physical plus sexual violence led to a 72% increase (p=0.04).

Figure 8.1.2: Intimate partner violence and risk of condom use (in women who have undergone IPV in the last 1 year



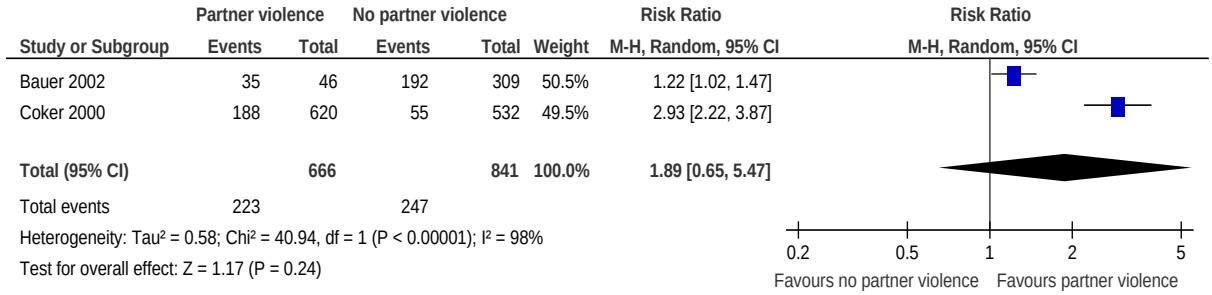
Citations to the included studies:
Gomez 2009[25], Bauer 2002[14],Salam 2006[8]

Figure 8.1.3: Intimate partner violence and risk of gynecologic morbidity (in women who have undergone IPV in the last 1 year



Citations to the included studies:
Stephenson 2006[15], Salam 2006[8]

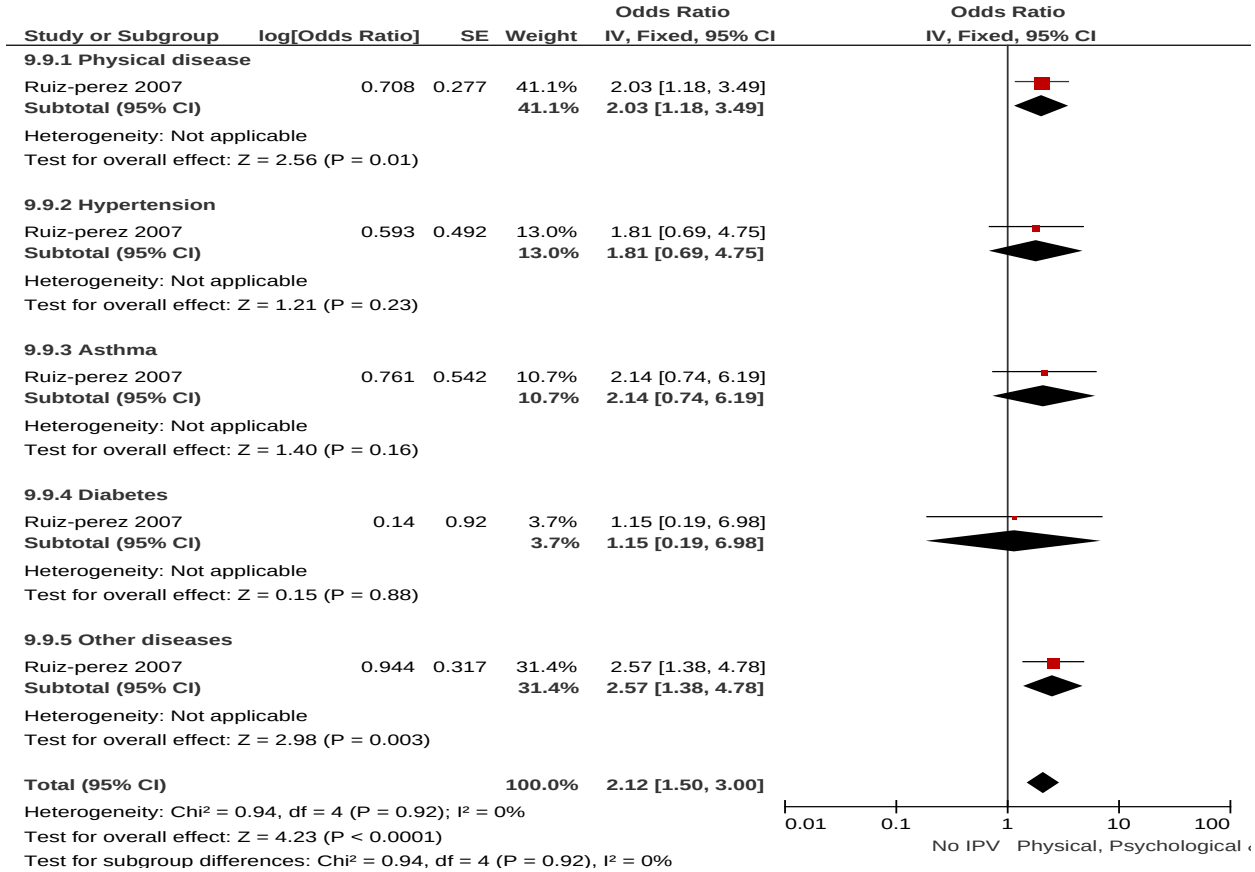
Figure 8.1.4: Intimate partner violence and risk of STIs (in women who have undergone IPV in the last 1 year



Citations to the included study:
Bauer 2002[14], Coker 2000[20]

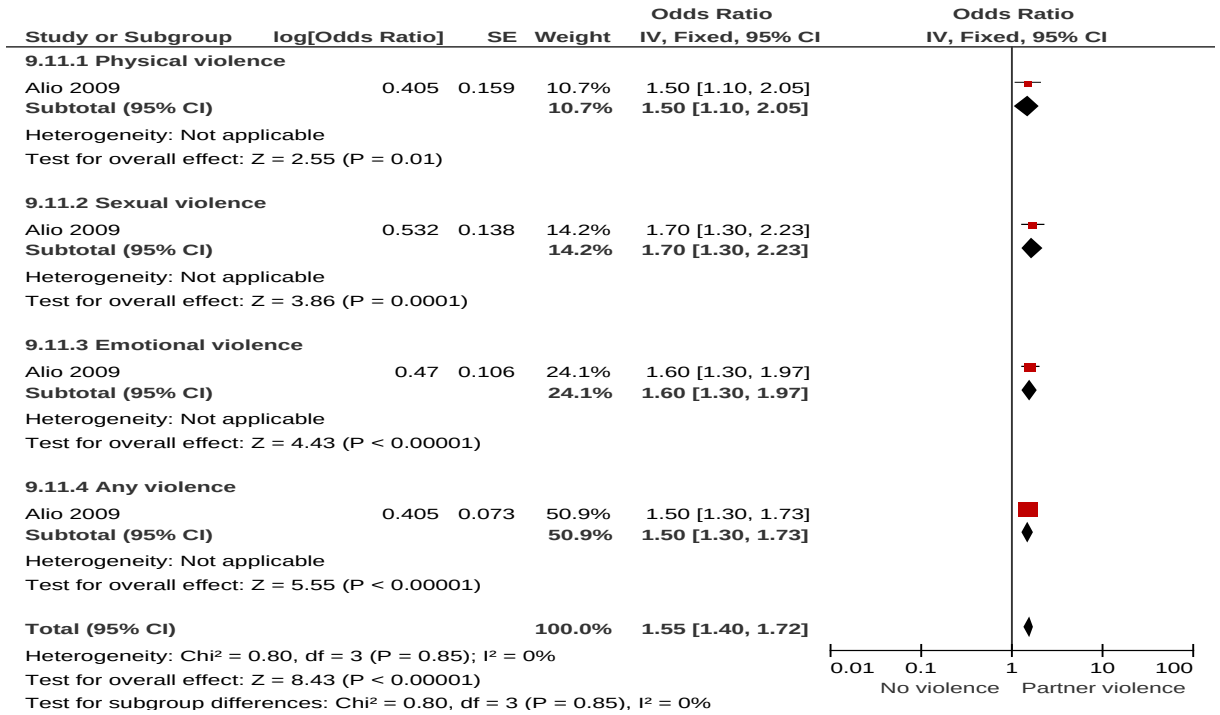
With regards to a woman's physical and mental health, IPV had serious detrimental effects on in those abused. Abused women developed chronic diseases at twice the rate as compared to those not abused (p< 0.001). Ruiz et al.[26] reported that women who had experienced physical, psychological and sexual violence were twice as likely to suffer a chronic disease as those who have not experienced abuse (OR 2.03; 95% CI: 1.18-3.51), especially diseases other than hypertension, diabetes and asthma (OR 2.57; 95% CI 1.38-4.77) (**Figure 8.1.5**), and fetal loss (**Figure 8.1.6**).

Figure 8.1.5: Intimate partner violence ever and physical health status in women



Citations to the included study:
Ruiz-perez 2007[27]

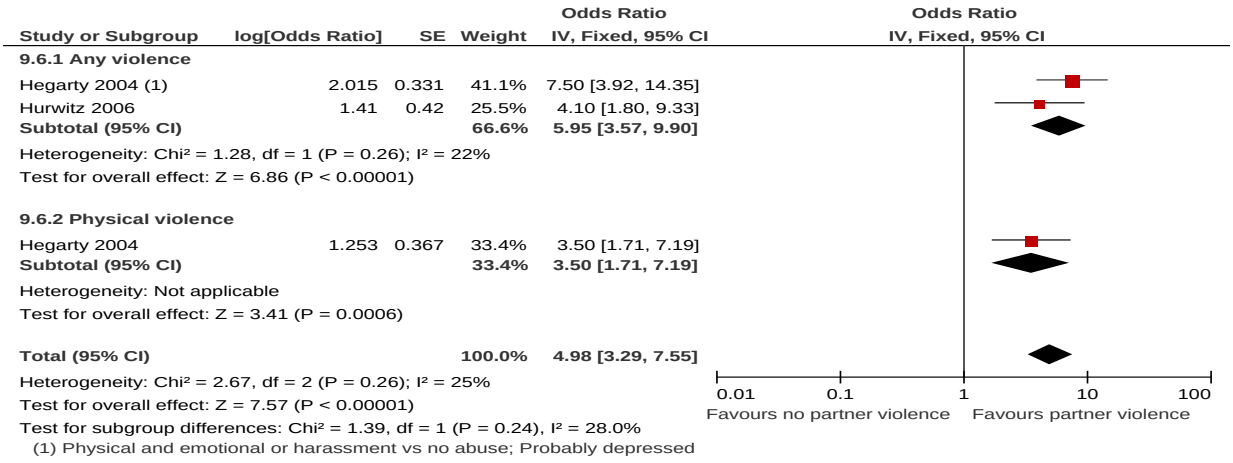
Figure 8.1.6: Intimate partner violence ever and Fetal loss



Citations to the included study:
Alio 2009[5]

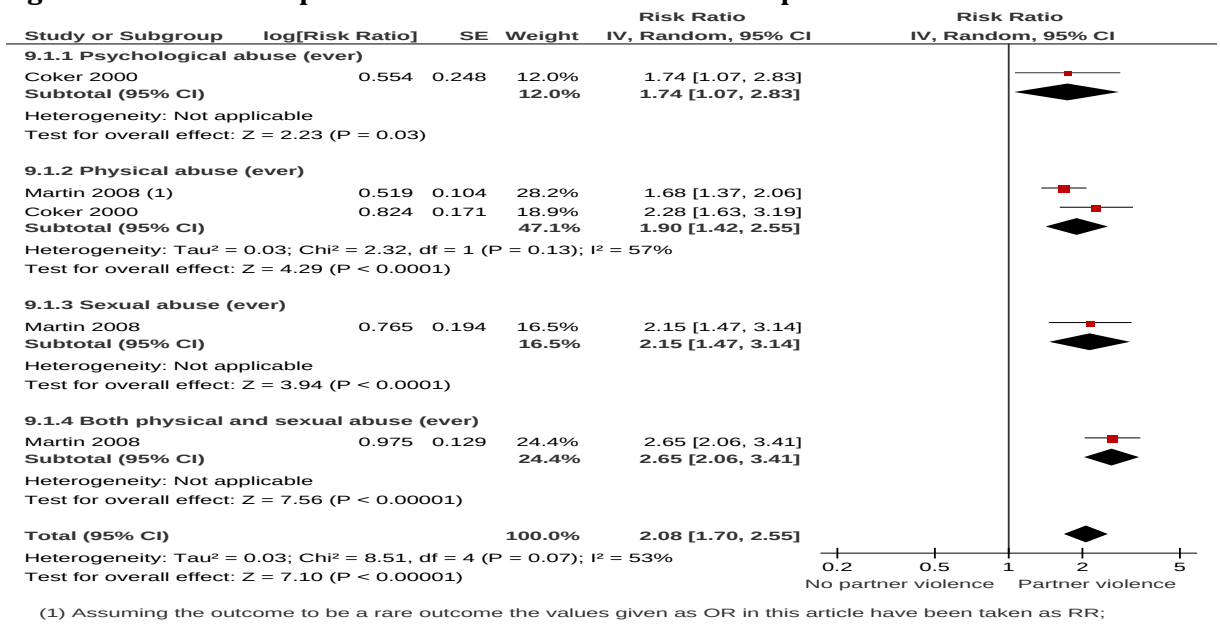
IPV leads to a towering five-fold increase in depression among the victims (p<0.00001) (**Figure 8.1.7**) and a two-fold increase in impairment of mental health in the past month only (RR 2.08; 95% CI: 1.70-2.55] (**Figure 8.1.8**). Abuse also makes these women 7 times more likely to contemplate suicide (**Figure 8.1.9**).

Figure 8.1.7: Intimate partner violence and risk depression (in women who have undergone IPV in the last 1 year



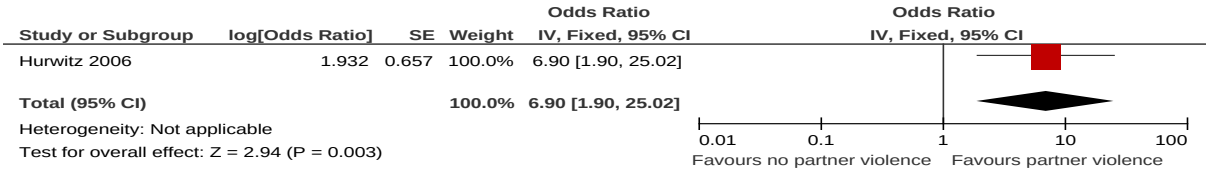
Citations to the included study:
Hurwitz 2006[28], Hegarty 2004[29]

Figure 8.1.8: Intimate partner violence and mental health problems*



*In the past month
Citation to the included studies:
Martin 2008[30]; Coker 2000[20]

Figure 8.1.9: Intimate partner violence and risk of suicidal ideation (in women who have undergone IPV in the last 1 year



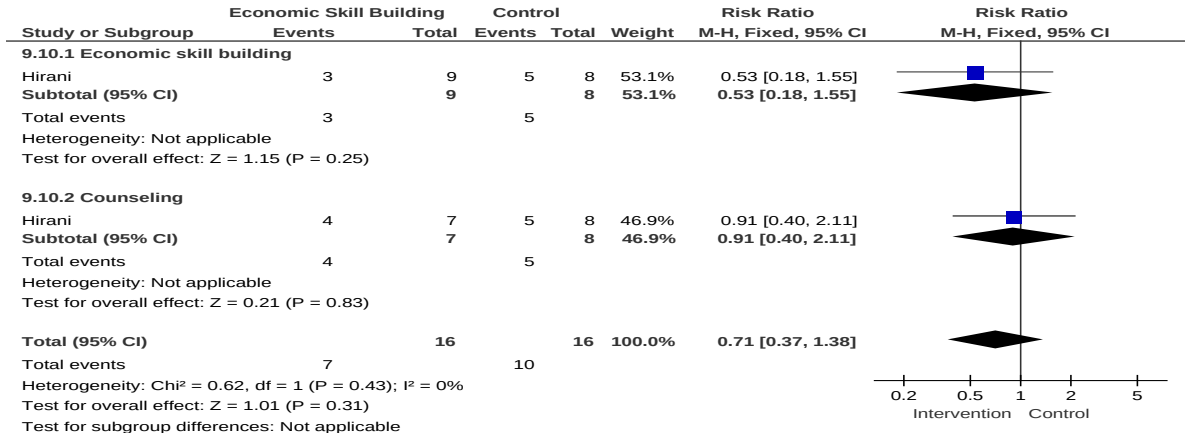
Citations to the included study:
Hurwitz 2006[28]

Interventions targeting intimate partner violence have mainly looked at behavioral therapies. These studies have yielded non-significant effects on the occurrence of new events of violence post-treatment. A meta-analysis of 4 trials comparing CBT versus no intervention showed a reduction favouring the intervention group.[31]

Behavioural couple's therapy, when compared to gender specific treatment, showed greater reductions in post-treatment aggression and recidivism rates, especially multiple couple's group sessions. A dual intervention targeting both IPV and substance abuse showed decreased rates of both in the intervention group (**Figure 8.1.10**).[32]

Interventions focusing on empowerment of women have been employed to reduce these risks, but their role in decreasing the rate of IPV have so far not been significant. A pilot on the effectiveness of an intervention to reduce male partner reproductive coercion was associated with a large reduction in pregnancy coercion among women who had recently experienced IPV (AOR: 0.29; 95% CI: 0.09-0.91).[33]

Figure 8.1.10: Intimate partner in women following an 8-week Economic skill building intervention.



Citations to the included study:Hirani[34]

Conclusion

Intimate partner violence is a serious, widely prevalent issue. Apart from being violations of human rights, acts of violence profoundly damage the physical, sexual, reproductive, emotional, mental and social well-being of not only individuals but families. IPV has untoward effects on women, leading to an increase in unplanned pregnancies, gynecologic infections and probable fetal loss. Abuse also leads to grave impairment of the physical and mental health of the victims. Current interventions for reducing IPV and related morbidities have mainly looked at behavioral therapies. Behavioural couple's therapy has shown greater reductions in post-treatment aggression and recidivism rates, especially multiple couple's group sessions. Although these interventions may not have shown significant effects yet, but there is every reason to believe that thorough outcome evaluations of present programmes alongwith development of new programmes based on sound supposition and identified risk factors will translate into a swift expansion in the near future.

Key messages

- Women being abused were twice as likely to have an unplanned pregnancy (p=0.008).
- Women suffering from IPV have a >50% risk of fetal loss.
- IPV leads to a significant increase in incidence of gynecologic morbidities (45%) in women, especially STDs (22%).
- Women experiencing any abuse in their lifetime are twice as likely to suffer from impaired physical health.
- Women experiencing any abuse in their lifetime are also twice as likely to suffer from impairment of mental functions. (p= 0.07); depression rates are increased 4-folds in women abused in the past year; suicidal ideation is raised 7-folds in women abused in the past year.
- There was no significant association between IPV and condom use, limited evidence was found on other sexual behaviours.
- An intervention to empower women seemed to have decreased the prevalence of violence by 30% in that community.

Table 8.1.1: Impact estimates of Intimate partner violence				
Maternal	**Pregnancy**	**Newborn**	**Infant**	**Others**
Risk aversion data:				
Maternal mortality: Risk of becoming an attempted/ completed femicide victim was three-fold higher (adjusted OR 3.08, 95% adjusted CI 1.86, 5.10) for women abused during pregnancy. [McFarlane 2002]**[255] Women abused during pregnancy had significantly more risk factors of homicide when compared with women abused prior to but not during pregnancy. [McFarlane 1995]**[35] **Depression**: Depression scale (SD) no IPV (n=118) 9.54 (2.95) vs. IPV (n=92) 11.43 (4.50) (p < 0.01) [Rodriguez 2009]**[36] Compared to women who never experienced IPV, women with any recent IPV (physical, sexual, or non-physical) had higher rates of severe (prevalence ratio [PR]=2.6; 95% CI=1.9-3.6) and minor depressive symptoms (PR=2.3; 95% CI=1.9-2.8) [Bonomi 2006]*[17] Most victimized mothers (84.3%) experienced the abuse before their pregnancy, and only a small proportion reported an increase in the violence during their pregnancies or after childbirth. odds of postpartum depression were significantly greater among women who reported partner violence in the past two years as opposed to those who did not (adjusted OR, 1.61; 95% CI, 1.06_2.45). [Beydoun 2010]++[9] Compared to women who never experienced IPV, women with any recent (within past 5 years) IPV (physical, sexual, or non-physical) had higher rates of severe (prevalence ratio [PR] 2.6; 95% CI 1.9 –3.6) and minor depressive symptoms (PR 2.3; 95% CI 1.9 –2.8) [Bonomi 2006]*[17]	**Ante-partum hemorrhage**: increased risk of antepartum hemorrhage (adjusted OR: 3.79, 95% CI 1.38-10.40) [Janssen 2003]**[4] **Abortion/ miscarriage/fetal loss**: Many women seeking abortion services may have abuse histories. Abused women were more likely to make the abortion decision without partner involvement [Glander 1998]**[6] In the group of abused women a higher proportion of women had undergone one or more abortions than in the non-abused group [Hedin 2000]**[7] Exposure to any type of spousal violence increased risk for any fetal loss by about 50%. Physical, emotional, and sexual abuse were each	**Intrauterine growth retardation:** (OR: 3.06, 95% CI 1.02-9.14) [Janssen 2003]**[4] **Perinatal death:** (OR: 8.06, 95% CI 1.42-45.63). [Janssen 2003]**[4] Abuse was significantly associated with an increased risk of perinatal death (aRR = 2.1, 95% CI 1.3, 3.4) [Coker 2002]**[3] **Low birth weight:** abuse during pregnancy was significantly associated with preterm low birth weight (aRR = 2.4; 95% CI 1.5, 4.0) and term low birth weight (aRR = 1.9; 95% CI 1.0, 3.4) [Coker 2002]**[3] Women reporting intimate partner violence in the year prior to pregnancy Vs those not reporting IPV had increased risk for: low-birth weight infant (AOR= 1.17), [Silverman 2006][18]	**Under-5 mortality**: There were no *overall* associations between any forms of violence against women and mortality under-five years of age of their offspring. However, stratified analysis showed an interaction between mother's education, gender of child and violence in relation to mortality. More educated women (>2 years of formal education),	**Risky sexual behaviour:** Women reporting a history of intimate partner violence were more likely to report risky sexual partners (AOR) = 2.00; 95% CI = 1.5–2.8), and [Seth 2010]*[16] Compared with women who had no history of abuse, women who reported abuse within the past 12 months were more than twofold more likely to report the use of alcohol or drugs at last sex (adjusted OR, 2.36; 95% CI, 1.17–4.77) and more than threefold more likely to report partners who had sex with someone else in the past 3 months (adjusted OR, 3.75; 95% CI, 1.94–7.26). [Bauer 2002][14] Compared to women with no IPV ever, women who reported any IPV in their adult lifetime were more likely to participate in risky behaviours (Risky behaviors include intravenous drug use, treated for sexually transmitted diseases, tested positive for HIV, or had anal sex without a condom) - No IPV 12.0% vs. any IPV 30.3% (p < 0.01) [Bonomi 2006]*[17]

Table 8.1.1: Impact estimates of Intimate partner violence				
Maternal	**Pregnancy**	**Newborn**	**Infant**	**Others**
Abused women, as compared with women reporting no history of abuse in their current relationship, were significantly more likely to report poor physical health (AOR = 4.0, 95% CI = 1.3–12.0), depression (AOR = 4.1, 95% CI = 1.8–9.3).* [Hurwitz 2006][28] Many women who are victims of IPV experience major depression and PTSD, often in combination* [Stein 2001][37] Probably depressed women were more likely to have experienced partner abuse, particularly severe combined abuse (8.0, 4.8 to 13.0) and physical and emotional abuse or harassment ((8.1, 4.4 to 15.0).* [Hegarty 2004][29] **Anxiety**: Abused women, as compared with women reporting no history of abuse in their current relationship, were significantly more likely to report anxiety (AOR= 2.8, CI =1.3–6.4)*[Hurwitz 2006][28] **Unintended pregnancy:** Women who had mistimed or unwanted pregnancies reported significantly higher levels of abuse at any time during the 12 months before conception or during pregnancy (12.6% and 15.3%, respectively) [Goodwin 2000][263] Nonphysical (verbal and emotional abuse) accounted for a greater part of the variance in sexual high-risk behaviour (beta = .32, p = .001). [Modie 2009]*[38] Women's adjusted odds of having had an unintended pregnancy were significantly elevated if they had been	independently associated with any fetal death and spontaneous abortions (early fetal demise). Risk for stillbirths (late fetal loss) was also significantly raised after exposure to physical and emotional, but not sexual, spousal abuse. Those exposed to spousal violence (n=1307) were 50% more likely to experience at least one episode of fetal loss compared with women not exposed to abuse (odds ratio 1.5; 95% CI 1.3-1.8). Recurrent fetal mortality was associated with all forms of spousal violence, but emotional violence had the strongest association (1.7; 1.2-2.3).* [Alio 2009][5] **Preterm labour:** No IPV vs IPV in the 12	**Preterm Delivery:** Women reporting intimate partner violence in the year prior to pregnancy Vs those not reporting IPV had increased risk for: Delivery preterm: (OR 1.37, 95% CI 1.16, 1.61) [Silverman 2006][18] **Infant requiring ICU:** Women reporting intimate partner violence in the year prior to pregnancy Vs those not reporting IPV had increased risk for: Infant requiring intensive care unit care (AOR= 1.31-1.33) [Silverman 2006][18]	ever exposed to severe physical violence, had an increased risk of under-five deaths of their female offspring (hazards ratio HR 2.2, 95% CI 1.06–4.50, adjusted for asset score and religion). More educated women who experienced a high level of controlling behavior (>2/7 items) in	Men who reported IPV perpetration during the past year were significantly more likely to report inconsistent or no condom use during vaginal sexual intercourse (OR_{adj}=2.4; 95% CI=1.1, 4.9) and anal sexual intercourse (OR_{adj}=3.3; 95% CI=1.1, 10.1) during the past 3 months, forcing sexual intercourse without a condom during the past year (OR_{adj}=5.2; 95% CI=2.5, 10.9), sexual intercourse with other women during the past 3 months (OR_{adj}=2.2; 95% CI=1.3, 3.7), and having fathered 3 or more children (OR_{adj}=2.5; 95% CI=1.2, 5.5). [Raj 2006][52] Women reporting a history of intimate partner violence were more likely to report risky sexual partners≅in the past 6 months (adjusted odds ratio (AOR) = 2.00; 95% confidence interval (CI) = 1.5–2.8). [Seth 2010][16] **Poor contraception:** Women reporting a history of

Table 8.1.1: Impact estimates of Intimate partner violence				
Maternal	**Pregnancy**	**Newborn**	**Infant**	**Others**
physically or sexually abused (OR, 1.4) [Palitto 2004]##[12] Women who reported ever experiencing physical violence perpetrated by their husband were 2.4 times more likely also to have reported experiencing interference with her attempts to avoid pregnancy, compared with women who did not report experience of physical violence. Women who reported ever experiencing sexual violence perpetrated by their husband were 3.1 times more likely also to have reported experiencing interference with her attempts to avoid pregnancy, compared with women who did not report sexual violence. [Clark 2008]*[13] Compared to women not abused, abused women are 3.4 times as likely to report unwanted pregnancy in the current relationship (95% CI = 1.33–8.66). [Raj 2005]*[24] In the preconception period, those with unintended pregnancies were more likely to be exposed to physical violence. Preconception physical abuse was also a significant risk factor for unintended pregnancy among white respondents [OR 1.48, CI (1.25–1.75)*] but not among black respondents [OR 0.94, CI (0.76–1.16)]. [Naimi 2003][39] Unplanned pregnancies were significantly more common among wives of abusive men, especially sexually abusive men who used force (OR, 2.62; 95% CI, 1.91-3.60). Unplanned pregnancy: Yes (11%)- No abuse 48%, Physical abuse 18%, sexual abuse without physical force 24%, sexual abuse with physical force 10%; No (89%)- No abuse 56%, Physical abuse 17%, sexual abuse without physical force 21%, sexual	months prior to pregnancy: 27.7% vs 42.3%; OR (95% CI) - 1.58 (1.38, 1.81). [Silverman 2006][18] **Other antenatal morbidities:** No IPV vs IPV in the past 12 months before pregnancy High blood pressure or edema 18.5% vs 25.0%; OR (95% CI) - 1.40 (1.19, 1.64) Vaginal bleeding 15.4% vs 22.3%; OR (95% CI) - 1.66 (1.42, 1.95) Placental problems 5.7% vs 7.7%; OR (95% CI) - 1.37 (1.05, 1.78) Severe nausea, vomiting, or dehydration 26.5% vs 40.4%; OR (95% CI) - 1.63 (1.42, 1.86) Diabetes 8.1% vs 10.1%; OR (95% CI) - 1.48 (1.17, 1.86) Kidney infection or UTI 16.9% vs 27.6%; OR (95% CI) - 1.43 (1.23, 1.67)		marriage also had an increased risks of under-five deaths of their daughters (HR 2.5, 95% CI 1.30–4.90, adjusted for asset score and religion). [Monemi 2008][51]	intimate partner violence were more likely to report inconsistent condom use (AOR = 1.60; 95% CI = 1.1–2.3) [Seth 2010]* [16] Women whose sexual partners have physically abused them, whether in the recent (past 12months) or distant past, are significantly less likely to use condoms than women who have not been abused, (relative risk ratio [RRR] = 0.56 for more recent abuse; 0.58 for past abuse). [Dude 2007]*[53] A significantly greater percentage of women who had ever experienced IPV had ever used contraception (91% compared with 85.2%, *P* < 0.0001). There was no significant difference in current use of contraception between women aged 18–49 years who had experienced IPV in the 12 months before the survey and those who had not. [Fanslow 2008]*[54] IPV perpetrators over twice as

Table 8.1.1: Impact estimates of Intimate partner violence				
Maternal	**Pregnancy**	**Newborn**	**Infant**	**Others**
abuse with physical force 6%, Chi-square (P) 13.41 (<0.01); N=6632 [Martin 1999][40] **Chronic disease**: In the case of women who have experienced the three types of abuse (physical, psychological and sexual), the association between abuse and physical health is statistically significant. These women are twice as likely to suffer a chronic disease as those who have not experienced abuse (OR-2.03; 95% CI-1.18–3.51), and just over twice as likely to suffer 'other diseases' [allergies, dermatitis and other skin problems, headache and migraine, thyroid related conditions and rheumatic and muscular problems.] (OR-2.57; 95% CI-1.38–4.77) and to spend more days in bed (t-2.35; P<0.019) [Ruiz-perez 2007]*[27] Women reporting intimate partner violence in the year prior to pregnancy Vs those not reporting IPV had increased risk for: High blood pressure or edema (AOR=1.37-1.40), Vaginal bleeding (AOR= 1.54-1.66), Severe nausea, vomiting or dehydration (AOR= 1.48-1.63), Kidney infection or urinary tract infection (AOR= 1.43-1.55), Hospital visits related to such morbidity (AOR= 1.45-1.48). [Silverman 2006][18] Significant associations between lifetime experiences of partner violence and self-reported poor health (odds ratio 1·6 [95% CI 1·5–1·8]). women with lifetime experiences of physical or sexual violence, or both, by a partner were significantly more likely to report within the past 4 weeks they had experienced difficulties with walking (1·6 [1·5–1·8])	Premature rupture of membranes 5.7% vs 9.5%; OR (95% CI) - 1.62 (1.33, 1.97) Related hospitalization or ER visit prior to delivery 48.9% vs 61.8%; OR (95% CI) - 1.45 (1.24, 1.70). [Silverman 2006][18]			likely to engage in anal sex (58.8% vs 39.2%; adjusted odds ratio (AOR) 2.12, 95% CI 1.70 to 2.64). IPV perpetrators demonstrated over three times the odds of engaging in sexual infidelity (AOR 3.91, 95% CI 3.10 to 4.91). Coercive condom were more prevalent among IPV perpetrators relative to non-abusers (30.8% vs 10.4%; AOR 3.71, 95% CI 2.82 to 4.88; 22.5% vs 5.6%, AOR 4.88, 95% CI 3.47 to 6.85, respectively). [Decker 2009][47] Lifetime history of injection drug use and association with men's IPV perpetration AOR 2.58 (1.75 to 3.81). Lifetime history of transactional sex with female partners and association with men's IPV perpetration AOR 6.22 (4.50 to 8.61). Prevalence of STI/HIV diagnosis and associations with men's intimate partner violence perpetration AOR 2.55 (1.77 to 3.67). [Decker 2009][47] Used contraception: spousal violence 46.6% (n=364) vs no spousal violence 61.0% (n=132),

Table 8.1.1: Impact estimates of Intimate partner violence				
Maternal	**Pregnancy**	**Newborn**	**Infant**	**Others**
or daily activities (1·6 [1·5–1·8]), pain (1·6 [1·5–1·7]), memory loss (1·8 [1·6–2·0]), dizziness (1·7 [1·6–1·8]). [Ellsberg 2008][41] % Rate own health as fair/poor: none-11.9, physical abuse - 14.0, Sexual abuse, intimate- 28.0, p<0 .01. Women who reported having experienced intimate sexual violence were 2.8 times more likely than women who had not experienced violence to rate their health as fair or poor. aOR 2.80, 95% CI(1.70, 4.61), p=0.01. % Report a chronic condition: none- 24.3, physical abuse - 28.9, sexual abuse, intimate- 39.7, p<0 .01. Women who experienced intimate sexual violence were 3.5 times more likely to report disabilities than women who had not experienced violence (with older age and lower income significant). aOR 3.51, 95% CI (2.19, 5.62), p=0.01. % Report a disability: none- 9.5, physical abuse - 12.1, sexual abuse, intimate- 29.1, p<0 .01. Women who experienced intimate sexual violence were over two times more likely to have a chronic condition that required treatment than women who did not experience violence. aOR 2.11, 95% CI (1.41, 3.15), p=0.01. [Plichta 2001][42] **Common mental disorders:** Abuse in the last 12 months and percentage of risk for CMD (CI) – Emotional: Yes 47.1% (42.9-51.3); No 23.4 (21.8-25.2) p < 0.001 Physical: Yes 55.5 (49.0-61.9) No 25.8 (24.1-27.5)) p < 0.001 Sexual: Yes 64.0 (54.9-72.2) No 26.6 (24.9-28.3)) p < 0.001 [Ishida 2010]*[43]				OR= 0.56, 95% CI (0.37, 0.85), p <0.01. [Salam 2006][8] Used condom: spousal violence 0.3% (n=364) vs no spousal violence 2.4% (n=132), OR= 0.10, 95% CI (0.01, 1.05), p<0.05. [Salam 2006][8] Women reporting a history of intimate partner violence were more likely to report inconsistent condom use in the past 30 days (AOR = 1.60; 95% CI = 1.1–2.3). [Seth 2010][16] **Association with substance abuse:** Compared to women with no IPV ever, women who reported any IPV in their adult lifetime were more likely to be current or former smokers and to have used recreational drugs in past year – No IPV 4.2% vs. any IPV 7.9% (p < 0.01) [Bonomi 2006]*[17] **Substance abuse (men):** Alcohol: Alcohol problem (past year) : no

Table 8.1.1: Impact estimates of Intimate partner violence				
Maternal	**Pregnancy**	**Newborn**	**Infant**	**Others**
Sexually assaulted women reported significantly (P = .02) more PTSD symptoms compared with nonsexually assaulted women.* [McFarlane 2005][44] Compared with women who had not experienced violence during adulthood, women who experienced both physical and sexual violence had more than twice the odds of experiencing such days during the past month (OR, 2.65; 95% CI, 2.06 –3.40), as did women who experienced sexual violence only (OR, 2.15; 95%CI, 1.47–3.13); women who experienced physical violence only also were significantly more likely to have experienced such days.* [Martin 2008][30] Women experiencing psychological IPV were significantly more likely to report poor physical and mental health (adjusted RR, 1.69 for physical health and 1.74 for mental health). Psychological IPV was associated with a number of adverse health outcomes, including a disability preventing work (adjusted RR, 1.49), arthritis (adjusted RR, 1.67), chronic pain (adjusted RR, 1.91), migraine (adjusted RR, 1.54) and other frequent headaches (adjusted RR, 1.41), stammering (adjusted RR, 2.31), sexually transmitted infections (adjusted RR, 1.82), chronic pelvic pain (adjusted RR, 1.62).* [Coker 2000][20] % Diagnosis, depression, or anxiety: none-9.5, physical abuse- 17.4, sexual abuse, intimate- 38.9, p<0 .01. Women who experienced intimate sexual violence are 4–5 times more likely to suffer from depression anxiety than women who did not experience violence, with odds ratios of 3.94 (2.70, 5.76) p=0.01, 4.42 (2.27, 8.60) p=0.01, and 5.32 (3.41,				IPV - 172/869 19.8% ref=1.00; Physical IPV only- 112/292 38.4% OR 2.52 (1.85, 3.44); Sexual IPV only- 16/46 34.8% OR 2.16 (1.01, 4.64); Both Physical and Sexual IPV- 34/68 50.0% OR 4.05 (2.49, 6.59) p< 0.0001. [Dunkle 2006][55] <u>Illegal drug use:</u> Illegal drug use (lifetime): No IPV- 309/869 35.6% ref=1.00; Physical IPV only- 129/292 44.2% OR 1.43 (1.08, 1.91); Sexual IPV only- 19/46 41.3% OR 1.28 (0.71, 2.29); Both Physical and Sexual IPV- 37/68 54.4% OR 2.16 (1.22, 3.83) p< 0.0001. [Dunkle 2006][55] male partners of the injured women were much more likely than the male partners of control subjects to use cocaine (odds ratio, 4.4; 95 percent confidence interval, 2.3 to 8.4) and to have been arrested in the past (odds ratio, 3.1; 95 percent confidence interval, 1.8 to 5.2). [Grisso 1999][56]

Table 8.1.1: Impact estimates of Intimate partner violence				
Maternal	**Pregnancy**	**Newborn**	**Infant**	**Others**
8.31) p=0.01, respectively, for symptoms, medication and diagnosis of depression/anxiety. % High score, depressive symptoms: none-30.6, physical abuse - 45.9, sexual abuse, intimate- 65.3, p<0 .01. Physician diagnosis of depression/anxiety during the past five years appears to most consistently distinguish women who experienced any violence from women who did not experience violence. odds ratios are 1.8 for physical violence, 2.6 for non-intimate sexual violence, and 5.3 for intimate sexual violence. % Medication, depression or anxiety: none-3.6, physical- 4.6, sexual abuse, intimate- 15.6, p<0 .01. [Plichta 2001][42] Women reporting abuse were 6 times more likely to experience emotional distress. An estimated 70% of all cases of emotional distress found among ever-married women were attributable to wife abuse. [Ellsberg 1999][45] **Suicidal ideation**: Abuse in the last 12 months and percentage of risk for suicidal ideation (CI) – Emotional: Yes 8.5 (6.4-11.1) No 1.9 (1.4-2.6) p < 0.001 Physical: Yes 16.6 (12.1-22.3) No 2.2 (1.7-2.8) p < 0.001 Sexual: Yes 16.5 (10.7-24.7) No 2.7 (2.1-3.4)) p < 0.001 [Ishida 2010]*[43] Abused women, as compared with women reporting no history of abuse in their current relationship, were significantly more likely to report suicidal ideation (AOR = 6.9, 95% CI = 1.9–25.1). [Hurwitz 2006][28] women who reported partner violence at least once in their				**Interventions**: Majority of participants supported informational interventions and individual counselling. Interventions not well regarded included "Receiving a follow-up telephone call from the doctor's office/clinic" and "Go stay at shelter". [Chang 2005]*[57] Among strategies used by rural women to stop, avoid, or escape from intimate partner violence, the category of strategies rated most helpful was safety planning [mean (SD) 3.8 (0.1)], while placating and resistance strategies were rated as least helpful. [Ridell 2009][58] The risk of sexual re-assault was decreased by 59% and 70% for women who contacted the police, or applied for a protection order, after the first sexual assault. Receiving medical care decreased the woman's risk of further sexual assault by 32%.* [McFarlane 2005][44] Women who received economic skill-building reported less

Table 8.1.1: Impact estimates of Intimate partner violence				
Maternal	**Pregnancy**	**Newborn**	**Infant**	**Others**
life reported significantly more emotional distress, suicidal thoughts (2·9 [2·7–3·2]), and suicidal attempts (3·8 [3·3–4·5]), than non-abused women. [Ellsberg 2008][41] **<u>Gynecologic morbidity:</u>** Adjusted OR (and 95% CI) from logistic regression analysis examining associations between self-reported gynecologic morbidity; Physical violence only 1.05 (0.71–1.49) Sexual violence only 1.42 (1.04–1.75) Physical and sexual violence 1.72 (1.05–2.58) [Stephenson 2006][15] IPV demonstrated an independent effect on vaginal irritation with discharge (adjusted OR 1.34) and vaginal discharge with odor (adjusted OR 2.08) [Decker 2008]*[46] Women reporting a history of intimate partner violence were more likely to test positive for an STI (AOR = 1.46; 95% CI = 0.99–2.1). [Seth 2010]*[16] Sexual violence was a significant risk factor for having ever been pregnant for women (OR = 3.2, 95% CI = 1.0–10.0) [Gomez 2009]#[25] Abused women suffered from gynecological problems at the time of pregnancy significantly more than non-abused women (p<0.05) and abused women suffered from reproductive tract infections significantly more than non-abused women (p<0.01). [Salam 2006]*[8] History of STD was significantly associated with history of				partner violence although the difference was not statistically significant. [Hirani][34] A meta-analysis of four trials comparing CBT with a no-intervention control (1771 participants) reported that the relative risk of violence was 0.86 (favouring the intervention group) with a 95% confidence interval (CI) of 0.54 to 1.38.. For the two studies where CBT was compared to another form of treatment the results were inconclusive. [Smedslund 2011 - MA][31] **<u>Others:</u>** About 47%of abused women used contraception compared to about 61%of non-abused women (p<0.01). Only 0.3% of abused women reported that their husbands used condoms compared to about 2.4% of nonabused women's husbands (p<0.05) [Salam 2006]*[8] Overall results showed 64 percent of female victims reported that their partner had

Table 8.1.1: Impact estimates of Intimate partner violence				
Maternal	**Pregnancy**	**Newborn**	**Infant**	**Others**
IPV. Compared with that for women with no history of abuse, the adjusted OR for combined recent and past abuse was 2.15 (95% CI, 1.23–3.77). [Bauer 2002][14] Compared with non-abusive husbands, abusive husbands demonstrated increased odds of HIV acquisition outside the marital relationship in adjusted models (adjusted odds ratio [AOR] = 1.91; 95% CI 1.11 to 3.27). Husbands' HIV infection was associated with increased HIV risk among wives; this risk was elevated 7-fold in abusive relationships in adjusted models (AOR = 7.22; 95% CI 1.05 to 49.88). [Decker 2009][47] Compared to women not abused, abused women are 2.6 times as likely to report discolored vaginal discharge in the past year (95% CI = 1.27–6.50), 3.1 times as likely to report burning during urination in the past year (95% CI = 1.52–6.31). [Raj 2005]*[24] Compared with women whose husbands reported no violence, those who had experienced both physical and sexual violence and those who had experienced sexual violence only had elevated odds of reporting gynecologic symptoms (OR, 1.7 and 1.4, respectively). [Stephenson 2006][15] Odds of having a gynaecological problem were three times greater than average for victims of spouse abuse. [McCauley 1995][48] Women with lifetime experiences of physical or sexual violence, or both, by a partner were significantly more likely to report vaginal discharge (1·8 [1·7–2·0]). [Ellsberg 2008][41]				engaged in mild violence, and 64 percent also reported that their partner engaged in severe violence. [Wupperman 2002]*[59] prevalence of abuse across the 16 states to be 7.2% (95% CI, 6.9-7.6) during the 12 months before pregnancy, 5.3% (95% CI, 5.0-5.6) during pregnancy, and 8.7% (95% CI, 8.3-9.1) around the time of pregnancy (abuse before or during pregnancy) [Saltzman 2003][60] During the 12 months before becoming pregnant, the victimized women experienced a greater number of physically violent (mean of 1.76 acts vs. 0.51 acts), psychologically violent (mean of 3.44 acts vs. 1.78 acts), and sexually violent (mean of 1.21 vs. 0.30) acts per month relative to the comparison women. [Macy 2007]^^[23]

Table 8.1.1: Impact estimates of Intimate partner violence				
Maternal	**Pregnancy**	**Newborn**	**Infant**	**Others**
45 of 253 women who reported more than one episode of intimate partner violence at baseline acquired HIV (9·6 per 100 person-years) compared with 83 of 846 who reported one or no episodes (5·2 per 100 person-years); adjusted multivariable Poisson model IRR 1·51, 1·04–2·21, p=0·032. The population attributable fractions show that 11·9% of new HIV infections could be prevented if women did not experience more than one episode of physical or sexual partner violence [Jewkes 2010][49] No physical or sexual abuse: HIV 68/128 (53·1%), No HIV 614/971 (63·2%); ≥5 incidents of abuse: HIV 29/128 (22·7%), No HIV 120/971 (12·4%). [Jewkes 2010][49] Any gynecological disorder during last pregnancy: any spousal violence 35.4% (n=364) vs no spousal violence 24% (n=132), OR=1.74 95% CI(1.04, 2.90), p <0.05. [Salam 2006][8] Suffering from Reproductive Tract Infection: spousal violence 52.2% (n=364) vs no spousal violence 36.9% (n=132), OR= 1.89 95% CI(1.24, 2.88), p <0.01. [Salam 2006][8] Women reporting a history of intimate partner violence were more likely to test positive for an STI (AOR = 1.46; 95% CI = 0.99–2.1). [Seth 2010][16] **<u>Women with disabilities:</u>** Among women who reported physical and/or sexual violence by an intimate partner in the previous 5 years, women with Activity Limitation (AL) were more likely to report emotional/financial abuse (88.0 vs. 79.9%, p<0.03), severe physical violence (59.9 vs. 46.8%, p<0.005) and sexual violence (29.3 vs. 17.5%, p<0.001) compared to women with				

Table 8.1.1: Impact estimates of Intimate partner violence				
Maternal	**Pregnancy**	**Newborn**	**Infant**	**Others**
no AL [Forte 2005]*[50]				

*Adult women in a union.
**Pregnant women
#randomly selected youth aged 15–24 years
Ever-married women who had given birth in the last five years or were currently pregnant
++Did not specify disaggregate pre-pregnancy and intra-pregnancy violence while calculating OR
^^Study sample was pregnant women but mean rates of violence 1 year before pregnancy were also assessed.
≅Risky sexual partner (i.e. partner recently releasedfrom jail, had an STI, used injection drugs or had a concurrentsexual partner)

Table 10.1.2- Interventions addressing intimate partner violence	
Intervention	**Results**
Batterer's treatment: [Babcock 2004][61]	<u>Recidivism rates:</u> The weighted percentage of non-treated offenders who recidivated was 21% based on police reports and 35% based on partner reports.
Gender Specific Treatment (GST) and Couples treatment (PACT). [Daniel 1999][62]	Husbands reduced their psychological aggression by 47%, their moderate physical aggression by 55%, and their severe physical aggression by 51%. Although two-thirds of the husbands maintained cessation of severe aggression during the year following treatment, only one-fourth of the husbands were violence-free. Physical aggression (past 14 weeks)Pretreatment vs post-treatment:- **GST**- Mild: mean 6.01, SD 7.58 vs mean 3.36, SD 4.99. Severe: mean 1.12, SD 1.61 vs mean 0.64, SD 1.08. **PACT**- Mild: mean 8.01, SD 8.26 vs mean 2.91, SD 4.53. Severe: mean 2.45, SD 3.52 vs mean 0.95, SD 2.26 Physical aggression (past year)Pretreatment vs post-treatment:- GST- Mild: mean 16.71, SD 12.34 vs mean 9.64, SD 12.83. Severe: mean 2.50, SD 2.95 vs mean 2.00, SD 3.98

	PACT- Mild: mean 19.48, SD 15.99 vs mean 7.95, SD 11.96. Severe: mean 3.65, SD 3.98 vs mean 1.52, SD 3.78. both mild aggression F(1, 34) = 13.34, p < .001 and severe aggression F(1, 34) = 10.61, p < .005 decreased significantly from pretreatment to post-treatment.
Premarital Relationship Enhancement Program (PREP) [Markman 1993][63]	Intervention couples reported significantly fewer instances of physical violence than did control couples, F(l, 79) = 3.76, p <.05. There were no significant differences between the intervention and decline couples on self-reported physical violence $(p$ <.65). Across Follow-Ups 2 through 4, the mean frequency of physical violence per year for intervention couples was calculated as 0.39 $(SD$ = 0.80) while that for control couples was 1.53 $(SD$ = 4.0). The decline couples showed a mean frequency of physical violence of 0.68 $(SD$ = 1.38).
Couple's therapy: Behavioral Couples therapy- 26 weekly sessions. [Simpson 2008][64] Multiple couple vs individual couple therapy [Stith 2004][65]	Of the 41 couples that completed the CTS-2 at the 2-year follow-up, 18 (43.9%) reported aggression prior to treatment and 13 (31.7%) reported aggression at the 2-year follow-up, indicating that physical aggression had not been completely eliminated. Psychological aggression decreased in overall frequency between the year prior to therapy and the year prior to the 2-year follow-up: For husband aggression, pretreatment M = 21.80, SD = 15.72; follow-up M = 12.99, SD = 12.49, $t(40)$ = 4.10, p <0.001; for wife aggression, pretreatment M =21.72, SD =15.51; follow-up M = 13.63, S = 13.59, $t(40)$ = 3.49, p <0.001. **<u>Recidivism rate:</u>** <u>6 months post-treatment</u> Individual couple- 43% of 14 vs Multi-couple- 25% of 16 vs comparison group- 67% of 9. <u>2 years post-treatment</u> Individual couple- 0% of 11 vs Multi-couple- 13% of 8 vs comparison group- 50% of 4 **<u>Acceptance rate (Inventory of Belief about Wife Beating- IBWB):</u>** Mean score (SD) Pretest vs follow-up Individual couple- n=10, 67.50(12.72) vs 66.60(16.10), F-value=0.05 Multi-couple- n=13, 61.31(12.83) vs 48.73(9.21), F-value=19.97 Comparison group- n=5, 68.70 (10.49) vs 73.60(22.87), F-value=0.28 **<u>Receipt of marital aggression(CTS2):</u>** Mean score (SD) Pretest vs follow-up

	Individual couple- n=9, 8.46 (4.83), F-value=0.99 Multi-couple- n=12, 12.47(5.36) vs 5.85(3.86), F-value=27.05 Comparison group- n=5, 8.97 (3.81) vs 10.10(9.09), F-value=0.72
CBT Four different interventions: (1) batterer program + monthly monitoring n=102, (2) batterer program + graduated monitoring n=100, (3) only monthly monitoring n=109, (4) Only graduated monitoring n=109. In total 202 were in a batterer program compared to 218 in control group being monitored. The batterer program lasted for 26 weeks with classes meeting weekly for 75 minutes. [Labriola 2005 - RCT][66]	Proportion of new violence: Treatment – 20/202 vs control – 11/218. RR = 1.96 [0.96, 3.99]
The intervention included defining domestic violence, understanding historical and cultural aspects of domestic abuse and reviewing criminal/legal issues. Batterers were encouraged to take responsibility for their anger, actions, and reactions. [Davis 2000 - RCT][67]	
Duluth Model, which is a feminist, cognitive psycho-educational curriculum provided in 26-week group sessions. Men in the control group were sentenced to 1 year's probation. [Feder 2000 - RCT][68]	Proportion of new violence: Treatment – 13/129 vs control 100/386. RR = 0.39 [0.23, 0.67]
Three different 12-month interventions for servicemen who had been substantiated as having physically assaulted their wives were used and the outcomes examined. The 861 couples of the study were randomly assigned to 4 groups: a men's group, a conjoint group, a rigorously monitored group, and a control group. Cognitive–behavioral interventions were implemented for the men's and conjoint groups [Dunford 2000][69]	Proportion of new violence: Treatment – 52/216 vs control 45/188. RR = 1.01 [0.71, 1.42]
CBT vs other treatment: Community-based domestic violence program, 218 men with a history of partner abuse were randomly assigned to either feminist-cognitive-behavioral [FCBT] or process-psychodynamic group treatments [PPT]. Each FCBT session included a didactic session on communication and cognitive skills, relaxation/ desensitivization training,	Proportion of new violence: Treatment – 63/218 vs control 75/214. RR = 0.82 [0.63, 1.09]

consciousness raising about sex roles and violence against women, and behavioral or cognitive rehearsal. PPT did not use agendas but focused on building trust and a sense of safety, uncovering childhood traumas and reconnecting with traumatic childhood events [Saunders 1996][70] Dual intervention: A 12 week Substance Abuse & Domestic Violence (SADV) group (grounded in CBT) (N = 32) or a 12 week Twelve Step Facilitation (TSF) group (N=32) studying the differences in treatment effect among substance dependent Caucasian and African-American male intimate partner violence (IPV) offenders court mandated to an integrated substance abuse and domestic violence treatment. [Scott 2010][32]	Rates of violence did not differ significantly between the two types of treatment; Proportion of new violence: CBT 28/91 vs other therapy 25/87, RR= 1.07 [0.68, 1.68]. Nor did reports from the women of their fear level, general changes perceived in the men, and conflict resolution methods At treatment completion, both groups showed a reduction in physical abuse and alcohol abuse. Frequency of violence: SADV n=29 mean (SD)0.95 (0.72) vs TSF n=29, mean(SD) 0.73 (0.75). any violence: SADV 3/29 vs TSF 2/29, RR=1.50 [0.27, 8.32]
Coping-Skills training and 12 step facilitation: compared the immediate and long-term efficacy of an empirically based coping skills training (CST) program and a theoretically distinct professionally administered 12-step, Al-Anon facilitation condition for women whose partners have alcoholism. Participants in the CST condition learned to conceptualize their distress from within a family stress and coping perspective. Participants in the TSF condition learned to view their problem as one of codependence; the 12 steps of Al-Anon then served as a blueprint to facilitate codependence recovery. [Rychtarik 2005][71]	CST participants reported a significantly lower incidence of partner physical violence per 6-month follow-up period. Similarly, among those with full follow-up data, analysis of pretreatment-to-follow-up change in the prevalence of violence found a Treatment x Time interaction, $F(1, 34) = 9.14$, $p < .01$. CST declined significantly from 50% to 37%, $t(124) = -2.74$, $p < .05$, $PV = .14$; but TSF showed a non-significant increase from 44% to 51%, $t(124) = 1.50$, *ns*, $PV < .05$. Notably, among those experiencing violence at pretreatment, 63% experienced violence during follow-up in CST, whereas 85% of those in TSF did. [Rychtarik 2005][71]
The interventions of economic skill-building and counseling were delivered through the trained community health workers for 8 weeks, one session per week. The economic skill-building intervention included skills for employment attainment and retention such as, effective communication, balancing personal and work life and time management, conflict resolution, dealing with abuse and harassment, enhancing self efficacy, effective parenting, and personal hygiene and grooming.[Hirani][34]	Women who received economic skill-building reported less partner violence although the difference was not statistically significant. [Hirani][34]

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Section XI

9. Infections

9.1. Sexually Transmitted Infections

Background

The incidence of STIs (sexually transmitted infection) remains very high in developing countries[1] being highest in urban men and women in their second to fourth decade of life when sexual activity is highest. adolescents continue to be at high risk for acquiring an STI owing to a greater likelihood than adults of entertaining multiple sexual partners, engaging in unprotected intercourse, selecting high-risk partners and older partners.[2]

Other risky behaviour that increases the incidence of STI includes substance abuse. Binge drinkers were more likely to have an STI (aOR 1.56; 95% CI: 1.00-2.41; P=0.048).[3] Crosby *et al.)*[3] have shown that marijuana use is a strong predictor of *Trichomonas vaginalis* infection in young African-American women.

STIs during pregnancy are associated with adverse pregnancy outcomes ranging from early abortion and premature births to congenital infections and death.[4, 5] Many studies have shown between a two- and fivefold increased risk for HIV infection among persons who have other STIs,[6] possibly increasing the occurrence of poor pregnancy outcomes even more.

Many modes of interventions have been tried in different populations. It is considered that interventions which target core groups are likely to have most impact[7] as managing or preventing STIs in core groups averts at least ten times as many secondary infections as would be averted by treating the same number of cases in the general opulation.[1] Kirby et al.[8] suggested that programs that incorporate both youth development and reproductive health components are effective over long periods.

It is well known that the best time to identify and address risk factors for poor reproductive health outcomes for mothers and babies is not after but before conception through preconception care.[9] It was shown that although STI counselors perceived preconception care to be an important issue, there was significant variation in the perception of whether preconception care should be delivered at STI clinics.[10]

Scope of intervention

We aimed to review literature pertaining to the effects of gynecologic infections in women in the preconception period on MNCH outcomes and interventions intended to reduce these infections and hence any associated morbitidy/mortality. Due to a shortage of preconception data being available we also used studies done among the general population.

One essential point to keep in mind is the great overlap between interventions targeting STIs, HIV, teenage pregnancies and unwanted pregnancies. As far as was possible the data found was disaggregated to focus only on the effect on and of STIs.

Impact estimates

Our analysis showed that post-intervention STI prevalence was significantly decreased by 22% (**Figure 9.1.1**). Behavioural treatments in conjunction with STI management reduced the incidence of gonorrhea by 57%. Healthcare interventions increasing access and availability of STI management led to a significant decrease in syphilis. Mass treatment with antibiotics significantly dropped the rates of syphilis, trichomoniasis and bacterial vaginosis.

For behavioural interventions, re-infection or new STD rates significantly declined (OR 0.65 95% CI 0.53-0.80) at 1 year after the intervention (**Figure 9.1.2**). The Magnolia Case Management project also showed significant reductions in the incidence and prevalence of STDs by educating women about well-woman care and making healthcare more accessible.[11] Schillinger et al (2003)[12] found a non-significant 20% decrease in the risk of re-infection, with Chlamydia, among women in the patient delivered partner treatment arm than among those in the self-referral arm. On the other hand, Branson et al (1998)[13] did not report any difference in the rate of new STDs among those receiving information, motivation and skills versus those receiving standard counseling. Similarly Boyer et al (1997)[14] found no difference in new STDs 6 months post skills sessions versus standard risk-reduction counseling.

Most studies reviewed for interventions for STD control reported outcomes related to safer sexual behaviors. Our analysis showed interventions promoted overall safer practices in the subjects especially in terms of a two-fold increase in condom use (**Figure 9.1.3**). This finding is in line with the systematic review[15] on effectiveness of condoms in reducing STDs like Chlamydia and gonorrhea. Other studies also showed improved condom use after motivational, skill-based interventions.[13, 14] In Thailand STI rates have been successfully reduced through enforced condom use.[16]

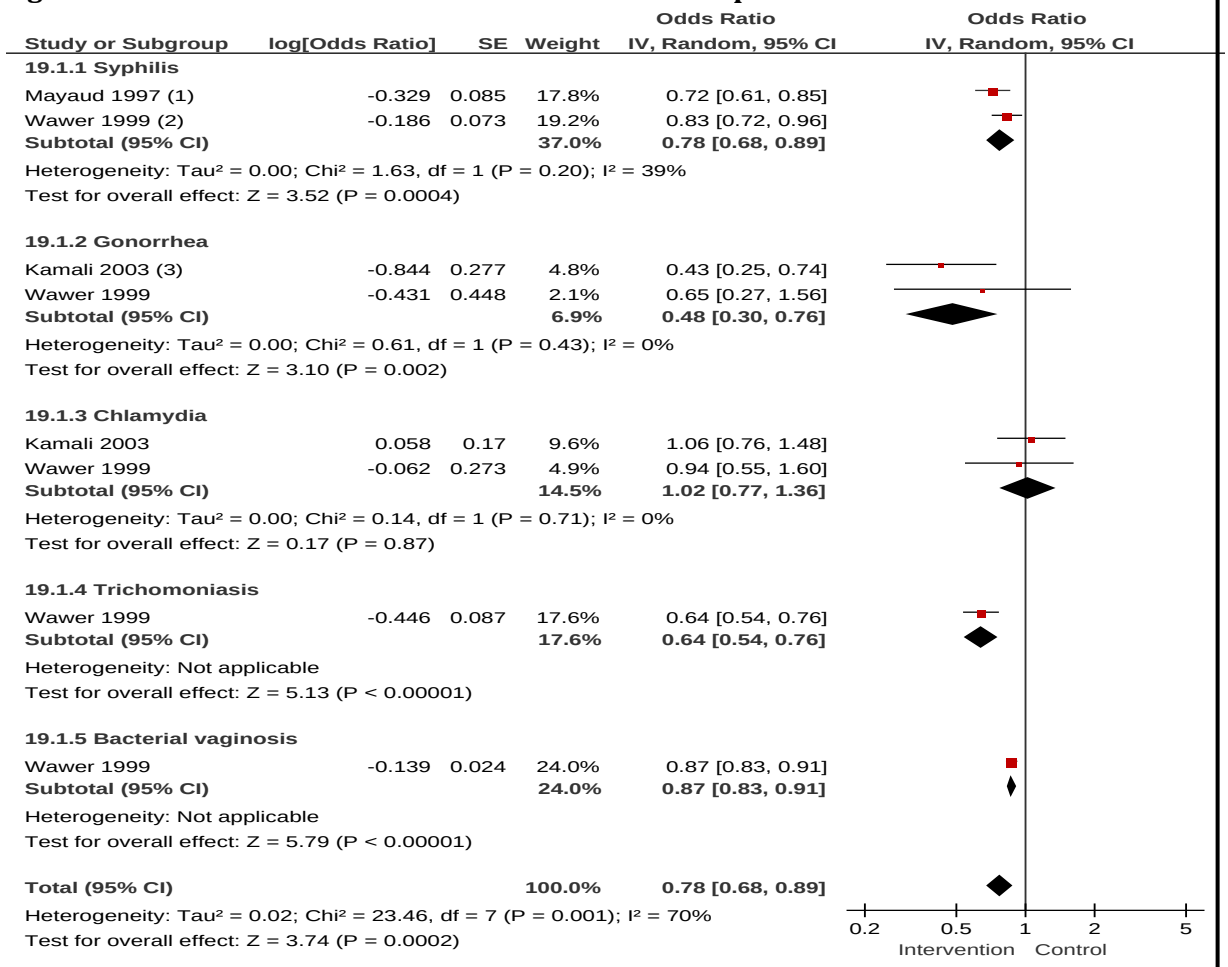
Results of a review[17] on the effectiveness of behavioural interventions for prevention of STIs in adolescents and young adults showed that these programs bring about increase in knowledge and self-efficacy and changes in behavioural outcomes to a lesser degree. MNCH outcomes were not studied. Henceforth it concluded that such school-based skills and information interventions play a significant role in improving overall knowledge about the subject, foster favorable attitudes and 'behavioural intentions'.

Conclusion

Sexually transmitted infections are a serious global reproductive health problem, the burden of which falls disproportionately on the young, the poor and women.

While many interventions have been tested they mostly look at endpoints other than MNCH outcomes like safer sexual behavior. These would eventually have an indirect effect on possibly reducing adverse pregnancy outcomes, however the need of the hour

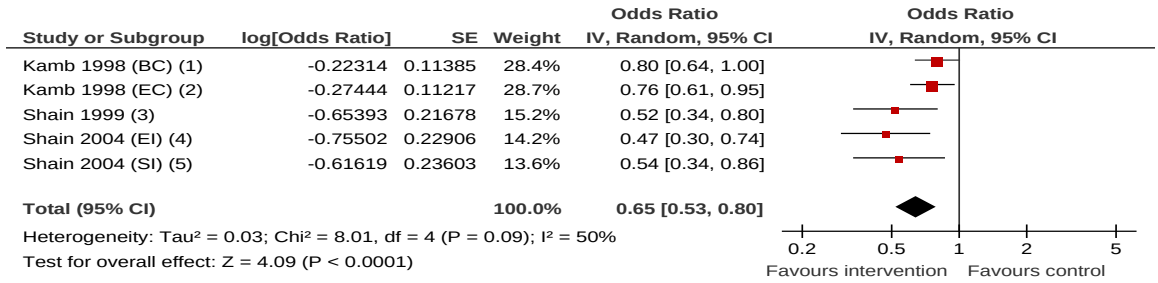
Figure 9.1.1: Prevalence of STDs in mass treatment vs. placebo



(1) Reference clinic, health provider training, effective drug supply, regular supervision & health education
(2) Mass treatment of all participants with azithromycin, ciprofloxacin, and metronidazole.
(3) Behavioral interventions & support vs behavioral interventiosn + syndromic STI management vs control group

Citations to the included studies:
Mayaud 1997[18], Wawer 1999[19], Kamali 2003[20]

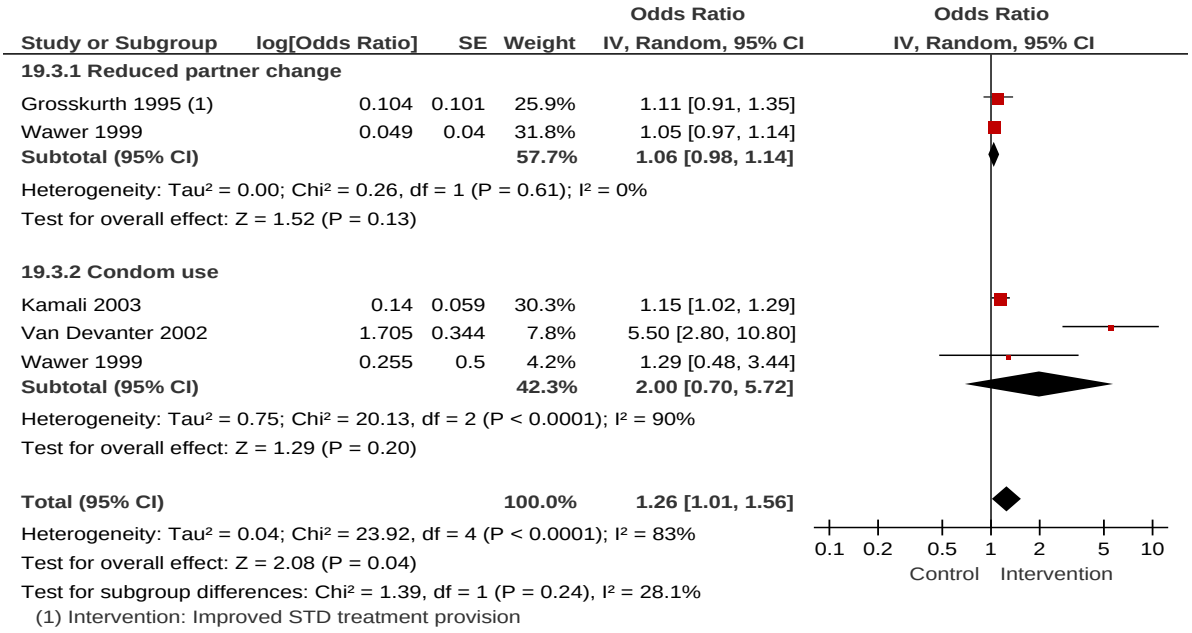
Figure 9.1.2: Post intervention re-infection or new STD



(1) Post Brief counseling at 12 months
(2) Post Enhanced counseling at 12 months
(3) Post Behavioural cognitive intervention at 12 months
(4) Enhanced intervention vs. control
(5) Standard intervention vs. control

Citations to the included studies:
Kamb 1998[21], Shain 1999[22], Shain 2004[23]

Figure 9.1.3: Safer sexual behavior in Intervention vs. Control groups



Citations to the included studies:
Grosskurth 1995[24], Wawer 1999[19], Kamali 2003[20], Van Devanter 2002[25]

are epidemiologic studies that better address the issue at hand - reducing STIs in women in the preconception period to have immediate and large impacts. Current interventions need to be put to test in this study group.

Key messages

- Reducing the burden of STIs in women of reproductive age could reduce transmission of infections to the newborns, as well as improve the health of women during pregnancy and in the first year after birth.
- Mass treatment of STIs with antibiotics leads to a 22% reduction in its prevalence. (p=0.003), similarly,
- Behavioral/counseling interventions led to a 35% decrease in STI incidence.
- Interventions targeting STIs led to a significant 26% increase in safer sexual behaviors, especially condom use.
- Current interventions need to be put to test in women in the preconception period.

9.2. HIV/AIDS prevention strategies

Background

Initially, HIV/AIDS largely infected high-risk populations, such as commercial sex workers and injecting drug users. Currently however, the demographic with the highest incidence rate is women of reproductive age[26]. Women are at particular risk of being infected in stable heterosexual relationships, since they often lack the skills to negotiate safe sexual behaviors. Approximately 15.9 million women who are HIV positive today could potentially transmit the virus to their future children. Babies born with HIV are

Table 9.1.1. Summary of impact estimates for STIs		
Intervention	**Morbidity related outcomes**	**Attitudes and behavior change**
Intervention-management of STI	**Post-intervention STI:** At month 15, the estimated probability of a Well Woman Program participant having an STI was 20% less than a Minimal Intervention participant. [Marion 2009][27] **Repeat STI**: Risk of reinfection was 20% lower among women in the patient delivered partner treatment arm (87/728; 12%) than among those in the self-referral arm (106/726; 15%); however, this difference was not statistically significant (OR, 0.80; 95% CI, 0.62–1.05; *P*<0.102). [Schillinger 2003][12]	
Intervention – behavioral/counseling	**Post-intervention STDs:** 6 months post counseling and condom distribution- BV aHR 2.4, CI 1.1–5.6; Chlamydia aHR 1.3, CI 0.3–6.0; Syphilis aHR 34.1, CI 4.0–288.1; Trichomoniasis aHR 1.1, CI 0.2–4.9. [Gallo 2008][28] Reported significant 12-month STI reduction (12%) with intensive group skills counselling. [Jemmott 2007][29]	

Table 9.1.2. SEXUALLY TRANSMITTED INFECTIONS		
N-9 [Louv 1988][30] N-9 [Barbone 1990][31] N-9 [Rendon 1980][32] [Quoted in Wilkinson 2002][33]	with N. gonorrhoeae (relative rate, 0.75; 90% confidence limits, 0.58 and 0.96) and C. trachomatis (relative rate, 0.79; 90% confidence limits, 0.64 and 0.97) trichomoniasis (relative rate 0.83; 0.61 to 1.12) and bacterial vaginosis (relative rate 0.86; 0.69 to 1.12) candidiasis (relative rate 1.02; 0.77 to 1.35) gonorrhea:0·60 (0·21, 1·76)	
N-9 [Cook 1998][34]	Gonorrhea: RR 0.62 (0.49-0.78) Chlamydia: RR 0.75 (0.62-0.91)	
Dextrin sulphate [Poynten 2009][35]	Bacterial vaginosis RR 0.61 (0.42–0.88)	
The intervention had five components:		At follow-up the prevalence of syphilis was 5.0% in the intervention community and 7.0% in the comparison community

Table 9.1.1. Summary of impact estimates for STIs		
Intervention	**Morbidity related outcomes**	**Attitudes and behavior change**
establishment of a reference clinic, training of health care providers, supply of effective drugs, regular supervision and health education in the target communities to encourage individuals with STD symptoms to seek treatment early. [Mayaud 1997[18]]		[adjusted RR, 0.71; 95% CI, 0.54–0.93; P < 0.02]. The prevalence of arthritis in males did not differ significantly between intervention and comparison groups at follow-up, but the prevalence of symptomatic arthritis was reduced by about 50% (adjusted RR, 0.51; 95% CI, 0.24–1.10; P = 0.08).In the intervention community and in the comparison community [adjusted RR, 0.71; 95% CI, 0.54–0.93; P < 0.02]. The prevalence of symptomatic urethritis was reduced by about 50% (adjusted RR, 0.51; 95% CI, 0.24–1.10; P = 0.08)
Men- Brief programs for STI clinic attendees- skills approach versus social approach versus condom distribution [Cohen 1992][36]		Re-infections: Skills RR 0.43(0.19-0.97) and social RR 0.42 (0.20-0.86)
STI clinic attendees - Soap-opera style video and coupon-exchange for condoms versus none [Solomon 1989][37]	Video group redeemed significantly more coupons (1.0 vs 0.8; difference in means, 0.20; 95% CI of difference, 0.02 to 0.38). more strategies for persuading partners to use condoms (difference in means, 0.5; 95% CI of difference, 0.2 to 0.8).	
STI clinic attendees - Information, motivation and skills versus standard counseling [Branson 1998][13]	Percentage using a condom from baseline to12 mo: I, 23% vs 48%; C, 30% vs 49%P = .09. No difference in percentage change reporting>1 partner: I, 42% vs 26%; C, 42% vs 22%;	No group difference in new infections of gonorrhea,chlamydia, or syphilis (19% vs 19.3%).
STI clinic attendees - Skills sessions versus standard risk-reduction counseling [Boyer 1997][14]	At 3 mo, the Intervention group showedgreater increase in percentage of time they usedcondoms (56.8% vs 42.3%; P<.05). At 5 mo,the mean number of sexual partners without useof condoms was lower in the Intervention group (0.6 vs 0.9;P<.01).	No difference in new/probable STI at 6 mo (13% vs 11%).

Table 9.1.1. Summary of impact estimates for STIs		
Intervention	**Morbidity related outcomes**	**Attitudes and behavior change**
STI clinic attendees – video and skills-building, versus video alone, versus standard STI prevention information. Coupons-for-condoms in all groups [O'Donnell 1995][38]	Men exposed to both video and group session morelikely to redeem coupons (OR, 1.28; 95% CI,1.17 to 1.40).	
6 weekly group sessions-information about STD/HIV, skills training in communication, goalsetting, and use of the male condom. Information and demonstration as well as free female condom. Control group had 1-hr nutrition education [Van Devanter 2002][25]	OR for use of condom after intervention= 5.5 (2.8-10.7)	
Female-dependent barrier methods [Rosenberg 1992][39]	aOR (versus male condoms)for gonorrhea: 0.45 (0.22-0.92) trichomoniasis: 0.33 (0.17-0.64) candidiasis: 1.62 (1.15-2.28)	
Harrison 2000[40]	The intervention consisted of two components: (i) training and supervision of health workers in a comprehensive approach to STD syndromic case management, and (ii) developing and implementing syndrome packets containing KwaZulu/Natal Provincial Health Department recommended drug treatment for each syndrome, condoms, partner cards, and a patient information leaflet	After the intervention, intervention clinics provided better case management than controls: 88 versus 50% (P <0.01) received recommended drugs; 83 versus 12% (P < 0.005) were correctly case managed; 68 versus 46% (P < 0.06) were adequately counseled; 84 versus 58% experienced good staff attitude (P < 0.07); and 92 versus 86% (P < 0.4) were consulted privately. A syndrome packet cost US$1.50; the incremental cost was US$6.80. The total intervention cost equaled 0.3% of annual district health expenditure.
Livingood 2010[11]	Building resilience to negative social determinants through social and behavioural case management distinguishes	Magnolia case management clients had lower repeat STD rates (10.8%) than did the similar risk-factor comparison group

Table 9.1.1. Summary of impact estimates for STIs		
Intervention	**Morbidity related outcomes**	**Attitudes and behavior change**
	Magnolia case management - Providing outreach, education and support to women in need of well-woman care, prenatal care and other services; - Increasing the availability of case management and care coordination to at-risk women who are either pregnant or ineligible for existing services because they are not pregnant; - Providing health education directed at specific risk factors identified through Fetal and Infant Mortality Review (FIMR) and other community studies; - Increasing the accessibility and availability of well-women health care and prenatal care.	clients (12.9%). Following the case management period, Magnolia case management clients who did have STDs since 1995 also reported lower STD rates than did the similar risk-factor group during a comparable time frame. The total incidence of post intervention STDs (10.4%) for case management was significantly lower (P = .022) than the incidence of STDs for the similar risk-factor comparison group (16.7%) at simulated post-intervention The total incidence of post-intervention STDs (10.4%) for case management was significantly lower (P = 0.022) than the incidence of STDs for the similar risk-factor comparison group (16.7%) at simulated post-intervention. [Livingood 2010][11] Magnolia case management clients had lower repeat STD rates (10.8%) than did the similar risk-factor comparison group clients (12.9%). Following the case management period, Magnolia case management clients who did have STDs since 1995 also reported lower STD rates than did the similar risk-factor group during a comparable time frame. [Livingood 2010][11]
Shain 1999[22]	SAFE project- The three stages of behavioural change incorporated into the Project SAFE intervention are (1) recognition of one's individual risk, (2) commitment to making changes to reduce that risk, and (3) acquiring the skills needed to implement changes to reduce risk.	In a randomized, controlled trial, minority women who received this culture- and gender-specific behavioural intervention were significantly less likely to have a new infection with gonorrhoea or Chlamydia during the 12 months of follow-up than women in the control group who received standard (15- to 20-minute) STI prevention counselling. Rates of new infection were significantly lower in the intervention group in both the 0- to 6-month visit windows (11.3% versus 17.2%; P = .05) and the 6- to 12-month visit windows (9.1% versus 17.7%; P = .008). At 12 months there was a 38% reduction in the rate of new infections in the intervention group (16.8%) compared with the control group (26.9%; P = .004). [Shain 1999][22]

Table 9.1.1. Summary of impact estimates for STIs		
Intervention	**Morbidity related outcomes**	**Attitudes and behavior change**
Shain 2004[23]	Project SAFE 2, used the standard intervention and control arms from Project SAFE but added a third enhanced intervention arm in which women received the intervention and were offered the option of attending monthly support group meetings for 6 months following the intervention	Women who attended the support group meetings had the lowest rate of new infections in the first year, in the second year, and for the cumulative 2-year follow-up period, with a 63% reduction in the first year as compared with the control group. Standard intervention vs. control aOR=0.54, CI (0.34–0.85). Enhanced intervention vs. control aOR=0.47, CI (0.30–0.73).
NIMH 1998[41]	Participants were assigned randomly to the control group (participants received a 1-hour AIDS education session including a videotape and a question-and-answer period) or to the intervention group. The intervention consisted of seven 90- to120-minute HIV risk reduction sessions conducted twice weekly for single-gender groups of 5 to 15 participants.	During follow-up, STI symptoms were reported more commonly by the control group than by the intervention group (35% versus 28%). In contrast, the rates of new STD acquisition by chart review (9.4% versus 9.1%) and by urine screening (2.8% versus 2.9% for chlamydia; 1.5% versus 0.9% for gonorrhoea) did not differ between the intervention and control groups.

more likely to develop AIDS sooner and have more serious complications. Additionally, HIV-positive women are more likely to terminate their pregnancies, give birth to low birth weight babies, deliver preterm, or experience stillbirths[42-45]. Although half of women who are pregnant and HIV-positive receive antiretroviral therapy, little data exists on prevention of mother-to-child transmission through interventions before pregnancy.[46]

Scope of intervention

As medical care for people living with HIV/AIDS enables them to live longer and healthier lives, serodiscordant couples naturally face a difficult choice, between their desire to have children and the risk of HIV transmission to their partner or newborn.

In a ten year prospective study[47] of serodiscordant couples- HIV-negative women who conceived naturally after preconception counselling- only 2 women seroconverted in the last trimester, and pregnancy outcomes were 92 deliveries, 4 abortions and 6 miscarriages. Among the HIV-positive partners, the mean CD4 count was 584/μL (from 60 who provided blood samples) and 21 were on antiretroviral therapy. This study illustrates two seemingly conflicting yet important points- HIV transmission can occur in a single sexual contact; and multiple factors influence transmission between serodiscordant partners.[48, 49]

Reducing the burden of HIV in women of reproductive age will prevent transmission of the virus to the next generation and ensure that children do not lose their mothers to AIDS. We reviewed studies of any intervention in women age 15-45 who were not currently pregnant, that improved MNCH outcomes or reduced the incidence of HIV. It was previously postulated that participants in HIV prevention efforts might perceive their risk for transmission to be reduced. Multiple studies have since confirmed that various interventions- including risk reduction,[50] antiretroviral therapy,[51] postexposure prophylaxis,[52] and VCT[53] increase safe sexual practices, even in people who are HIV-positive[54] which would presumably reduce HIV transmission. Hence this review also includes HIV preventive interventions that showed an impact on safe sex behaviors. Since our outcome was reduced transmission, we also included studies in which the outcome was incidence in men of reproductive age. We did not however, include studies where couples used assisted reproductive technologies (such as ICSI or sperm washing) to conceive, since such procedures are expensive and not yet accessible to the population in general, even though they minimize the risk of transmission. Although the risk of transmission is much higher in certain groups, such as commercial sex workers and intravenous drug users, we have only described some studies. However, it must be noted that in Thailand, for example, the promotion of safe sex among female sex workers has resulted in a drastic decline in the prevalence of HIV from 10.4 to 6.7% and in STIs from 42.2 to 15.2% among young Thai men.[55] Thus public health programs to prevent HIV must target men and women, adolescents and adults, couples and individuals, as well as focus more intensive efforts at high-risk populations and their partners.

The content of preconception care for women living with HIV/AIDS or HIV-positive partners[56, 57]

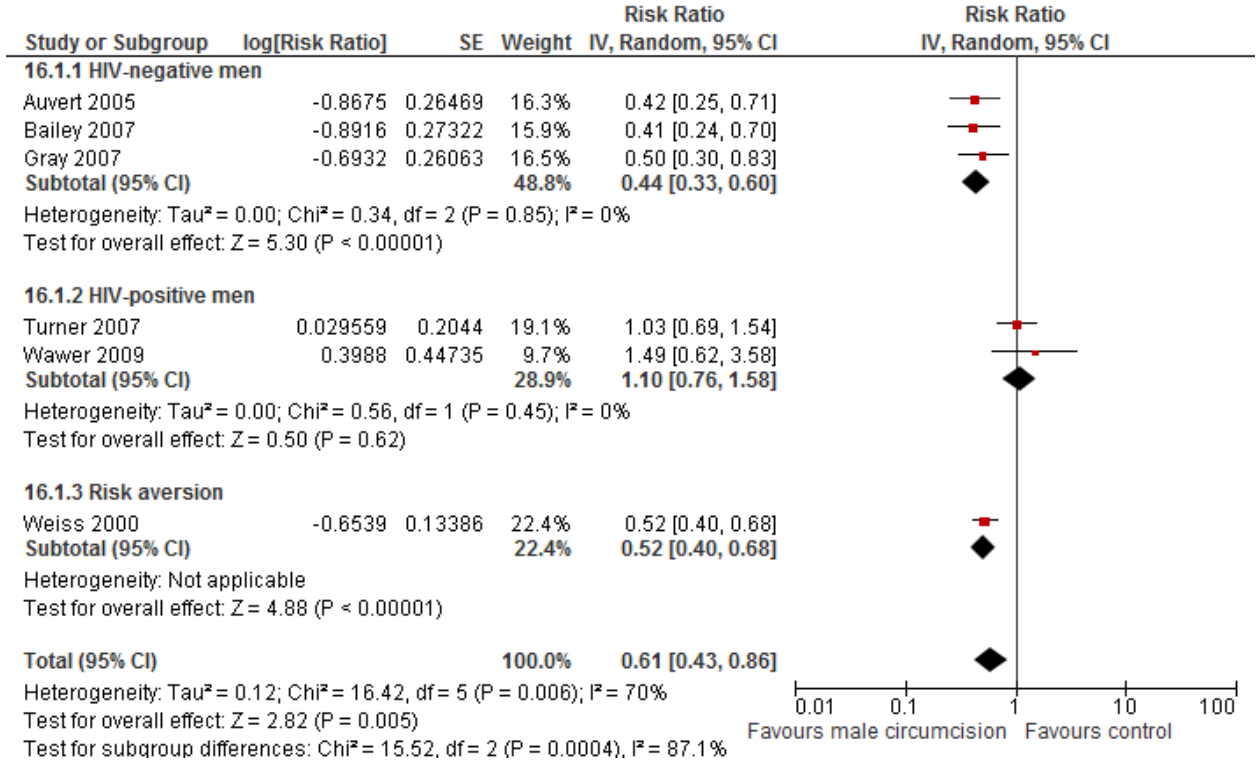
- Effective and appropriate contraception to reduce the chance of unintended pregnancy, and until lowest possible viral load- consider dual contraception to prevent pregnancy and STIs (male condom, female condom, hormonal contraceptives -prevent pregnancy but may interact with HAART, emergency contraception, NOT diaphragm or IUD alone or spermicide (IPPF 2005)[58]
- Psychological and emotional support to encourage disclosure of serostatus to partner
- The risks of perinatal transmission and strategies for prevention:
  - 25% risk of perinatal transmission without intervention or breastfeeding (highest risk is intrapartum)
  - Benefits of antiretroviral therapy (efavirenz, hydroxyurea) must be weighed against the risk of adverse events to the woman, fetus, and newborn (hepatotoxicity, hyperglycemia, anemia, preterm birth, stillbirths); however pregnancy is generally not a reason to defer standard therapy. It should be offered with the addition of ZDV for prevention of perinatal HIV transmission (70% reduction)
- Discuss reproductive options- besides the use of assisted reproductive techniques (sperm washing and ICSI), self-insemination or unprotected intercourse at the time of ovulation. HIV-positive partner should be on HAART and achieve minimal viral load before attempting to conceive. Couples should understand that even if both partners are HIV-positive frequent unprotected sexual intercourse can still transmit different strains of the virus
- Partners should also be screened and treated for STIs which could increase the chance of HIV transmission
- Safe sexual practices to continue throughout pregnancy to prevent transmission of other strains of HIV or other STIs
- Prophylaxis, including immunization for opportunistic infections
- Maternal nutritional evaluation and counselling

Impact estimates

Preconception counseling should be offered to women of reproductive age as soon as they test HIV-positive, and conversely women of reproductive age should be screened with their partners before pregnancy. The focus on possible intervention in the immediate preconception period is currently on pre-exposure prophylaxis,[59] which entails the seronegative partner using antiretroviral drugs, especially tenofovir –a method for vaginal application is also being studied- around the time of conception to minimize the risk of transmission. One clinical trial[60] has been conducted thus far and found an incidence rate ratio of 0.35 (0.03–1.93), however the trial lacked study power due to inadequate person-years of follow-up. Concerns with PrEP include adherence, the risk of developing resistant viral strains, safety, cost and behavioral risk compensation. Ongoing trials with expected completion in the next few years may provide more evidence in favour of PrEP. On the other hand, antiretroviral therapy for people who are HIV-positive (treatment as prevention) has consistently been shown to lower the incidence rates of HIV, not just among serodiscordant couples[61], but even in the entire population. The caveats are that antiretroviral therapy must suppress the viral load to very low counts, and that in resource-poor countries therapy would need to be started at higher CD4 counts. Further information on ongoing trials for antiretroviral therapy and PrEP is available from the Global Advocacy for HIV Prevention website (http://www.avac.org/ht/d/sp/i/176/pid/176).

As a rather proximal intervention, this review found that male circumcision significantly reduces the risk of acquiring HIV (RR 0.49; 95% CI 0.40-0.59), but is not effective in preventing transmission from HIV-positive men to their partners (**Figure 9.2.1**).

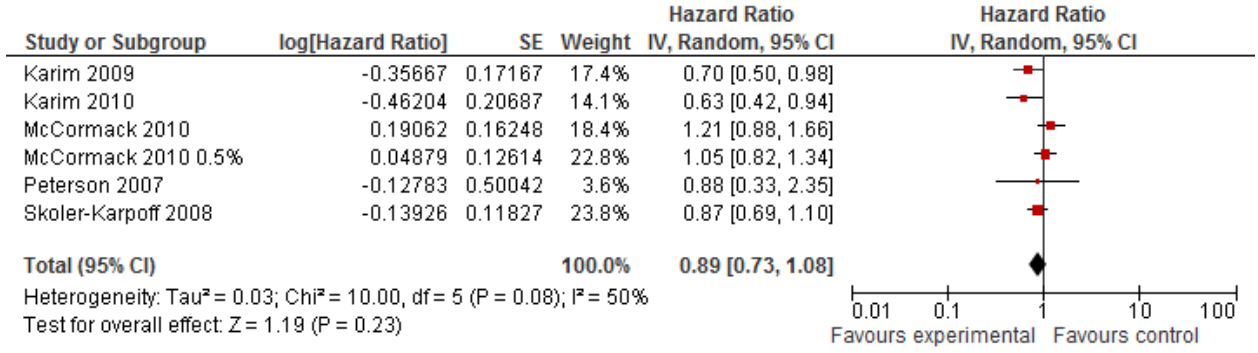
Figure 9.2.1: Male circumcision and the risk of HIV infection



Citations to the included studies:
Auvert 2005[62], Bailey 2007[63], Gray 2007[64], wawer 2009[65], weiss 2000[66]

It was hoped that microbicides might provide a way for women to control their risk for HIV infection, however, microbicides do not provide protect from HIV and might even increase harm through increased risk of genital ulceration and injury (**Figure 9.2.2**).[33, 67]

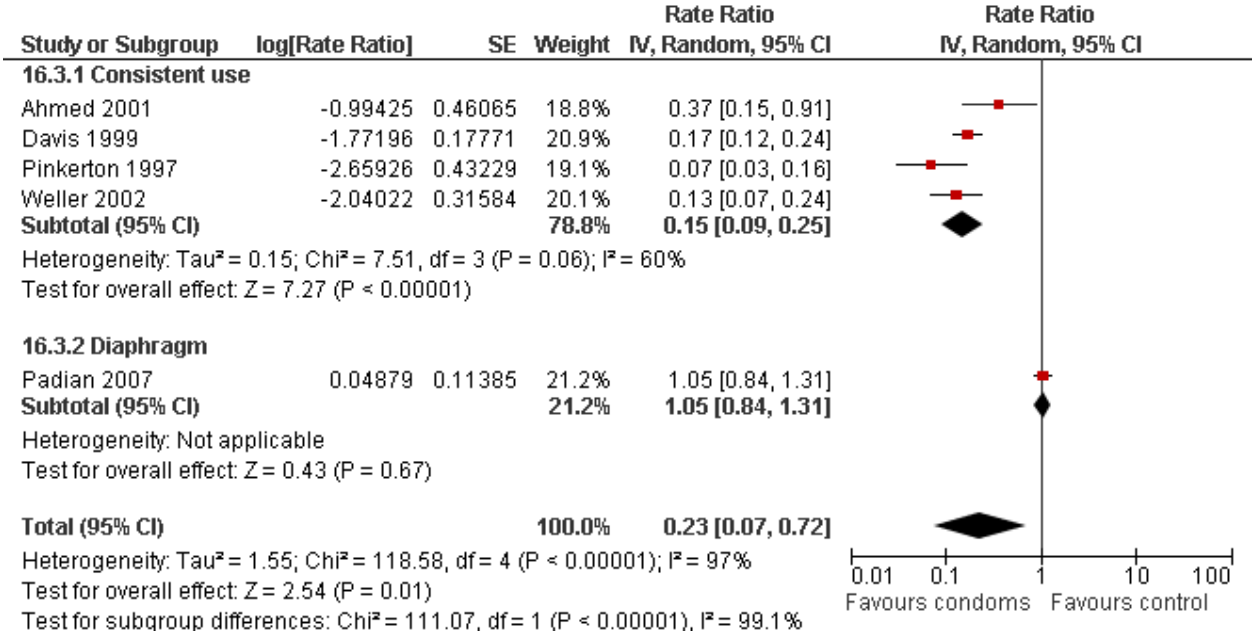
Figure 9.2.2: Microbicides and the risk of HIV infection



Citations to the included studies:
Karim 2009[68], Karim 2010[69], McCormack 2010[70], Skoler-karpoff 2008[71], Peterson 2007[60]

To date, condom use has been shown to be the most effective way to prevent HIV infection (85% protection in prospective studies) through sexual intercourse. The use of condoms has the added advantage of protecting against most other STIs and unplanned pregnancy[72]. Serodiscordant couples should be encouraged to use condoms consistently during sexual intercourse until there is another proven means to clear vaginal secretions and semen of the HIV virus.[73] Research should now focus on developing effective interventions, assessed through rigorous methods, to promote the use of condoms during all sexual exposures (**Figure 9.2.3**)..[74]

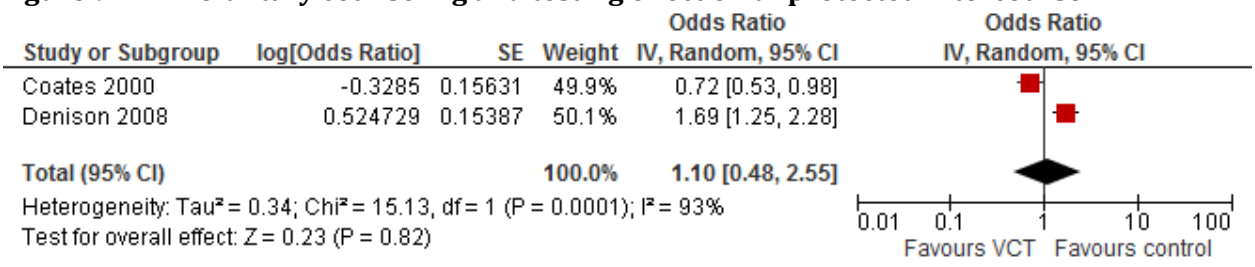
Figure 9.2.3: Barrier methods (especially condom use) and the risk of HIV



Citations to the included studies:
Ahmed 2001[75], Davis 1999[76], Pinkerton 1997[77], Weller 2002[78], Padian 2007[79].

Voluntary counseling and testing, while being effectively promoted especially through the mass media,[80] has not reduced risky sexual behavior or HIV incidence in previous studies. This does not mean that VCT should be disregarded, rather that there is a need to expand VCT services to make them more accessible and to evaluate the outcome of such programs more carefully (**Figure 9.2.4**).[81]

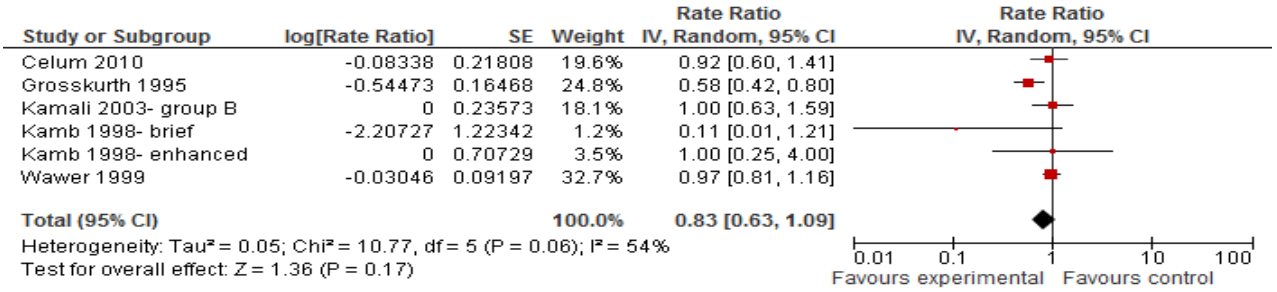
Figure 9.2.4: Voluntary counseling and testing effect on unprotected intercourse



Citations to the included studies:
Coates 2000[82], Denison 2008[81].

Strong empirical evidence illustrates that other sexually transmitted diseases, especially ulcerative diseases and HSV-2, promote HIV transmission with risk increased by 2-5 times that in the general population.[83, 84] STDs can therefore interfere with the effectiveness of other interventions to prevent HIV.[85] Management of STIs, including screening, counseling and treatment, has been shown to reduce the risk of HIV. This review found a non-significant slightly decreased risk (RR 0.83; 95% CI 0.63-1.09) since we only included arms of factorial trials in which STI management was the only difference from the other trial arms (**Figure 9.2.5**).

Figure 9.2.5: Management of STIs and the risk of HIV



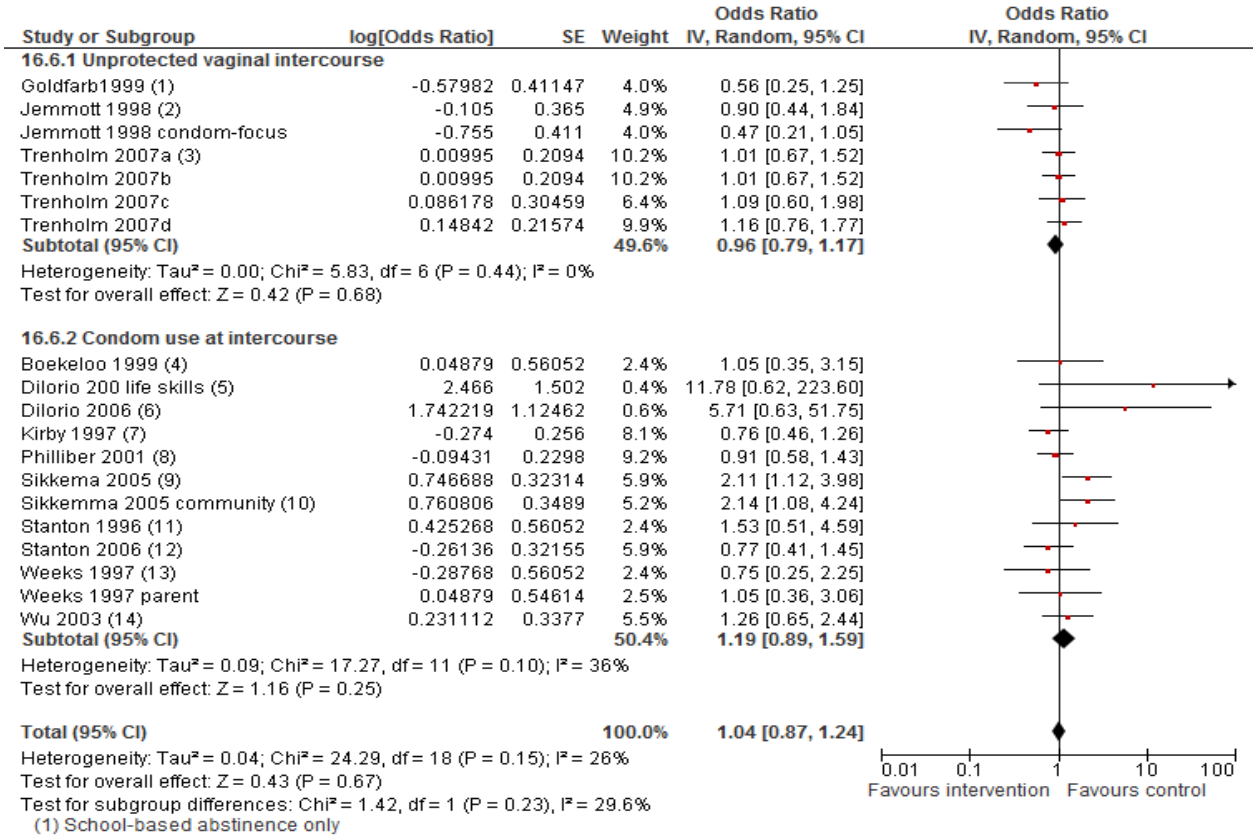
Citations to the included studies:
Celum 2010[86], Grosskurth 1995[24], Kamali 2003[20], Kamb 1998[21], Wawer 1999[19].

Behavioral interventions to reduce the risk of HIV are heterogeneous and target different populations,[87, 88] but broadly may incorporate HIV/AIDS education, condom promotion and skills, peer educators, skills to negotiate safe sexual behavior, address sociocultural barriers and personal risk reduction, counseling and testing. Overall, these interventions showed a beneficial impact through reduction of risky sexual behaviours, and on decreased STI incidence.[89] However, the reduction in HIV incidence was less convincing. The lack of consistent effect across studies might be due to differing sites and populations,[90] and the use of different control groups. Despite variation, it appears that interventions are more effective for HIV-positive individuals[9, 91, 92] and serodiscordant couples as well as high-risk ethnic populations;[93-98] and if they are multicomponent, based on cognitive-behavioral theory and provide participants with the skills to ensure safe sexual practices. It remains unclear whether interventions have more effect if targeted specifically by gender. Amongst IDUs, interventions (except counseling) to prevent HIV infection do result in reduced injection and sexual risk behavior.[99-103] Risk reduction in this high-risk population through harm reduction, substitution treatment, and peer education is important to prevent transmission to the rest of the population.

A number of best practice interventions have been identified to prevent HIV infection in high-risk individuals.[104] Adolescents are a special group with unique social influences, and are at extremely high risk. Many reviews have been conducted in this area, but data synthesis has tended to be qualitative, or has focused on a single type of intervention. It is crucial to note here that interventions which aim to prevent STIs including HIV, and teenage and unintended pregnancies, overlap to a large extent. Further, there is a lack of uniformity in the outcomes that trials report- for instance, some report STI incidence

and others prevalence or repeat infections; and some discuss unprotected intercourse while others assess condom use at last intercourse. On the other hand, such outcomes may have been assessed in more than one way to ensure response accuracy. Surprisingly few trials report public campaigns as an intervention or HIV incidence as an outcome, despite evidence to show the high rates of infection and risky sexual behavior among teens. We therefore resorted to pooling intervention trials that reported whether intercourse (especially vaginal) was protected through use of condoms. Meta-analysis showed that interventions did not significantly affect adolescents' condom use during intercourse (OR 1.04; 95% CI 0.87-1.24), however, these results must be interpreted cautiously since the outcome was not uniformly defined (**Figure 9.2.6**).

Figure 9.2.6: Interventions to prevent HIV in adolescents



Citations to the included studies:
Goldfarb 1999[105], Jemmott 1998[106], Trenholm 2007[107], Boekeloo 1999[108], Dilorio 2006[109], Kirby 1997[110], Philliber 2001[111], Sikkema 2005[112], Stanton 1996[113], Stanton 2006[114], weeks 1997[115], Wu 2003[116].

Table 9.2.1. HIV/AIDS		
Intervention	**BEHAVIORAL (condom, partners, intercourse/abstinence/initiation, IDU)**	**BIOLOGIC (STDs, HIV, pregnancy)**
MALE CIRCUMCISION (as quoted in Siegfried 2009[117] and Mills 2008[118])		
[Auvert 2005][62]		Incident rate ratio= 0.40 (0.24–0.68, p<0.001) Controlling for behavioral factors, results were similar
[Bailey 2007[63], Mattson 2008[119]]	Sexually active: RR 1.01 [0.98, 1.05] Multiple partners: 0.88 [0.79, 0.99] Casual last contact: 0.97 [0.81, 1.15] Inconsistent/no condom use: 1.07 [1.00, 1.14] Unprotected sex: 1.08 [1.00, 1.17]	Incident risk ratio= 0·47 (0·28–0·78). Protection increased to 60% after adjusting for non-adherence and seropositive at enrollment.
[Gray 2007[64], Gray 2009[120]]	Sexually active: RR 1.02 [0.99, 1.05] Multiple partners: 0.99 [0.90, 1.10] Non-marital partner: 1.01 [0.92, 1.10] Inconsistent/no condom use: 1.02 [0.98, 1.07] Transactional sex: 1.23 [0.65, 2.33]	Incidence rate ratio= 0·49 (0·28–0·84, p=0·0057). No significant difference in sexual behavior between groups <u>Effect on female partners' genital tract symptoms:</u> adjPRR =0.78(0.63–0.97) for genital ulceration adjPRR =0.52 (0.05–0.98) for trichomoniasis adjPRR 0.60 (0.38–0.94) for bacterial vaginosis
HIV +ve men [Wawer 2009][65]	Multiple partners: RR 1.35 [0.26, 6.94] Inconsistent/no condom use: 0.79 [0.53, 1.16]	adjusted hazard ratio=1·49 (0·62–3·57; p=0·368) for HIV infection in female partners. For early versus late resumption of sexual activity relative to wound healing, rate ratio 2.92-3.44 (significant) Bacterial vaginosis: 1.07 [0.89, 1.30] Trichomoniasis: 0.43 [0.20, 0.93] Genital ulceration: 1.02 [0.64, 1.61]
Observational studies [Weiss 2000 MA][66]		21 studies crude RR = 0.52 (0.40-0.68). 15 studies adjusted anlaysis (aRR= 0.42, 95% CI 0.34-0.54). Among men at high risk aRR= 0.29, CI 0.20-0.41. Among men in general population adjusted RR = 0.56, CI 0.44-0.70
Cohort study for **female partner's risk**[Turner 2007][121]		HR 1.03 (0.69–1.53)
CONDOM USE (& OTHER BARRIER METHODS)		
Diaphragm and latex gel and condoms versus condoms alone [Padian 2007][79]		relative hazard =1.05 (0.84–1.32)

Table 9.2.1. HIV/AIDS		
Intervention	**BEHAVIORAL (condom, partners, intercourse/abstinence/initiation, IDU)**	**BIOLOGIC (STDs, HIV, pregnancy)**
Consistent use versus inconsistent use [Pinkerton 1997][77]		Pooled risk ratio= 0.07 [0.03, 0.20]
Always use versus never use [Davis 1999][76]		Pooled risk ratio= 0.17 [0.12, 0.23]. For always versus inconsistent use 0.17 [0.12, 0.24]
Consistent use versus never use [Ahmed 2001][75]		Incidence rate ratio= 0.37 (0.15-0.88) Syphilis: OR 0.71 (0.53-0.94) Bacterial vaginosis: OR 0.89 (0.74-1.07) Trichomoniasis: OR 0.93 (0.73-1.19) Gonorrhea or chlamydia: OR 0.50 (0.25-0.97)
[Weller 2002][78]		Pooled risk ratio= 0.13 [0.07, 0.25]
[Weller 2009][122]		Effectiveness: Proportionate reduction in HIV sero-conversion is approx 80% Always users OR 1.14 (0.56-2.04) Never users OR 5.75 (3.16-9.66) [weller 2009]94
MICROBICIDES		
Tenofovir gel [Karim 2010][69]		Incidence rate ratio= 0.61 (0.40-0.94, p=0.017). In adjusted analyses, hazard ratio=0.63 (0.42-0.94, p=0.025)
PRO2000 intravaginal gel [McCormack 2010][70]		hazard ratio =1·05 (0·82–1·34, p=0·71) for 0.5% gel, and HR= 1·21 (0·88–1·68) for 2% gel. No significant difference in odds of HSV-2, gonorrhea or chlamydia; or adverse effects
Carraguard gel + condoms [Skoler-Karpoff 2008][71]		aHR= 0·87 (0·69–1·09).
0.5% PRO 2000/5 gel [Karim 2009][68]		HR= 0.7 (0.5-1.1) versus placebo, and 0.7 (0.4-1.0, p = 0.06) versus no gel
Cellulose sulfate [Halpern 2008][123]		HIV HR= 0.8 (0.3, 1.8) STD HR=0.8 (0.5, 1.1)
SAVVY gel 1% C31G [Peterson 2007][60]		HR= 0.88 (0.33, 2.27)

Table 9.2.1. HIV/AIDS		
Intervention	**BEHAVIORAL (condom, partners, intercourse/abstinence/initiation, IDU)**	**BIOLOGIC (STDs, HIV, pregnancy)**
VOLUNTARY COUNSELING AND TESTING		
Voluntary counseling and testing versus basic HIV information (video). Condom demonstration provided to both groups [Coates 2000][82]	Unprotected intercourse decreased by 35% vs 13% for men in the VCT vs health information groups; women, 39% vs 17%. Mean number of casual partners with whom participants had unprotected intercourse decreased by 38% vs 15% for men in the VCT vs health information groups; women 43% vs 22% Results similar at second follow-up OR=0·72 (0·53–0·99, p=0·014) for enrolled couples to have unprotected intercourse in VCT vs health information groups	
[Weinhardt 1999][124] *includes antenatal population and one study on female sex workers	Versus untested participants, weighted mean effect size Condom use: HIV +ve 0.65 (0.42-0.87) Serodiscordant 1.31 (1.14-1.48) Unprotected intercourse: HIV+ve 0.47 (0.32-0.61) Serodiscordant 0.75 (0.59-0.92) Number of partners: HIV +ve 0.34 (0.20-0.47)	
[Denison 2008][81] *includes studies during antenatal period	VCT recipients were significantly less likely to engage in unprotected sex when compared to behaviors before receiving VCT, or as compared to participants who had not received VCT [OR 1.69; 1.25–2.31]. VCT had no significant effect on the number of sex partners [OR 1.22; 0.89–1.67].	
Free individual and couples VCT while larger community HIV prevention program ongoing [Matovu 2005][125]		HIV IRR= 0.94 (0.53, 1.66)
Men- STI clinic attendees-	level of consistent condom usewith CSWs increased:	

Table 9.2.1. HIV/AIDS		
Intervention	**BEHAVIORAL (condom, partners, intercourse/abstinence/initiation, IDU)**	**BIOLOGIC (STDs, HIV, pregnancy)**
individual counseling and condom promotion [Bentley 1998][126]	men at 24 mo were 4.7times more likely to use condoms every time(P<.001). Among the 56% of men with a historyof STI, the likelihood of visiting CSWs hadincreased at follow-up, with men at 24 mo3.2 times more likely to visit CSWs (P<.001).	
HIV testing as well as specialized (gynecological) and primary health care services for non-pregnant women[Ickovics 1994][127]	Average level of sexual risk was lower for tested than nontested women. However, there was no significant change in sexual risk from baseline to 3-month follow-up. There was no difference in the number of women who decreased or increased sexual risk. For tested women, their perceived estimated chance of getting AIDS decreased after counseling and testing.	
Intensive VCT at the workplace, versus standard VCT. Condom provision and pre-test counseling to both groups, and HIV care if positive. [Corbett 2007][128]		adjusted rate ratio 1.49 (95% confidence interval 0.79–2.80).
ANTIRETROVIRALS: PRE- or POST-EXPOSURE PROPHYLAXIS: TREATMENT AS PREVENTION		
300 mg of tenofovir daily or placebo in HIV-negative women [Peterson 2007[60], Okwundu 2009[129]]		Rate ratio= 0.35 (0.03–1.93) however low study power due to limited person-years follow-up
ART (Partners in prevention Coh)[Donnell 2010][130]		adjusted incidence rate ratio= 0·08 (0·00–0·57, p=0·004) Greatest risk of transmission if CD4<200 and viral load >50,000
Serodiscordant couples, infected partner on HAART, plasma HIV RNA levels <500 copies/mL on HAART at the time of natural conception, if		68 newborns- 9 fetaldeaths (OR 6.1), 1 twin pregnancy, 6 couples with 2 consecutive babies, and4 couples with 3 consecutive newborns. There were no cases of HIVseroconversion in uninfected sexual partners. One case of verticalHIV transmission occurred

Table 9.2.1. HIV/AIDS		
Intervention	**BEHAVIORAL (condom, partners, intercourse/abstinence/initiation, IDU)**	**BIOLOGIC (STDs, HIV, pregnancy)**
mother HIV-positive must have undetectable viremia during pregnancy and delivery, babies received zidovudine prophylaxis during delivery and after birth [Barreiro 2006][131]		
Free HAART to all HIV positive citizens[Fang 2004][132]		HIV transmissionrate decreased by 53% (0.391 vs. 0.184 new cases/prevalent case-year [95% confidence interval, 31%–65%]). Therewas no statistically significant change in the incidence of syphilis, in the general population or among HIV-positivepatients, during the same period.
TREATMENT OF SEXUALLY TRANSMITTED INFECTIONS (Ng 2011)[133]		
Arm 1 enhanced counselling, Arm 2 brief counselling. Arms 3 and 4 brief didactic messages (standard care)- Arm 4 was control for frequent follow-up [Kamb 1998][134]	"No unprotected sex": enhanced counseling RR 1.14 (1.01-1.28). Brief counseling: RR 1.12 (1.00-1.25)	At the 12-month follow-up visit, acquisition of a new STI was less common in Arms 1 (11.5%) and 2 (12%) than in Arm 3 (14.6%). HIV: 4/1443 new infections among those in the didactic messages arm, 4/1438 in those assigned to the enhanced counselling arm, and none/1447 in those assigned to the brief counselling arm (*P*= .06) Through the 6-month interval, 30% fewer participants had new STDs in both the enhanced counselling (7.2%; P = .002) and brief counselling (7.3%; P = .005) arms compared with those in the didactic messages arm (10.4%). Through the 12-month study, 20% fewer participants in each counselling intervention had new STDs compared with those in the didactic messages arm (P = .008).
Intervention consisted of establishment of an STD reference clinic, staff training, regular supply of drugs, regular	Reduced frequency of partner change: RR 1.11 [0.91, 1.35] Multiple partners RR: 1.08 [0.78, 1.50]	HIV RR 0.58 (0.42-0.79, p = 0.007). Syphilis: 0.92 (0.78-1.07) Gonorrhea or chlamydia: 0.65 (0.26-1.62)

Table 9.2.1. HIV/AIDS		
Intervention	**BEHAVIORAL (condom, partners, intercourse/abstinence/initiation, IDU)**	**BIOLOGIC (STDs, HIV, pregnancy)**
supervisory visits to health facilities, and health education about STDs. [Grosskurth 1995][24]		
Information and education activities with improved management of STIs (group B), or routine government health facilities with general community development activities (group C). Implemented social marketing of male condoms and voluntary HIV counselling and testing in all three groups. [Kamali 2003][20]	Sexual initiation: RR 1·01 (0·71–1·43) Prevalence ratio of use of condoms with last casual partner was 1·27 (1·02–1·56) in group B. Multiple partners: 782/5030(B) vs 382/4768 (C)	Compared with group C, the incidence rate ratio of HIV was 1·00 (0·63–1·58, p=0·98) in group B Syphilis incidence rate ratio, 0·77 [0·61–0·96] Gonorrhoea prevalence ratio, 0·25 (0·10–0·64). HSV-2 1·00 [0·54–1·85] Chlamydia 0·99 (0·71–1·39)
Mass treatment (azithromycin, ciprofloxacin, metronidazole in the intervention group, vitamins/Antihelminthic drug in the control) [Wawer 1999][19]	Reduced frequency of partner change: RR 1.05 [0.97, 1.15] Multiple partners: RR 1.08 [1.01, 1.15] 14% of residents of intervention communities and 11% of residents of control communities reported condom use in the preceding six months, and 5.5% vs. 4.1% reported consistent condom use with a primary partner. Regular condom use with casual partner: RR 1.29 [1.17, 1.42]	HIV: incidence rate ratio 0·97 [0·81–1·16] The prevalence ratio of syphilis between intervention and control groups at the end of the trial was 0.80 (0.71-0.89), of trichomoniasis 0.59 (0.38-0.91), and of bacterial vaginosis 0.87 (0.74-1.02). Chlamydia 0.88 (0.50-1.53). Genital ulceration: 1.02(0.80-1.29) Incidence rate ratios: Syphilis: 0·65 [0·06–6·82] Trichomoniasis: 0·52 [0·35–0·79]). Risk ratio gonorrhea: 0.65 (0.27-1.55)
400 mg acyclovir twice daily in co-infected person with serodiscordant partner, not currently on ART (Partners in	Among HIV-infected persons, unsafe sexual behavior decreased similarly between groups. Among HIV-negative persons, casual sex increased similarly between groups.	Hazard ratio= 0.92 (0.60-1.41; p=0.69), despite significant reduction in genital ulcers and mean plasma HIV concentration.

Table 9.2.1. HIV/AIDS		
Intervention	**BEHAVIORAL (condom, partners, intercourse/abstinence/initiation, IDU)**	**BIOLOGIC (STDs, HIV, pregnancy)**
Prevention HSV/HIV) [Celum 2010][86]		
BEHAVIORAL (INCLUDING COUNSELLING, EDUCATION, COMMUNITY) **Adolescents**		
Adolescents- 2 workshops on safe sex skills training OR Community intervention (workshops, parental involvement, teen health council, follow-up and community activities) OR control video. All groups given condoms and brochure [Sikkema 2005][112]	aOR 1.97 (1.06-3.67, p<0.05) that youth in community intervention would remain abstinent at second follow-up versus controls aOR 3.96 (1.44-10.88, p=0.01) that youth in workshop intervention used condoms at last intercourse versus controls. At second follow-up aOR 2.50 (1.01-6.22, p=0.049) for youth in community intervention versus controls	
Participatory college-based HIV education led by teachers (Teens on Smart Sex) [Baker 2003][135]	Males experiencing first sexual intercourse: increased 6% in intervention versus 5% in control Condom use at last intercourse among females increased 8% in intervention versus 4% in control Sexually-naïve females discussing HIV with partner: 19% in intervention versus 9% in control (p<0.001) Sexually-experienced males discussing HIV with a teacher/counselor: 40% intervention versus 28% control	
Adolescents- Training and resources regarding the care of PLWH/A. Both sites received training in HIV prevention and recreational equipment [Esu-Williams 2004][136]	Among the youths who reported that they had had sex, ever-use of condoms was similar between the two study areas at baseline, but increased significantly only in the intervention area: among males from 61 % to 81 % (p < 0.05), and among females from 67 to 81 % (p < 0.05). Among those who reported that they had ever used a condom,	

Table 9.2.1. HIV/AIDS		
Intervention	**BEHAVIORAL (condom, partners, intercourse/abstinence/initiation, IDU)**	**BIOLOGIC (STDs, HIV, pregnancy)**
	reported condom use at last sex was high and changed little, fluctuating at around 80 to 90 % of males and females.	
Adolescent and young adult-Sexual Reproductive Health facilitated participatory single-sex group sessions after school versus single safe sex workshop. VCT for both groups (Stepping Stones) [Jewkes 2008][137]	No difference in substance abuse, IPV, safe sex behaviors or pregnancy between intervention and control **women** at either follow-ups aOR= 0.39 (0.17- 0.92, p=0.031) for men in intervention having transactional sex with a casual partner. Effect absent at second follow-up. aOR= 0.62 (0.38-1.01, p= 0.054) for men in intervention perpetrating IPV at second follow-up. aOR= 0.68 (0.49-0.94, p=0.021) for men in intervention abusing alcohol, effect absent at second follow-up	Incidence rate ratio= 0.95 (0.67-1.35) HSV-2: 0.67 (0.47-0.97, p=0.036)
School based counseling plus condom distribution-adolescents. Doyle 2010[138]		risk of HIV (males adjusted prevalence ratio [par] 0.91, 95%CI 0.50–1.65; females aPR 1.07, 95%CI 0.68–1.67)
Adults (Medley 2009)[139]		
HIV-positive- 6-monthly risk assessments (4 in total) and 2 brief patient-centred counseling sessions by doctor during regular visits between assessments [Fisher 2006][140]	Mean unprotected vaginal/anal/oral sexual intercourse decreased from 7.15 to 1.53 (p<0.05) in intervention versus increased from 2.06 to 9.61 in control (p<0.01). With HIV negative or status unknown partner in intervention group decreased from 10.56 to 5.65 but with control group increased from 5.66 to 11.72 (p<0.05) Mean unprotected vaginal/anal sexual intercourse decreased from 5.33 to 1.51 in intervention versus increased from 1.49 to 9.34 in control (p<0.01). With HIV negative or status unknown partner in intervention group decreased from 8.2 to 5.45, but	

Table 9.2.1. HIV/AIDS		
Intervention	**BEHAVIORAL (condom, partners, intercourse/abstinence/initiation, IDU)**	**BIOLOGIC (STDs, HIV, pregnancy)**
	with control group increased from 4.52 to 10.58 ($p<0.05$) Number of HIV negative or status unknown partners involved in unprotected intercourse decreased in intervention and increased in control, but not significantly	
HIV-positive Safe sex group intervention versus standard care (contact-matched health-maintenance support group) [Kalichman 2001][141]	Significant difference in unprotected vaginal or anal intercourse with HIV-negative or unknown partners OR 0.6 (0.38–0.94)	
Communities were randomly allocated to receive information, education, and communication activities alone (group A), or routine government health facilities with general community development activities (group C). Implemented social marketing of male condoms and voluntary HIV counselling and testing in all three groups. [Kamali 2003][20]	Sexual initiation: 0·98 [95% CI 0·71–1·35], prevalence ratio of use of condoms with last casual partner was 1·12 (95% CI 0·99–1·25) in group A Multiple partners: 605/4532(A)	Compared with group C, the incidence rate ratio of HIV-1 was 0·94 (0·60–1·45, p=0·72) in group A Incidence of HSV2 was lower in group A than in group C (incidence rate ratio 0·65, 0·53–0·80) Syphilis IRR= 1·02 [95% CI 0·66–1·57] 0·64 (95% CI 0·25–1·59 gonorrhea 0·59 (0·20–1·72) chlamydia
Microfinance, gender and HIV education (IMAGE) versus standard government services [Pronyk 2006][142]		HIV IRR= 1.27 (0.87, 1.85)
Peer education and condom distribution amongst *sex	Regular condom use with casual partners RR; 1.11 [1.04, 1.18]	IRR HIV= 1.27 (0.92–1.75

Table 9.2.1. HIV/AIDS		
Intervention	**BEHAVIORAL (condom, partners, intercourse/abstinence/initiation, IDU)**	**BIOLOGIC (STDs, HIV, pregnancy)**
workers and clients, income generating projects (NOT microcredit), strengthened management of STIs, and IEC at heath centers. Social marketing of male and female condoms in both groups. [Gregson 2007][143]	Sexual initiation: POR 1.90 (1.13–3.18) Multiple new partners in last year: POR 1.25 (0.65–2.40) >2 regular partners: 0.84 (0.45–1.55) Multiple casual partners: 1.61 (0.97–2.66) Unprotected sex with regular partners: 1.09 (0.72–1.65)	
Relationship and gender-based counseling and skills for couples or women alone, versus video on HIV/STD prevention [El-Bassel 2003][144]	% of protected intercourse: • Intervention vs control0.07* (0.035) • Couples vs women alone –0.04 (0.03) number of sexual partners: • Intervention vs contro- 0.38 (0.41) • Couples vs women alone–0.48 (0.33)	number of STD symptoms: • Intervention vs control –0.02 (0.06) • Couples vs women alone–0.03 (0.05)
Peer educators from among high-risk groups (*including sex workers), condom distribution and STI management [Williams 2003][145]	Condom use: men- OR 2.02 (0.84- 4.89), women 1.49 (1.25- 1.79)	STI prevalence: men- OR 1.28 (0.75 2.20), women- 1.14 (0.66-1.96)
Community education activities (through drama/videos), individual counseling, condoms and VCT [Quigley 2004][146]	Multiple partners: OR 0.86 (0.31–2.43) for women, 0.75 (0.40–1.42) for men Casual partners: OR1.00 (0.49–2.02) for women, 0.92 (0.40–2.09) for men Condom use:OR 2.69 (1.10–6.63)for women,0.67 (0.31–1.47) for men Condom use with last casual partner: OR 20.75 (0.21–2086) for women, 0.76 (0.14–4.12) for men	HIV IRR= 0.41 (0.19, 0.89) for women, 0.66(0.25–1.79) for men
HIV +ve men and women. Intervention- safe sex skills, including disclosure of	Practise safe sex behavior at 6 months: OR 1.7 Intervention group less likely to have unprotected intercourse, more likely to use condoms during	

Table 9.2.1. HIV/AIDS		
Intervention	**BEHAVIORAL (condom, partners, intercourse/abstinence/initiation, IDU)**	**BIOLOGIC (STDs, HIV, pregnancy)**
serostatus and personal risk reduction. Group sessions for men and women separately with facilitator and peer educator. Controls had support groups with health maintenance including nutrition, adherence to medication, HIV information (*including homosexuals) [Kalichman 2001][147]	intercourse, even though they had more HIV-negative partners	
Men (Elwy 2002)[148]		
Peer education regarding STI/HIV prevention including distribution of educational materials [Morisky 2004][149]	Condom use: OR 1.16 (1.09 -1.24)	STI prevalence: OR 0.66 (0.49-0.88)
Peer educators, safe sex role modeling [Wang 2005][150]		
Men- STI clinic attendees- Group motivational sessions or HIV education sessions [Kalichman 1999][151]	At 3 mo, more I group participants said that theyused condoms almost every time they had sex(69% vs 47%; P = .02) and that they had talkedwith a sex partner about AIDS (92% vs 70%;P = .01), and they reported lower rates ofunprotected vaginal sex (mean = 1.8 vs 7.4;P.05) and more use of condoms duringintercourse (71% vs 54%; P.05). At 6 mo, Igroup participants were more likely to discusscondoms (86% vs 68%; P.05) and plan safersex (93% vs 74%; P = .01).	
[NIMH 1998][152]		
Men- Individual education		Rates of gonorrhea lower at 6-mo follow-up than

Table 9.2.1. HIV/AIDS		
Intervention	**BEHAVIORAL (condom, partners, intercourse/abstinence/initiation, IDU)**	**BIOLOGIC (STDs, HIV, pregnancy)**
versus video versus standard care [Wagstaff 1999][153]		at baseline (34% vs 35%), chlamydia (15% vs 23%), and herpes (3.2% vs 3.7%).
Men-STI clinic attendees- skills training and counseling and practice condom use versus HIV risk education [Kalichman 1997] [154]	No differences between groups in any outcome	
Men- mass communication campaign to promote awareness of avoiding brothels, provision of condoms to CSWs, condom use promotion. [Celentano 1998][155]	Inconsistent condom use significantly less common in 1993 than in 1991 (1991, 16%; 1993, 3%; P<.001).	Significant decline in STI incidence within1991 cohort (18.6 per 100patient-years; P<.0001); borderlinetrend was observed within the 1993cohort (1.7 per 100 patient-years;P = .06).
Women (McCoy 2009)[156]		
Women- Year-long community intervention (workshops, health councils and community activities) versus control (condoms and brochures, also provided to intervention) [Sikkema 2000][157]	Women having unprotected intercourse decreased 12.4% in intervention versus 3.3% in control. Proportion of protected intercourse increased (17%) in intervention versus (3.6%) in control Mean % of women discussing condom use with partner increased 11.9% in intervention versus 6% in control Mean % of women discussing AIDS risk with partner increased 5.4% in intervention versus 3.6% in control	
Peer-led HIV education [Norr 2004][158]	Condom use: OR 1.09 (0.83-1.43)	
Information materials, outreach specialists and peer educators [Lauby 2000][159]		
Microfinance and gender and	14-35 yr old co-residents:	Participiants themselves- aRR experience of IPV in past year = 0·45

Table 9.2.1. HIV/AIDS		
Intervention	**BEHAVIORAL (condom, partners, intercourse/abstinence/initiation, IDU)**	**BIOLOGIC (STDs, HIV, pregnancy)**
relationship education and skills. In phase 2, engaged young people and men, activities focused on HIV and IPV (SFL and IMAGE) [Pronyk 2006][142]	-having been HIV tested= 1·18 (0·73–1·91) -sexual initiation= 1·12 (0·93–1·36) -multiple partners= 1·16 (0·85–3·32) -unprotected sex with casual partner= 1·02 (0·85–1·23) Community residents: -having been HIV tested= 1·09 (0·81–1·47) -sexual initiation= 1·00 (0·86–1·15) -multiple partners= 0·64 (0·19–2·16) -unprotected sex with casual partner= 0·89 (0·66–1·19)	(0·23–0·91) Community residents: HIV incidence 1·06 (0·66–1·69)
Analysed only females in community overall age 14-35- not participants themselves [Pronyk 2008][160]	VCT= aRR 1.64 (1.06–2.56) Multiple partners= 0.95 (0.40–2.27) Unprotected sex with casual partner= 0.76 (0.60–0.96)	
Review of HIV prevention interventions for women in the USA [Mize 2002][161]	<2 months: χ^2 54.75 df 4 (p<0.001) 2-3 months:χ^2 54.11df 20 (p<0.001) >6 months:χ^2 25.63df 8 (p=0.001)	
Outreach sessions that emphasized ethnic and gender pride, HIV risk-reduction information, sexual self-control, assertiveness and communication skills, condom use skills, and developing partner norms supportive of consistent condom use. [DiClemente 1995][162]	Consistent condom use= aOR 2.1 (1.03- 4.15; P=.04), Sexual self-control= aOR 1.9 (1.00-3.60; P=.05) Improved communication= aOR 4.1 (1.67-10.01; P=.002) Sexual assertiveness= aOR 1.8 (1.01-3.27; P=.05) Increased partners' adoption of norms supporting consistent condom use= aOR 2.1 (1.08-3.87; P=.03).	
4 weekly group sessions with HIV/AIDS education and role	No significant difference in mean number of sexual partners between groups or mean frequency of	

Table 9.2.1. HIV/AIDS		
Intervention	**BEHAVIORAL (condom, partners, intercourse/abstinence/initiation, IDU)**	**BIOLOGIC (STDs, HIV, pregnancy)**
playing safe sex negotiation, condom demonstrations, person risk situations identified. Controls had 3 group sessions on nutrition [Kelly 1994][163]	unprotected intercourse. However, condom use did increase significantly with women in the intervention group using condoms during vaginal intercourse 24% more than controls	
HIV +ve women- 4 weekly group sessions with facilitator and peer educator- emphasized gender pride, taught social skills, HIV/AIDS education for seropositive women, and safe sex skills. Control received groups sessions on medication adherence, nutrition and provider interaction [Wingood 2004][164]	fewer episodes of unprotectedvaginal intercourse (1.8 vs. 2.5; P = 0.022); were less likelyto report never using condoms (odds ratio [OR] = 0.27; P = 0.008);	had a lower incidence of STIs (Chlamydia and gonorrhea)(OR = 0.19; P = 0.006);
DRUG USERS		
IDUs- peer mentoring PMI (group and individual) versus movie discussion VDI. Resources and information, male and female condoms distributed to both groups [Purcell 2007][165]	At 12-month follow up aOR 1.01 (0.63-1.61) that PMI versus VDI participants had unprotected vaginal/anal sex with HIV negative or status unknown partners. aOR 0.77 (0.42-1.41) that PMI versus VDI participants shared needles or drug paraphernalia with HIV negative or serostatus unknown partners aOR 1.14 (0.82-1.58) that PMI versus VDI participants utilized HIV care frequently aOR 1.41 (0.66-2.98) that PMI versus VDI participants had >90% adherence to HIV medication in past week	
Peer educators, enhanced	Equipment sharing; OR 0.32 (0.26- 0.40), at second	

Table 9.2.1. HIV/AIDS		
Intervention	**BEHAVIORAL (condom, partners, intercourse/abstinence/initiation, IDU)**	**BIOLOGIC (STDs, HIV, pregnancy)**
education session at clinic, harm reduction kits. Free HIV counseling and testing and needle exchange [Broadhead 2006][166]	study site: 0.54 (0.34-0.86) Condom use: OR 1.45 (1.01- 2.09), at second site 1.06 (0.70-1.63)	
Peer education, information material, needle exchange and condoms [Hammett 2006][167]	Equipment sharing: OR 0.09 (0.07- 0.12), at second study site 0.46 (0.35- 0.61	
Peer education [Li 2001][168]	Equipment sharing: OR 0.88 (0.65- 1.18) Condom use: 1.97 (1.45-2.68)	
Peer education, testing, information material, needle exchange and condoms [Sergeyev 1999][169]	Equipment sharing: OR 0.40 (0.27-0.59)	

Preventing HIV, STIs and pregnancy in adolescents- What works[170-172]
• Tailor approach to subpopulation • Cognitive and social theory-based interventions more likely to change behavior • Interventions work in community, clinics, schools and special settings • Target specific behavioral changes, especially condom use during vaginal intercourse • Although there is conflicting evidence for duration and intensity of intervention, multi-tiered interventions may be more effective- ie. school-based abstinence plus education plus community youth development programs • Involve communities and families in reducing adolescent risk behavior • Incorporate intervention components to maintain behavior change • Use experiential and interactive methods • Develop skills and skill efficacy- especially to verbally negotiate safe behavior- through practice and preparedness • Peer education (formal or informal) in groups and through peer leadership • Sexual and reproductive health services easily accessible, and included in program • Discuss myths and concerns in a straightforward manner, and enable adolescents to rationalize decisions • Respect and build values, autonomy and worth, relationships • Present other pleasurable activities as alternatives to high-risk behavior • View sexual and other risk behaviors in the context of the stage of adolescence rather than in isolation • Trained facilitators • Conducive environment- confidential, free of judgement

Conclusion

Most of the literature in this area focuses on prevention through antiretroviral therapy (zidovudine) *during pregnancy* and lactation. However, there is a 25% chance of perinatal transmission, and antiretroviral therapy may cause side effects for the mother and fetus. As more women are infected, and treatment prevents them from developing AIDS, there will increasingly be HIV-positive women who wish to become pregnant. In addition to optimizing their health status, HIV-positive women must have access to sexual and reproductive health services so that they can be counseled about their reproductive options to prevent transmission to their partners and newborns (Wilcher 2009).[173]

While there is a definite need for more HIV prevention interventions that are specifically effective in women, reducing HIV incidence in the general population will decrease the probability that women are exposed to HIV. Ongoing trials may provide evidence for pre-exposure prophylaxis and prove that treatment is effective as prevention. Men who are circumcised halve their chances of becoming infected, and of further transmitting it to their female partners. Condom use is scientifically proven to radically diminish the risk of HIV transmission (85% risk reduction), and condoms have the additional advantage of protecting against other STIs and unintended pregnancy. Since other contraceptive methods, especially those that are female-dependent, are not effective, there is a real need for methods to increase condom use among serodiscordant partners and other individuals that are high-risk for HIV transmission. Voluntary counseling and testing is not shown to reduce the risk of transmission through unprotected intercourse, however it is still advocated for individuals to determine their serostatus, in order to better protect themselves and others.

Sexually transmitted infections, especially ulcerative types such as HSV-2, significantly increase the risk of becoming HIV-infected. However, pooling results of participants in

randomized trials who only differed from the controls in terms of STI management, did not yield significant evidence of effect (RR 0.83; 95% CI 0.63-1.09). Screening and management of STIs is still promoted, because individuals with STIs have both increased biologic and behavioral risk.

The components of behavioral interventions that increase likelihood of success in preventing HIV have been documented; however non-uniform reporting of outcomes limits comparison of effect for populations and high-risk groups. Even in endemic regions, such as sub-Saharan Africa, there have been few interventions carried out in youth, who are at high-risk of HIV infection.[174]Proof of efficacy must now be translated into effectiveness, through replication of successful interventions in various contextual settings and target populations, and reporting of standardized and biologic outcomes (especially HIV incidence).

Key messages

- The HIV pandemic contributes significantly to worldwide maternal mortality. Reducing the burden of disease in women of reproductive age could reduce transmission of the virus to newborns, as well as improve the health of women during pregnancy and in the first year after birth.
- Ongoing trials may provide urgently needed evidence as to whether prophylactic or therapeutic use of antiretroviral drugs is safe and effective in women of reproductive age, and improves MNCH outcomes. Thus far, it seems that antiretroviral therapy is successful in preventing transmission to partners and newborns if viral load is significantly suppressed.
- Male circumcision reduces the chances of HIV infection by 51%, but has not been proven to reduce transmission to female partners of HIV-positive men
- Condom use reduces the risk of HIV by 85%. Microbicides and other female-dependent contraceptive methods do not significantly lower risk. Condom use should be promoted among all couples who are serodiscordant or HIV-positive, even during pregnancy. Couples should be made aware of reproductive options that reduce the risk of transmission to their partner and newborns.
- Voluntary counseling and testing does not lower the risk of transmission through unprotected intercourse (RR 1.10, 0.48-2.55). However, public health efforts should still encourage VCT so that people are aware of their HIV-status. Further risk-aversion studies and subsequent trials should assess whether VCT can reduce HIV incidence or risk behaviors in various target populations.
- Management of STIs has been promoted as a risk-reduction strategy, however, we found an insignificant reduction in HIV incidence with improved STI screening and treatment (RR 0.83; 95% CI 0.63-1.09). Comparing outcomes in different populations, or of individual STIs (especially HSV-2) might yield further evidence of effect
- Behavioral interventions show efficacy in high-risk groups such as adolescents. However, replication of successful programs and standardized outcome reporting will be necessary to show consistent effect in reducing high risk behaviors in those populations who are at higher risk or more vulnerable, including adolescents, women and injection drug users.

9.3. Vaccine usage pre-conceptionally

Background

Immunization during the preconception period can prevent many diseases which may have serious consequences or even prove fatal to the mother ornewborn. For example, rubella exposure during early pregnancy can result in pregnancy loss, stillbirths or congenital rubella syndrome. Further, live-virus vaccines are recommended in the preconception period because they cannot be safely administered during pregnancy; others have maternal benefits because they avoid treatment that might have adverse consequences for the pregnancy.

Scope of intervention

Much research has been conducted on the effect of maternal intra-pregnancy infections on pregnancy outcomes. Work has also been done on the efficacy of immunization of women during pregnancy. We intended to look at the feasibility of vaccination of women while they are contemplating a pregnancy. We focused on how this may further decrease the morbidity and mortality associated with gestational infections and how such interventions could be successfully implemented.

The content of preconception care- immunization

- Women of reproductive age should be made aware of the risks of contracting an infectious disease during pregnancy, and the risk of adverse outcomes in the newborn- especially neonatal tetanus, congenital rubella syndrome, congenital varicella and Hepatitis B.
- All women of reproductive age should have their immunization status for tetanus (Tdap) reviewed annually and updated as indicated.
- At any contact with the healthcare system, women of reproductive age should be asked whether they have received the full course of immunization for Hepatitis B, and providers should initiate the primary series or give booster vaccines as indicated
- Girls aged 9-26 (who presumably have not been sexually active) should be immunized against HPV
- Healthcare providers should screen women for previous MMR and varicella vaccination. Women of reproductive age should provide evidence (documented history of previous vaccination or previous infection that is verified by a healthcare provider, or laboratory evidence of immunity). Non-immune women should be vaccinated and counseled to avoid pregnancy for at least 3 months after receiving the vaccine.
- Women who will be pregnant during flu season and women who are at greater risk of complications (such as those who have cardiopulmonary disease) from influenza infection should also be vaccinated against influenza (strain-specific for that year)

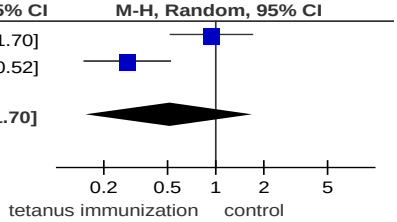
Impact estimates

We found evidence from 2 **intervention**trials for the effectiveness of tetanus toxoid in women of child-bearing age. Analysis showed that vaccination against tetanus averted a significantnumber of neonatal deaths (including those specifically due to tetanus) when compared to placebo in women receiving more than 1 dose of the vaccine (OR 0.28; 95% CI: 0.15-0.52) (**Figure 9.3.1**); (OR 0.02; 95% CI: 0.00-0.28) (**Figure 9.3.2**) respectively. This was also true for tetanus-diphtheria toxoid (OR 0.52; 95% CI: 0.29-0.91) (**Figure 9.3.3**). These findingswere confirmed by observational data from mass immunization programs of several countries[175-177] and a review.[178] We didn't find any trial comparing preconception vaccination with immunization done during pregnancy.

Figure 9.3.1: women immunized with Tetanus toxoid versus influenza vaccine and Odds of neonatal deaths

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
1 Dose	22	224	28	270	50.3%	0.94 [0.52, 1.70]
2-3 Doses	14	341	46	347	49.7%	0.28 [0.15, 0.52]
Total (95% CI)		**565**		**617**	**100.0%**	**0.52 [0.16, 1.70]**
Total events	36		74			

Heterogeneity: Tau² = 0.64; Chi² = 7.78, df = 1 (P = 0.005); I² = 87%
Test for overall effect: Z = 1.09 (P = 0.28)

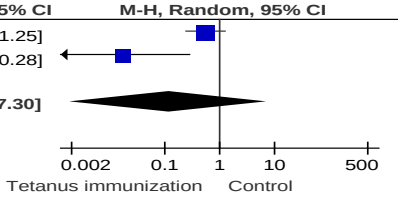


Citation to included study:
Newell 1966[179]

Figure 9.3.2: women immunized with Tetanus toxoid versus influenza vaccine and odds of tetanus specific neonatal deaths

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
1 Dose	9	224	19	270	55.2%	0.55 [0.25, 1.25]
2-3 Doses	0	341	27	347	44.8%	0.02 [0.00, 0.28]
Total (95% CI)		**565**		**617**	**100.0%**	**0.12 [0.00, 7.30]**
Total events	9		46			

Heterogeneity: Tau² = 7.91; Chi² = 8.14, df = 1 (P = 0.004); I² = 88%
Test for overall effect: Z = 1.02 (P = 0.31)

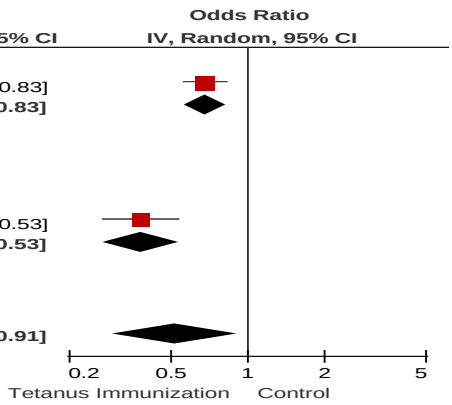


Citation to included study:
Newell 1966[179]

Figure 9.3.3: women immunized with Tetanus Diphtheria toxoid versus Cholera toxoid and odds of neonatal tetanus deaths

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
17.3.1 Neonatal Mortality				
Black 1980	-0.386	0.099	53.0%	0.68 [0.56, 0.83]
Subtotal (95% CI)			**53.0%**	**0.68 [0.56, 0.83]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 3.90 (P < 0.0001)				
17.3.2 4-14 day Neonatal Mortality				
Black 1980	-0.968	0.174	47.0%	0.38 [0.27, 0.53]
Subtotal (95% CI)			**47.0%**	**0.38 [0.27, 0.53]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 5.56 (P < 0.00001)				
Total (95% CI)			**100.0%**	**0.52 [0.29, 0.91]**

Heterogeneity: Tau² = 0.15; Chi² = 8.45, df = 1 (P = 0.004); I² = 88%
Test for overall effect: Z = 2.27 (P = 0.02)



Citation to included study:
Black 1980[180]

Congenital rubella syndrome is a devastating disease, and a vaccine against rubella was developed in 1970. The evidence for preconception vaccination against rubella was from separate **interventional** studies for screening and vaccination, and from **observational** data of national vaccination campaigns. Antibody screening is not advised before vaccination since it has a high rate of false negatives. Premarital screening increases the rates of vaccination only when providers advise vaccination and offer it directly after counseling, or other motivation is provided with screening, such as a letter or brochure. National vaccination campaigns for girls and women are cost-

effective or cost-saving, and even if vaccination occurs within a few months before preconception, the risk of the fetus developing congenital rubella syndrome is at most 1.7%. In only one trial was the rate of neonatal death higher in the vaccination arm (1.2% versus 0% in controls). Finally, if women are found to be non-immune after delivery, it is advisable that they be vaccinated in the postpartum period to provide protection for the subsequent pregnancy.

The advantage of administering the HPV vaccine to prevent cervical cancer means that girls must be vaccinated before the onset of sexual activity. HPV vaccination provides further advantage, however, to young women and their newborns by reducing the possibility of preterm birth due to cervical incompetence and the rate of laryngeal papillomatosis in the newborn. In phase 3 **clinical trial** and post-licensure surveillance, the only significant difference in neonatal outcomes was found for miscarriage when Cervarix was administered within 3 months preconception.

Table 9.3.1: Interventions for vaccine

Intervention	**Outcomes**
Tetanus immunization	**Neonatal mortality:**
Yusuf 1991[175]: (two doses of tetanus toxoid)	85% reduction in neonatal tetanus mortality during this period, from 32.1/1000 live births to 4.9/1000 live births.
Koenig 1998[177]: (1 or 2 doses of 0.5 mL adult-dose aluminum-phosphate- adsorbed tetanus-diphtheria toxoid)- RCT	Children of women who received either 1 or 2 injections of tetanus toxoid experienced 4- to 14-day mortality levels consistently lower than those of children of unimmunized mothers. Analysis of neonatal-tetanus-related mortality showed that 2 injections of tetanus toxoid provided significant protection for subsequent durations of up to 12 or 13 years.
Black 1980[180]: (two doses of aluminum-adsorbed tetanus-diphtheria toxoid)	Reduced neonatal mortality by one-third during a period of9-32 months after vaccination. The reduction in mortality rate was attributable almost entirely to a 75% lower mortality rate among 4-14-day-old infants, when tetanus was the predominant cause of death. In the period up to 20 months following vaccination, the reduction in deaths among 4-14-day-old infants after a single dose of tetanus-diphtheria toxoid was about the same as that after two doses. However, beyond 20 months a single dose did not appear to provide protection.
Newell 1966[179]: (RCT to test the effectiveness of one-dose and two or three-dose tetanus toxoid)	The RR of death after one dose was 0.57 (95% CI 0.26 to 1.24) and the vaccine effectiveness was 43% (95% CI -24% to 74%). The RR of death after 2-3 dose course was 0.02 (95%CI 0.00 to 0.30) and the vaccine effectiveness was 98% (95% CI 70% to 100%).
Rubella immunization	
[Mayson-White 1976 Obs- antibody testing in family planning clinics – abstract only][181]	Acceptance rate 50%. Of the 100 women tested, 15 were not immune and 8 of these were subsequently vaccinated. The cost of the service was estimated to be £1-50 per woman, or approximately £5000 to prevent one case of congenital rubella. On this basis the assessment of rubella immunity in women using reliable contraception is considered to be feasible

Table 9.3.1: Interventions for vaccine	
Intervention	**Outcomes**
[Lieberman 1981 Obs- premarital screening legally mandated – abstract only][182]	Of 203 susceptible women detected, 37% had been immunized, 21% were pregnant or infertile, and 42% were eligible for immunization but had not received vaccine. Premarital immunization occurred most frequently when physicians advised and directly offered vaccine. 24% of physicians did NOT immunize their rubella-susceptible patients detected by premarital screening.
[Bart 1985 Obs- exposure -3 to +3 months around conception][183]	119 women susceptible to rubella received RA27/3 vaccine, 94 received either Cendehill or HPV-77 vaccine, and one received a vaccine of unknown strain in the 3 months before or after conception. They gave birth to 216 living infants free of congenital rubella syndrome (CRS). The maximum theoretical risk for CRS for these infants was 1.7%. 4 of these infants born to susceptible women had laboratory evidence of subclinical infection but were normal at birth and at follow-up. Rubella virus was isolated from the products of conception for only 1 of 32 cases involving susceptible women who received RA27/3 vaccine
[Enders 1985 Obs- * preconception and during pregnancy][184]	Of 365 women so far (in 59%, vaccination within two weeks before and up to six weeks after conception), 194infants have been born without signs of congenital rubella syndrome. 7.7% of seronegative postpubertal women had a history of vaccination. The rate of seronegativity among pregnant women with a history of vaccination is 2.4%, and among women without a history of vaccination, 10%. However, low positive titers of antibody occurred more frequently in women with a history of vaccination (22.8%)than in women without vaccination (9.5%, P < .005).
[Gudnadottir 1985 Obs and cost-analysis- selective vaccination of seronegative women and teenage girls][185]	Nationwide vaccination increased immunity levels from 80-90% (natural immunity among teenagers and older residents)to 98.8% in the group aged 14-20 years and 97.2% in the group aged 21-35 years. Estimated cumulative state expenses for extra education and financial help to *one* such rubella victim is almost equal to the *total* cost of the rubella vaccine campaign that was carried out among Icelandic females during 1979-1981. Direct costs during epidemic amounted to $113,155 versus total cost of screening and vaccination, $83,000.
[Menser 1985 Obs- national vaccination program for schoolgirls aged 10-14 yrs, and nonpregnant or postpartum seronegative women in family planning and obstetric clinics][186]	National incidence of congenital rubella decreased from a mean of at least 120 cases annually (1 in 2000live births) to <20 6 yrs after program. Ten years after program, 96% of 8,226 pregnant women were seropositive, as compared with only 82% of a similar group of women pre-intervention.
[Miller 1985 Obs- vaccination for school-age girls and screening + vaccination for women of childbearing age][187]	Number of seronegative women fell from 5% after an epidemic to 3.5% the year before the vaccination campaign to 2.7% the year after. In 1984, 4.2% of nulliparous women were susceptible compared with 1.4% of women in their second or subsequent pregnancy. 85% of pregnant women screened and found to be non-immune were vaccinated post partum before leaving hospital. However only 65% of non-pregnant women who were screened were also vaccinated.

Table 9.3.1: Interventions for vaccine	
Intervention	**Outcomes**
[Serdula 1986 controlled trial- premarital screening and vaccination, motivational letter][188]	Screening identified 21% of those women who required testing as susceptible. At 9 month follow-up Rate ratio 1.3 (95% CI 1.1-1.6) that women who received motivational letter were immunized compared to controls.
[Sewell 1986 Obs- premarital screening and vaccination][189]	Screening identified 10.8% of those women who were tested as susceptible. Of the thirty-three percent completing the survey, 26.8% were unaware of their test results; however, 46.8% of the rubella-susceptible women had received a rubella vaccination after they were informed of the results (largely due to physician advice and a health brochure on congenital rubella syndrome). 1/3 of those who were not vaccinated received no information from their physicians.
[Vogt 1985 Obs- premarital screening and vaccination, letter to both patient and physician if susceptible][190]	After the first screening 37% of susceptible women had been vaccinated. Of those women who were pregnant and therefore not vaccinated, a reminder 9 months later resulted in 25% being vaccinated.
[Su 2002 CS- nationwide vaccination for teen girls and women of childbearing age][191] Taiwan	Seronegative rate was 5.7% after both vaccination programs. The susceptible rate was much lower among women who were covered by both programs than women who were not (4% versus 23%, P < 0.001) ie. teen and young women. However, there were still women who were susceptible.
[Wang 2007 CS- nationwide vaccination for teen girls and women of childbearing age, as well as young children][192] Taiwan	For the age groups of 15–17, seropositivity was 96.8% 19–22, seropositivity was 92.4% 25–33, seropositivity was 81.4% 34–44, seropositivity was 89.5% (rates were slightly lower among teen and young women and higher among women >25 yrs compared to Su 2002)
[Bar-Oz 2004 Obs controlled- exposure -3 to +3 months around conception][193]	Relative risk for vaccinated versus control group for spontaneous abortion= 0.74 (0.25–2.3) Relative risk for preterm birth= 0.93 (0.32–2.7) Relative risk for malformations= 1.08 (0.21–5.5) Relative risk for induced abortion= 2.09 (1.8–2.43) Neonatal death 1.2% vaccinated group versus 0% control
[Nasiri 2009 Obs- exposure 1-4 weeks pre or postconception][194]	The median gestational age was 38 wk. 6.7% of neonates were Preterm. Mean neonatal weight was 3108±581.75 grams. None of the neonates had evidence of IUGR, cardiovascular, ophthalmic, CNS, or other CRS anomalies at birth and one month later. IgM anti- rubella antibody was negative in all neonates.
HPV immunization	
[Garland 2009- combined analysis of phase III clinical trials of Gardasil][195]	Risk difference for congenital or other anomalies= 0.7 (-0.2 to 1.8) Risk difference for other medical conditions= 1.1 (-0.3 to 2.5) Risk difference for Caesarean delivery= 1.2 (-2.0 to 4.5) Risk difference for spontaneous abortion= -0.1 (-5.6 to 5.3) Risk difference for late fetal death= 0.5 (-1.4 to 2.6) Ectopic pregnancy= 0.1% vaccinated versus 0.15% placebo No significant clustering associated with time from vaccination to conception (from <1 to >36 months)
[Dana 2010- Gardasil postlicensure safety registry in USA, Canada, France- vaccine exposure up to 1 month preconception OR	96% of the newborns were normal. The overall rate of spontaneous abortion among these prospective cases was 6.9 per 100 outcomes. The rate of major birth malformations in

Table 9.3.1: Interventions for vaccine	
Intervention	**Outcomes**
during pregnancy][196]	the pregnancy registry was 2.2 per 100 live-born neonates (95% CI, 1.05-4.05). Fetal deaths 1.5 per 100 outcomes (95% CI, 0.60-3.09).
[Wacholder 2010- combined analysis of phase III clinical trials of Cervarix][197]	Miscarriage 11.5% in HPV arm and 10.2% in the control arm (p=0.16) If conception within three months after nearest vaccination miscarriages were 14.7% in the HPV vaccine arm and 9.1% in the control arm (p=0.031)

Conclusion

Tetanus vaccination (with Tdap) of women of childbearing age has been found to be effective in reducing neonatal deaths from the disease (OR 0.52), especially when immunization is complete. Immunization during pregnancy with tetanus toxoid is the general practice in current obstetrics guidelines. We recommend pre-pregnancy tetanus immunization of women to reduce the overall burden of tetanus-related mortality.

All women of reproductive age should receive immunization against rubella if they have no evidence of immunity. Rubella vaccination before pregnancy is safe, even in the periconception period, and protects newborns from congenital rubella syndrome.

Clinical trials of HPV vaccination in the preconception period have been shown to be safe, and as national campaigns immunize more women, further evidence of benefit on preterm birth might be found.

The effects of prepregnancy immunizationon MNCH outcomes need to be compared with immunization during pregnancy. Also the duration for which these may be efficacious should be investigated, so that if necessary, women receive booster vaccinations before subsequent pregnancies.

Key messages

- Neonatal deaths are reduced by 48% by tetanus toxoid given to women of reproductive age. A single dose in preconception period may not be effective in reducing either neonatal death in general or neonatal tetanus-related deaths, 2-3 doses reduce the rates by 72% and 98% respectively.
- Tetanus-diphtheria toxoid significantly reduces overall neonatal tetanus-related mortality by 32% and 4-14 day tetanus mortality by 62%.
- The Rubella vaccine is safe and effective in protecting against congenital rubella syndrome.
- The HPV vaccine when given before pregnancy is safe, but does not reduce the rates of adverse neonatal outcomes (compared to women in the control group)
- Future research should compare the effect of vaccination before pregnancy with vaccination during pregnancy for tetanus and hepatitis B. More evidence is also needed as to whether preconception vaccines have secondary advantages on MNCH outcomes (beyond protection against the specific infection)

9.4. Periodontal disease and dental caries

Background

Preterm birth and low birth weight is a leading cause of neonatal and infant mortality and morbidity. In attempting to reduce this burden of disease, it was first necessary to understand the mechanism by which preterm birth occurs; Goldenberg [198] was the first to suggest that infection of the maternal-fetal membranes was responsible for early spontaneous preterm birth. While it was easily conceivable that direct infection, for example from bacterial vaginosis, could lead to preterm labour, around the same time Offenbacher[199] demonstrated that periodontitis was also a risk factor for preterm birth.

Scope of intervention

Given the surprisingly high odds (OR 7.5) that maternal periodontal disease could result in preterm low birth weight babies, researchers sought to confirm this effect and examine whether improving maternal oral health would improve pregnancy outcomes. Systematic reviews incorporating epidemiologic and interventional evidence have not consistently supported the association.[200-203] Meta-analyses of **risk aversion**, however, seem to acknowledge the relationship (ORs for association with preterm low birth weight ranging from 2.83-4.28; and ORs for association with other adverse pregnancy outcomes including miscarriage, IUGR, GDM and preeclampsia range from 1.10-20.0) with reservation.[204-206] Further, clinical trials that assess periodontal treatment have found differential effects on pregnancy outcomes.[207] Reviews[208, 209] seeking to explain these inconsistencies have cited lack of uniform definitions for exposure and outcomes; failure to control for confounders that are known risk factors for preterm birth; the use of just a single session of treatment; and the possibility that ameliorating this risk might only improve outcomes in a subpopulation.

Since periodontal infection is presumably chronic, it is reasonable to suppose that prevention and/or treatment before pregnancy might help women maintain good oral health during pregnancy and prevent adverse outcomes. However, most risk-aversion studies and clinical trials have been conducted during pregnancy.

Impact estimates

Oittinen 2005[210] was the only study found that exclusively focused on prepregnancy periodontal infection and adverse pregnancy outcome (miscarriage and preterm birth not disaggregated) and showed an OR= 5.5 (95% confidence interval 1.4–21.2; P 0.014). Interestingly they found no effect for dental caries (OR 1.0). A cohort study[211] was excluded since periodontal treatment or prevention were not explicity stated as being provided before pregnancy. Currently, preconception screening and treatment of periodontal disease can only be recommended to improve women's oral health.

Conclusion

While it is tempting to extrapolate the evidence for periodontal treatment during pregnancy to the preconception period, high level evidence is still lacking to prove that prevention or treatment of periodontal disease before or during pregnancy consistently prevents adverse outcomes. Further large-scale randomized controlled trials are

necessary to establish that such therapy is warranted. Further, it must be noted that like many other interventions, such therapy might need to be a process that is instituted before, but continues throughout pregnancy, in order to achieve the maximum benefit.

Key messages

- Poor oral health has been shown to be a risk factor for adverse pregnancy outcomes, especially preterm low birth weight. However, stronger evidence is needed to define what constitutes "poor oral health" and in which subpopulations prevention and treatment of periodontal disease will be most beneficial.
- Virtually no evidence has been generated to show whether periodontal disease present *before* pregnancy is also a risk for adverse outcomes, or whether treatment at this time could reduce the risk of preterm low birth weight.

9.5. Cytomegalovirus

Background

Cytomegalovirus is the most common congenital viral infection, and is a leading cause of congenital deafness and neurodevelopmental disability. Between 0.2% and 2.5% of all live newborns are infected.[212] 10% of these will be symptomatic at birth, and of the remaining, another 10% will also go on to develop disease sequelae.[213] Managing children with the permanent consequences of congenital CMV costs over $300,000 annually per child, and more children suffer from such outcomes each year than from any other congenital defect.[212] The annual seroconversion rate for pregnant women is 2.3%,[214] and the greatest risk is incurred by newborns whose mothers acquire the primary infection during pregnancy (1% of pregnancies) since the intrauterine transmission rate is 40% or higher and decreases with increasing gestational age.[215]

Scope of intervention

The propensity for newborns to acquire the infection from their mothers and the devastating consequences of congenital CMV infection has motivated researchers to try and develop a vaccine. Such efforts have been hampered, however, by confusion as to whether maternal immunity actually provides protection for the fetus- 60% of infants with CMV are born to mothers who were immune before pregnancy.[216] Our purpose, therefore, was to examine the neonatal outcomes for women who were infected prepregnancy, and therefore developed immunity to CMV.

Preconception care for women with cytomegalovirus infection
• Women should be made aware that CMV is the most common viral infection in pregnancy and that it places newborns at risk of congenital hearing loss and other neurodevelopmental problems • Women (especially those who have or work with young children) should be counseled to avoid exposure to young children's saliva and urine in the preconception period and during early pregnancy, and to was hands thoroughly if such exposure occurs. If primary exposure occurs, women should delay becoming pregnant for 6 months • Women should understand the risks of contracting the infection and transmission to the fetus (1% of all pregnant women have primary infection, transmission greater if contracted in early pregnancy and less if contracted preconceptionally, most children are asymptomatic at birth however just over 10% of those with infected mothers will develop permanent sequelae) • Counsel women that if infected, they can be screened with serological testing and ultrasound

scanning, and that fetal infection can be confirmed through amniotic fluid PCR testing after 21 weeks of pregnancy. As for treatment, hyperimmune globulin has only been tested in one trial.

Impact estimates

The studies pertaining to preconceptional immunity to CMV and fetal infection were all **observational** (including cohort) studies. In one study,[217] of 46 newborns to women with preconceptional immunity, 16 were infected with CMV. 62% of the mothers with infected infants versus 13% of those with uninfected infants had acquired new antibody specificities, indicating that maternal reinfection with a different strain of CMV could still lead to congenital infection.

Fowler (2003)[218] showed that preconceptional immunity (seropositive at a previous birth) resulted in a significantly lowered risk (aRR 0.31) of infection in the newborn. Shaamash (2003)[219] also showed that preconceptional (not clearly defined, since blood sample taken during antenatal visit) immunity ameliorates disease, even if it does not block transmission with infants of 132 seropositive women all being asymptomatic- this includes 2 infant-mother pairs with recent infection.

Further research tried to delineate whether the timing of the primary infection in relation to conception was a risk factor: Daiminger 2005[220] showed that women with primary infection 2 months to 2 weeks prepregnancy did not have infected infants, whereas women with primary infection in 1 week before to 1 month after conception had similar rates of transmission as those women acquiring CMV during pregnancy. These results are somewhat misleading, however, since exposure for 10 women could not be definitively categorized as preconceptional or periconceptional. The distinction between primary preconceptional (3 months before) and periconceptional (1 month after) exposure was also made by Revello (2002)[221] with a higher rate of congenital infection in the periconceptional exposure group. Fowler (2004)[222] also demonstrated that among mothers who seroconverted between pregnancies, the risk was greatest for those with birth intervals <24 months. Moreover, the risk may also depend on endemicity, indicated by maternal seroprevalence rates.[223]

More recently, Revello (2006)[224] showed that of 14 women who had primary CMV infection 2 weeks to 4.5 months before pregnancy, only 1 had an infected newborn (another 1 terminated her pregnancy). Hadar (2010)[225] confirmed these results (periconception defined as 1 month prior to 3 weeks after conception) in a larger group of women with primary infection. with Zalel (2008)[226] however, studied 6 women with preconceptional immunity, all of whom had severely infected fetuses, proving that recurrent infection can be as hazardous as primary infection in pregnancy.

Conclusion

Although the evidence is still far from concrete, it appears that preconceptional immunity does provide some protection to the fetus from CMV infection. However, recurrent or periconceptional maternal infection are as risky as infection during pregnancy. For the same reason, and due to cost constraints, maternal screening is also not advised unless the woman is symptomatic or there is evidence of fetal infection. While observational studies with larger sample sizes may provide clarity as to whether

a vaccine could be effective, women of reproductive age should be counseled on how to reduce their exposure to CMV around pregnancy.[212, 215] Young children are the main source of CMV infection, and therefore women planning to conceive should be counseled to avoid contact with children's saliva or urine, and wash hands thoroughly if such contact occurs. Further, women of reproductive age diagnosed with primary CMV infection should be counseled to delay pregnancy, although the minimum interval is not yet clear.[213] Some evidence also suggests that CMV hyperimmune globulin could be administered for both therapeutic and preventive purposes.[227]

Key messages

- Cytomegalovirus is the most common congenital viral infection, and may result in sensorineural hearing loss or intellectual disability in infancy
- Women who acquire **primary CMV infection preconceptionally are at less risk** of transmitting the virus to their newborns than those who become infected during pregnancy. However, women who are **infected at conception or very early in pregnancy or have recurrent infection in pregnancy have a high rate of transmission** to the fetus.
- Women who are planning a pregnancy or already pregnant should be counseled to avoid contact with young children's saliva or urine, and practice strict hygiene if such contact occurs. If women become infected with CMV, they should wait 6 months before attempting to become pregnant.
- Screening and CMV hyperimmune globulin administration have currently been shown as effective only for women with confirmed evidence of CMV infection in pregnancy.
- A vaccine against CMV has not been developed to date, since it is unclear whether immunity before pregnancy would protect the newborn from congenital infection.
- Effective strategies to increase awareness of CMV and the methods to prevent its transmission among women of reproductive age are needed, as well as to improve healthcare providers' counseling regarding the risk of transmission and newborn outcomes

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Section X

10. Substance abuse prevention and life style changes

10.1. Reducing periconceptional caffeine intake

Background

Caffeine consumption during pregnancy has been suspected to increase the risk of spontaneous abortions and low birth weight. However, the current epidemiologic studies provide conflicting evidence. Those that show a small but significant increase in the rates of these adverse outcomes may fail to completely dissociate the possible effects of confounders[1-3] while others call any such association to be an artifact[4-6] or have no positive association.[7-10] Still others claim to have found a dose-related association with moderate levels of intake being unlikely to increase the risk of SAB[11] but heavy consumption being associated with increased risk of spontaneous abortion,[12-18] fetal death,[14, 19, 20] and low birth weights/small for gestational age babies.[21-26] Case control studies for various congenital anomalies do not provide sufficient convincing evidence for a strong linkage with prenatal caffeine intake[27] with the body of evidence for any individual malformation being limited. A negative association was reported between caffeine intake during pregnancy and heavy weight babies.[28]

With regards to preconception caffeine intake, some studies have concluded that a high daily intake of caffeine prior to pregnancy led to an increased risk of spontaneous abortion[2, 29, 30] while others reported no association.[12]

Scope of intervention

Given that caffeine intake during pregnancy has the ability to increase the risk of adverse fetal outcomes and that consumption may decrease to lower than pre-pregnancy levels[21] it is imperative to address the issue before the crucial period of organogenesis and hence intervene preconception. Caffeine consumption tends to decrease during the early weeks of pregnancy, coinciding with increasing pregnancy symptoms and aversions.[31-33]

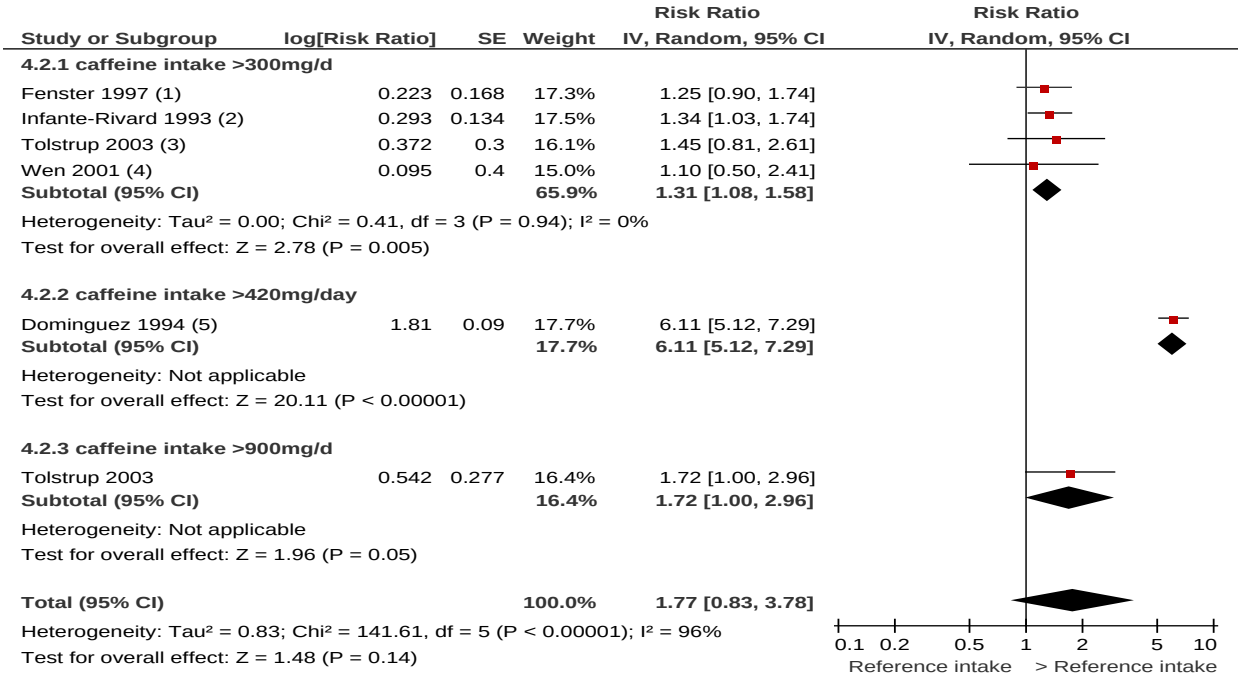
Preconception care requires early identification of women who consume caffeine more than occasionally. Such women need to be informed of the potential risks of adverse pregnancy outcomes associated with caffeine intake (spontaneous abortion, low birth-weight). Cutting down/abstinence from caffeine should be the goal well in advance of a conception.

Impact estimates

We found a total of 6 studies on the effect of preconception caffeine intake on fetal loss. We pooled data from these in terms of mg/d of caffeine consumed. One study [30] despite showing a non-significant 33% elevation in risk of fetal loss with >3 cups/d of coffee, failed to provide intake in terms of grams of caffeine ingested was hence excluded from the analysis. For the remaining 5 studies, every study had a different referent level of

intake. In order to analyse the data from these we categorized intake level into >300mg/day, >420mg/day and >900mg/day. For an intake of >300mg compared to the referent intake (for all practical purposes we took referent intake <150mg/day) of caffeine per day before conception we found a strong statistically significant association with fetal loss (RR 1.31; 95% CI: 1.08-1.58). However, this may be falsely so due to unavailability of disaggregated data and our assumption of a referent intake instead of any of the greatly differing ones used in the studies. Also if we remove the only retrospective cohort[34]. from this pool the impact of exposure becomes insignificant (RR 1.27; 95% CI: 0.97-1.66). There was only one study that studied at the effect of >420mg/d[35] This found a strong positive association between preconception caffeine consumption of >420mg/d compared to <150mg/d (RR 6.11; 95% CI: 5.12-7.29). Similarly Tolstrup et al.[29] found a 72% increase in the risk of fetal loss with an intake of >900mg/d (compared to its reference intake of <75mg/d). Although our forrest plot cannot be interpreted for a dose-response relationship due to limitations with regards to a comparison group, all the individual studies reported a non-significant increase in risk as the daily caffeine consumption increased (**Figure 10.1.1**).

Figure 10.1.1: Periconception Caffeine intake and risk of Spontaneous abortions



(1) Referent intake: 0 mg/d; pregnant women; Prospective cohort
(2) Reference intake: 48 mg/d. data taken for >321 g/d; Retrospective cohort
(3) Reference intake < 75mg/day; Women from the general population; Prospective Cohort
(4) Reference intake < 20mg/day; Prepregnancy; Prospective Cohort
(5) Reference intake < 140mg/day; Female hospital workers; Retrospective Cohort

Citations to the included studies:
Fenster 1997[2], Tolstup 2003[29], wen 2001[12], Dominguez 1994[35]

Conclusion

Caffeine consumption during pregnancy leads to adverse pregnancy related outcomes. Our analysis shows that heavy preconception consumption of >300mg/d significantly

Table 10.1.1: Summary impact estimates for Preconception caffeine consumption			
Maternal	**Pregnancy**	**Newborn**	**Infant**
	<u>Down's affected pregnancy</u>: Periconceptional maternal consumption of four or more cups of coffee per day was inversely associated (OR = 0.63; 95% CI: 0.41, 0.96). These results suggest that among nonsmoking mothers, high coffee consumption is more likely to reduce the viability of a Down syndrome conceptus than that of a normal conceptus. [Torfs 2000][36]	**<u>Spontaneous Abortions</u>**: Compared to women with a pre-pregnancy intake of <75 mg caffeine per day, the adjusted OR for spontaneous abortion was 1.26, 1.45, 1.44 and 1.72 for a pre-pregnancy intake on 75±300, 301±500, 501±900 and >900 mg caffeine per day respectively (P = 0.05 for trend) [Tolstrup 2003][29] Caffeine consumption before pregnancy did not increase the risk of spontaneous abortion, but caffeine consumption during the first trimester of the pregnancy appeared to be associated with an elevated risk. >300mg/d of preconception caffeine intake compared to the reference of 20 mg/day RR 1.1 (0.5-2.4 CI) [Wen 2001][12] The risk by coffee consumption increased on average by a factor of 1.017 (1.004-1.030) for each cup per day; this trend was also statistically significant (P = .01). [Armstrong 1992][37] The following adjusted ORs of spontaneous abortion by caffeine consumption were calculated: 141-280 mg/day, 2.20 (1.22-3.96); 281-420 mg/day, 4.81 (2.28-10.14) and 421 or more, 15.43 (7.38- 32.43); p < 0.05 [Dominguez 1994][35] **Others: Anorectal atresia:** Compared with the lowest level of caffeine intake (<10 mg/day), the association for the highest caffeine intake (> or =300 mg/day) was OR = 1.5 [95% CI 1.0, 2.2]. [Miller 2009][38] Adjusted hazard ratio (aHR) of 1.42 (95% CI 0.93 to 2.15) for caffeine intake of less than 200 mg/day, and aHR of 2.23 (1.34 to 3.69) for intake of 200 or more mg/day, respectively. [Weng 2008][15] mean caffeine intake of > or = 300 mg/day showed a significantly increased risk of fetal death (OR 2.33 [1.23; 4.41])[Matijasevich 2006][6] **LBW*:***Maternal caffeine intake of more than 300 mg daily during pregnancy was associated with lowered birth weight and smaller head circumference of the infant after accounting for maternal nicotine use [Watkinson 1985][21] Caffeine consumption throughout pregnancy was associated with an increased risk of fetal growth restriction (OR 1.2 (95% CI 0.9 to 1.6) for 100-199 mg/day, 1.5 (1.1 to 2.1) for 200-299 mg/day, and 1.4 (1.0 to 2.0) for >300mg/day compared with <100mg/day; test for trend P<0.001) [CARE Study Group 2008][39] A significant reduction in birth weight was found to be associated with an average caffeine intake of a71 mg per day, after adjustment for gestational age, infant sex, parity, and maternal height and weight, but only in infants born to nonsmoking mothers [Vlajinac 1997][40]	

increase the risk of a subsequent fetal loss. Having said that, we still standby the point that, a yet undiscovered association still exists between pre-pregnancy caffeine intake and serious MNCH consequences. Future research should focus on these avenues. Also while individual studies report a non-significant dose-response relationship pertaining to pre-gestational use of caffeine and spontaneous abortion, more directed work needs to be done to elaborate on this in order to find a relatively safe cut-off, if there may beone. While conducting such research one should keep in mind that caffeine consumption rates among most populations would be greater than zero.

Key Messages

- >300mg/d of periconception caffeine use is associated with a 31% increase in the risk of subsequent fetal loss.
- Individual studies report a non-significant dose-response relation between periconception consumption and fetal loss.
- Highlighted areas of research include conducting a large-scale study with a universal reference intake (not zero) to reconfirm the current evidence and also assess for a relationship between other possible MNCH outcomes, along-with finding a 'safe level'.

10.2. Reducing alcohol intake

Background

Considered the leading cause of birth defects and developmental disabilities in the US, prenatal alcohol exposure is associated with significant maternal and fetal health risks including spontaneous abortion[41-43] prenatal and postnatal growth restriction birth defects. It is one of the leading causes of neuro-developmental deficits in children, including those of fetal alcohol spectrum disorder (FASD).[44-48]

The National Drug use and Health Survey (2006) found that 53% of non-pregnant women of childbearing-age (15-44 years) reported current use of alcohol and 23.6% reported binge drinking. Studies from the CDC show that roughly 50% of women of childbearing age (18–44 years) report alcohol use in the past month, and one in eight reports binge drinking. Preconception alcohol exposure has been linked to adverse fetal outcomes like spontaneous abortion[29, 37, 41, 49] and neural tube defects.[50] The evidence for associating preconception alcohol intake to spontaneous abortions is still controversial with American studies[37, 41, 51, 52] citing a positive connection as opposed to many European studies[35, 53-57] that show no harmful effect of a moderate alcohol intake compared with non-drinkers. Naimi et al.[58] found that women with unintended pregnancies were more likely to have engaged in binge drinking in the preconception period compared with women whose pregnancies were intended and that these binge drinkers were more likely to involve engage in other risky behaviours, including drinking during pregnancy.

A recent review[59] assessing the effectiveness of 12 brief, multi-contact behavioral counseling interventions (those with up to 15 minutes of initial contact and at least 1 follow-up) in primary care settings, showed that 6-12 months post-interventions participants reduced the average number of drinks per week by 13-34% more than controls did, and the proportion of participants drinking at moderate or safe levels was 10-19% greater compared with controls. Fleming et al.[60] reported maintenance of

improved drinking patterns for up to 48 months. However, this review[59] found limited evidence for their effectiveness in reducing alcohol-related morbidities. A randomized controlled trial[61] of a brief motivational intervention (consisting of 4 counseling sessions and 1 contraception consultation and services visit) was conducted to assess its effect on reduction of the risk of an alcohol-exposed pregnancy (AEP) in preconceptional women by focusing on both risk drinking and ineffective contraception use. Women could decrease their risk for an AEP by reducing risky drinking, initiating effective contraception use, or both. This showed that in the follow-up the odds of being at reduced risk for AEP were twofold greater in the intervention group.

Keeping in mind that, owing to binge drinking paired with ineffective contraception use, a significant number of college women are at risk for AEP, a trial of a one-session motivational interviewing-based intervention to reduce AEP risk conducted in this population showed a significant result with 74% of intervention women no longer being at risk for AEP at 1 month as compared with control subjects (54%). Another study targeting childbearing aged women attending physicians' offices in community health practice settings found that alcohol use screening and brief advice from a physician significantly decreased alcohol use among women who received the intervention compared with those who did not receive the intervention.

Scope of intervention

Although a positive pregnancy test may lead to a significant decrease in the alcohol use of many women, the intervening time lapse between that and conception is a critical period of fetal susceptibility to alcohol. In order to target this time period it is essential to intervene before conception and hence focus interventions on women of the reproductive age. Population-based behavior modification interventions show improved drinking habits. Trials, in women of child-bearing age, targeting behaviors (reduction of alcohol use and improved contraception), and show promise.[61-63]

Content of preconception care for reducing alcohol intake is given in table 12.2.1

Table 102.2.1 - Content of preconception care for reducing alcohol

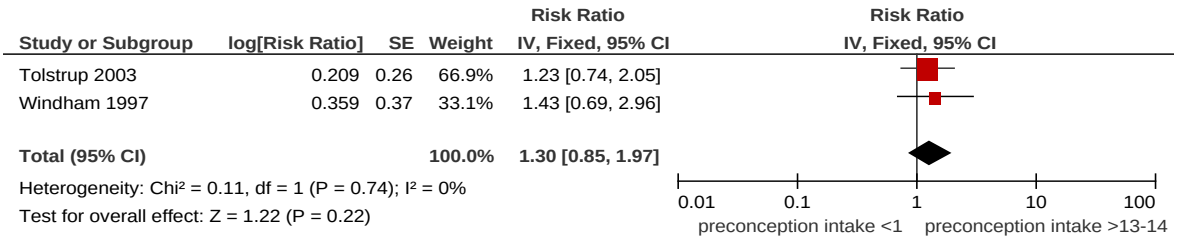
- screening of all women of reproductive age using a pre-validated tool
- identifying and intervening for those who are consuming it excessively (>7 drinks/week or > 3 drinks on 1 occasion),
- counseling about the benefits of abstaining from alcohol and about its adverse effects on pregnancy outcomes (spontaneous abortion, prenatal and postnatal growth restriction, birth defects, fetal alcohol spectrum disorders),
- promoting abstinence programs for those with alcohol dependency
- encouragement of strict contraception for those not in control of their drinking habits

Includes screening of all women of reproductive age and identifying and intervening for those who are consuming it excessively (>7 drinks/week or > 3 drinks on 1 occasion), counseling those who drink about the adverse effects on pregnancy outcomes (), promotion of abstinence programs for those with alcohol dependency and encouragement of strict contraception for those not control of their drinking habits.

Impact estimates

We looked into risk aversion studies dealing with both pre- and peri-conception drinking as well as interventions during these same periods to alter drinking behavior among women. Our analysis showed a non-significant 30% increase in the risk of occurrence of spontaneous abortions with preconception alcohol consumption (**Figure 10.2.1**).

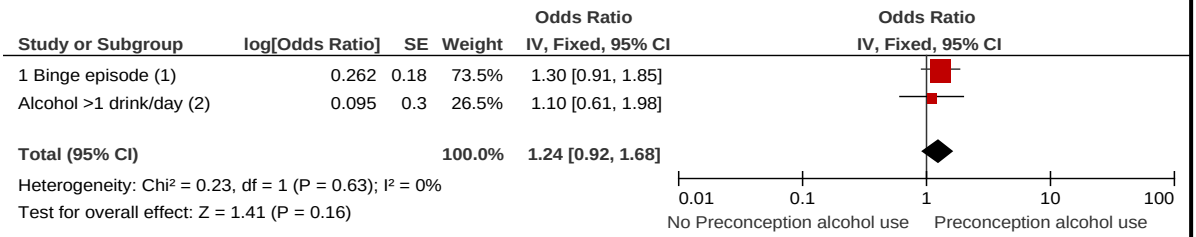
Figure 10.2.1: Preconception alcohol intake and risk of Spontaneous abortions



Citations to the included studies:
Tolstrup 2003[29], Windham 1997[41]

We included one study[50] on the effect on neural tube defects. This showed an increase in the rate of NTDs with preconception alcohol intake; however the finding was not significant (OR 1.24; 95% CI: 0.92-1.68) (**Figure 10.2.2**). Preconception binge drinking led to a 20% greater risk of NTDs than having >1 drink/day (reference was no alcohol intake).

Figure 10.2.2: Preconception alcohol intake and risk of Neural tube defects



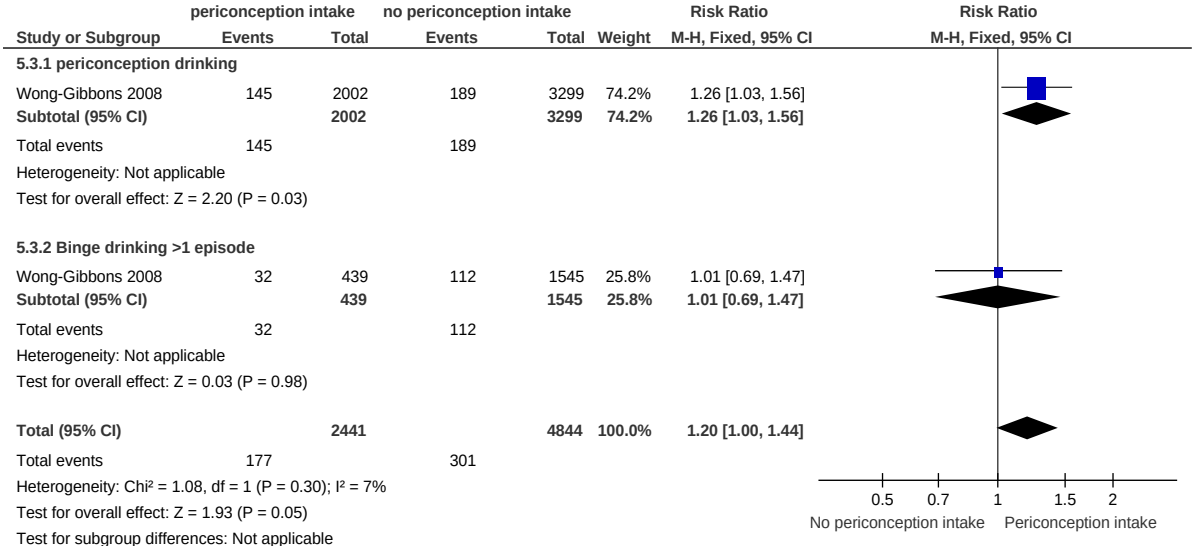
(1) More than 5 drinks on one occasion. Reference is no Preconception alcohol intake
(2) Reference: No preconception alcohol intake

Citations to the included study:
Shaw 1996[50]

Periconception consumption was also found to be associated with esophageal atresia +/-tracheoesophageal fistula (RR 1.26; 95% CI: 1.03-1.56) (**Figure 10.2.3**); this association was significant. However periconception drinking plus >1 episode of binge drinking compared to drinking without any binge episodes did not yield any association with these gastrointestinal malformations. The study[64] itself in their paper showed a non-significant 40% increased risk with binge episodes compared to a 20% increase without such episodes.

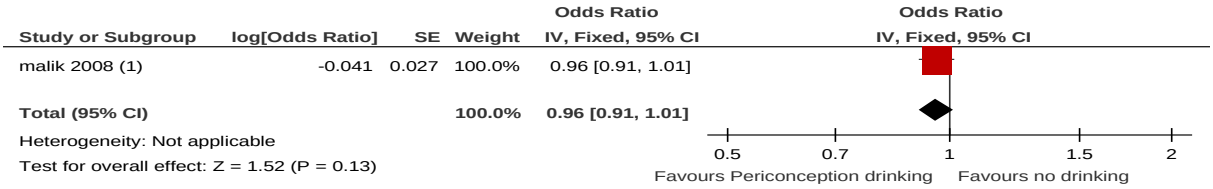
Two studies evaluating the effect of periconceptional alcohol exposure on the occurrence of congenital heart defects showed no significant association, save with risk of TGA. (**Figure 10.2.4a-b**).

Figure 10.2.3: Preconception alcohol intake and risk of EA +/- TEF



Citations to the included study:
Wong-Gibbons 2008[64]

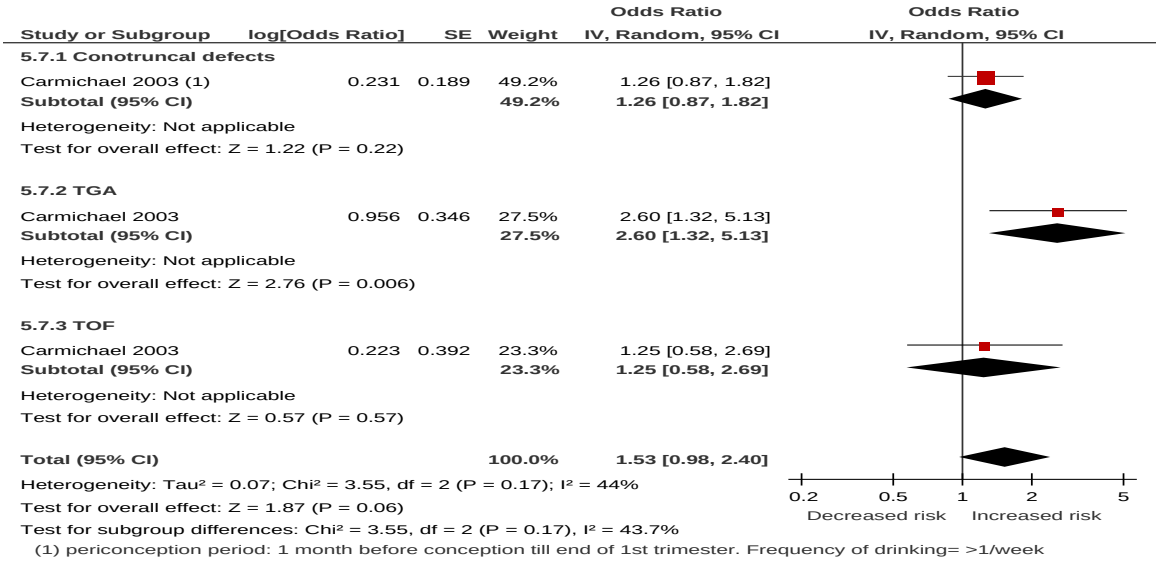
Figure 10.2.4a: Periconception alcohol intake and risk of congenital heart defects



(1) periconception period: 1 month preconception till end of 1st trimester

Citation to the included study:
Malik 2008[65]

Figure 10.2.4b: Periconception alcohol intake and risk of congenital heart defects

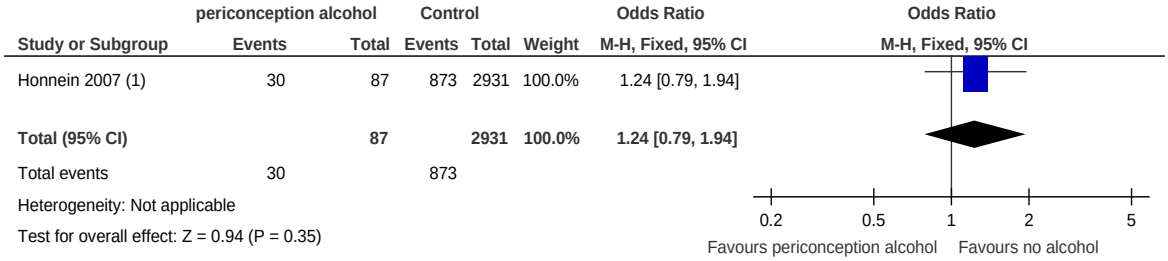


(1) periconception period: 1 month before conception till end of 1st trimester. Frequency of drinking= >1/week

Citation to the included study:
Carmichael 2003[66]

No significant association was found between alcohol intake in the periconception period and orofacial defects (**figure 10.2.5**) or congenital diaphragmatic hernias (**figure 10.2.6**).

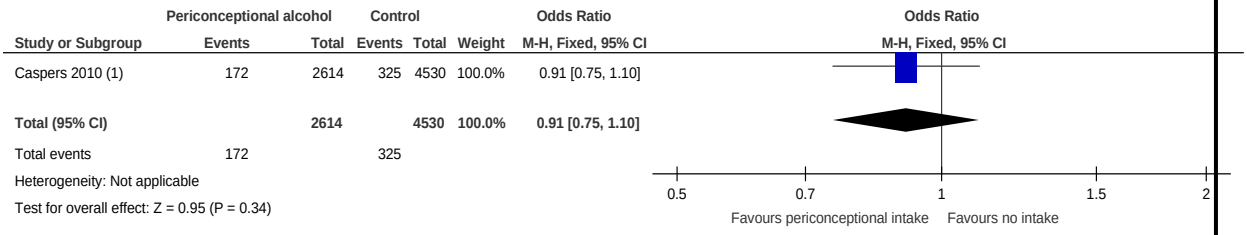
Figure 10.2.5: Periconception alcohol intake and risk of orofacial defects



(1) >1.5 drinks/day in the periconception period (b1-p3) vs no drinking

Citation to the included study:
Honein 2007[67]

Figure 10.2.6: Periconception alcohol intake and risk of congenital diaphragmatic hernia



(1) Periconceptional period: 1 month before conception till end of 1st trimester. OR for reported average drinks/month, binge drinking, and type of alcohol were near unity for all comparisons

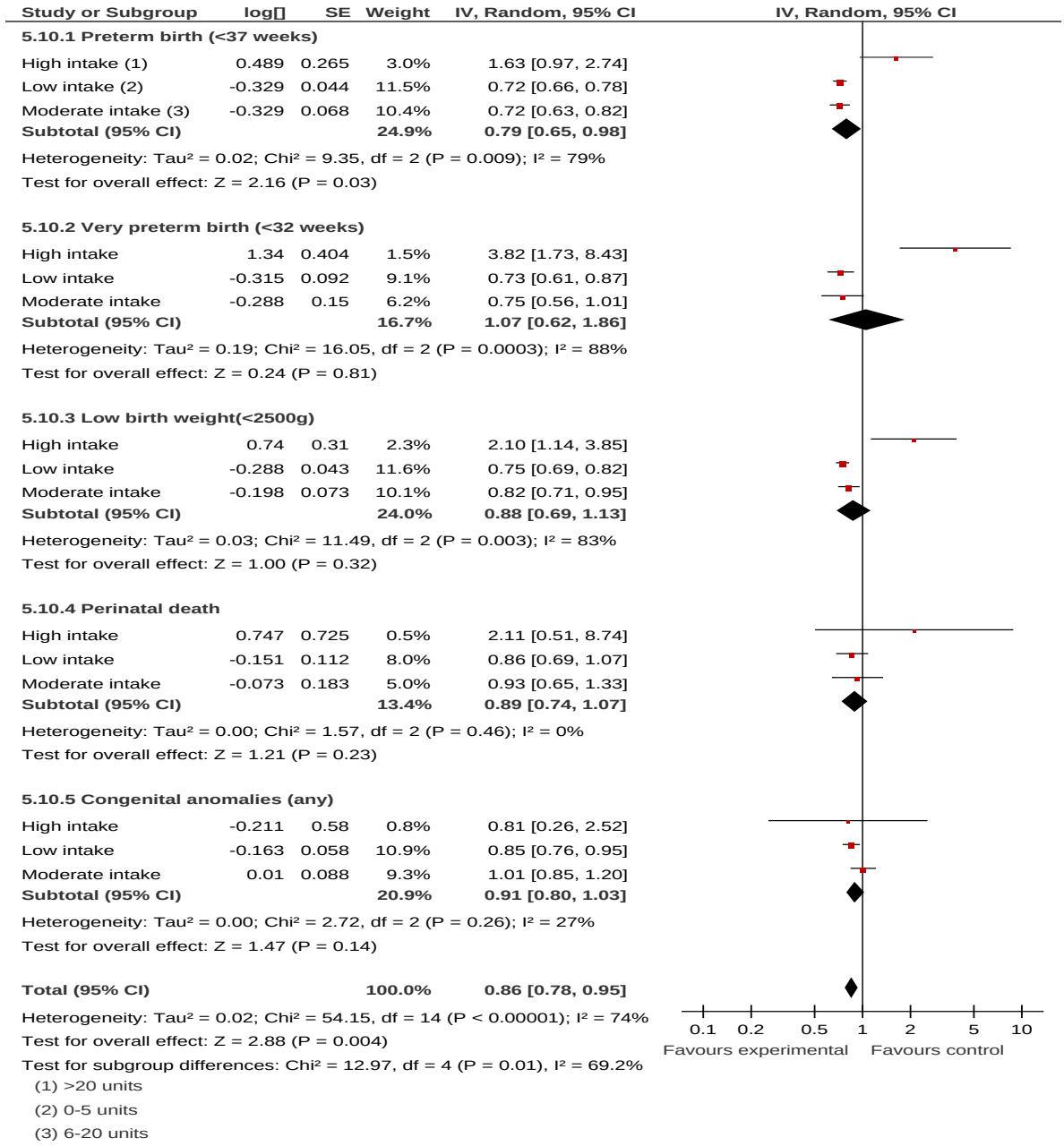
Citation to the included study:
Caspers 2010[68]

Periconception alcohol intake was not associated with any adverse pregnancy outcome (**Figure 10.2.7**); however there was a dose response relation between alcohol consumption and these. High alcohol intake (>20 units) led to a significant almost 4-fold increase in very preterm birth and a 2-fold increase in low-birth-weight.

We also found a study[70] reporting the association between preconception substance abuse and depression. Analysis showed that for depression, the highest rates were seen among alcohol users, whether they used drugs along with it or not. This association was statistically significant. Drug usage plus alcohol intake showed a 35% greater association with depression than alcohol use alone (RR 1.94; 95% CI: 1.38-2.73) and (RR 1.59; 95% CI: 1.22-2.07) (**Figure 10.2.8**) respectively.

For preconception interventions, preconception counselling led to a significant decrease in the consumption of alcohol during the trimester (OR 1.79; 95% CI: 1.08-2.97). The association with other drinking behaviours, like binge episodes (OR 1.51; 95% CI: 0.63-3.62) (**Figure 10.2.9**), was not significant. There was, however, no association of preconception counselling and continuing to drink through the rest of pregnancy.

Figure 10.2.7: Periconception alcohol intake and risk of adverse pregnancy outcomes

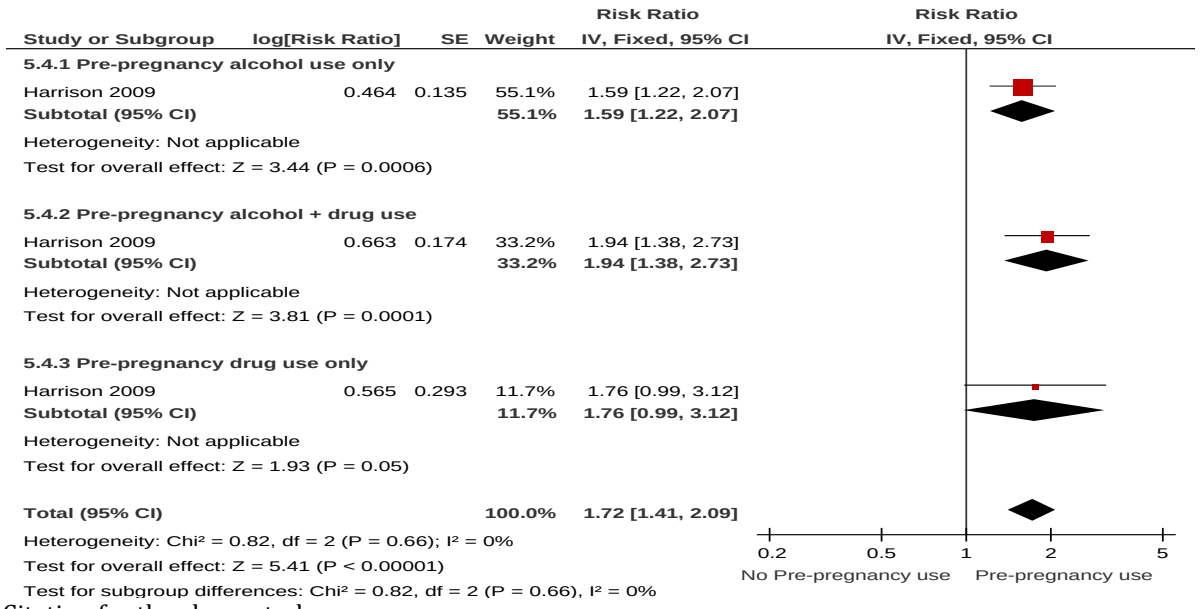


Citation to the included study:
Mullally 2011[69]

Another preconception motivational intervention led to a highly significant decrement in risk drinking (OR 1.66; 95% CI: 1.36-2.02). This reduction was highest in the 3 months following intervention as compared to at 6 months and at 9 months post-intervention (79%, 64% and 54% respectively). This intervention also led to a significant increase in the use of effective contraception (OR 2.18; 95% CI: 1.80-2.64) thereby significantly reducing the risk of an alcohol-exposed pregnancy (OR 2.20; 95% CI: 1.81-2.68). This finding was in accordance to the results of another trial[63] of a

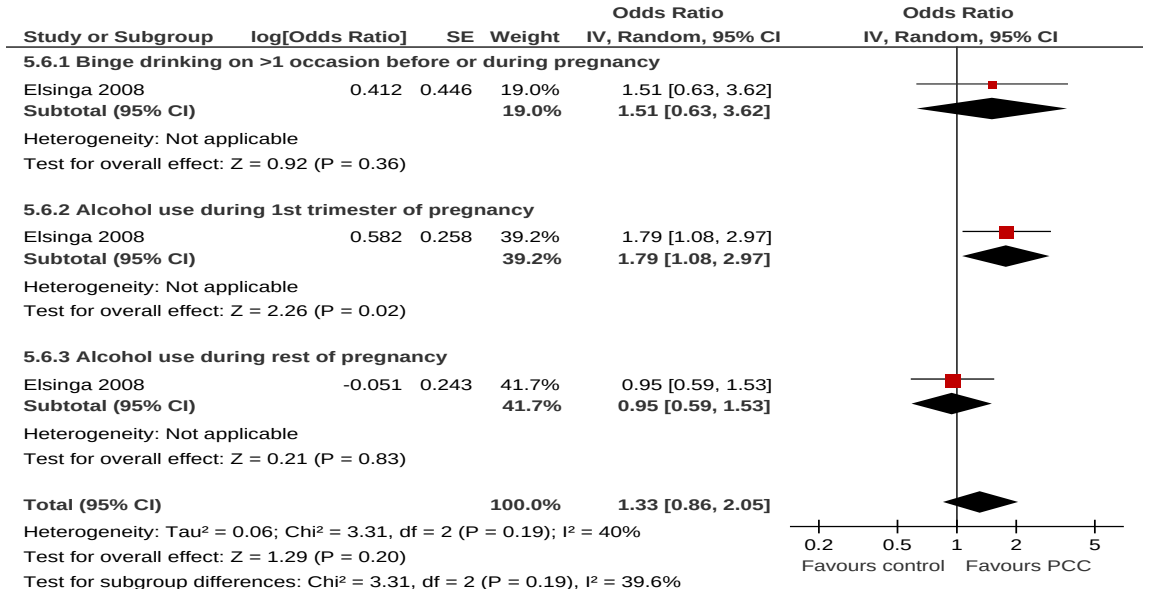
behavioural intervention where 74% of women were no longer at risk for alcohol-effected pregnancies at 1 month post-intervention. (**Figure 10.2.10**). Table 11.2.1 summarizes the salient features and findings of various interventional studies to reduce the occurrence of Alcohol Effected Pregnancies (AEP) and subsequently FAS infants.

Figure 10.2.8: Relationship between pre-pregnancy substance abuse and depression



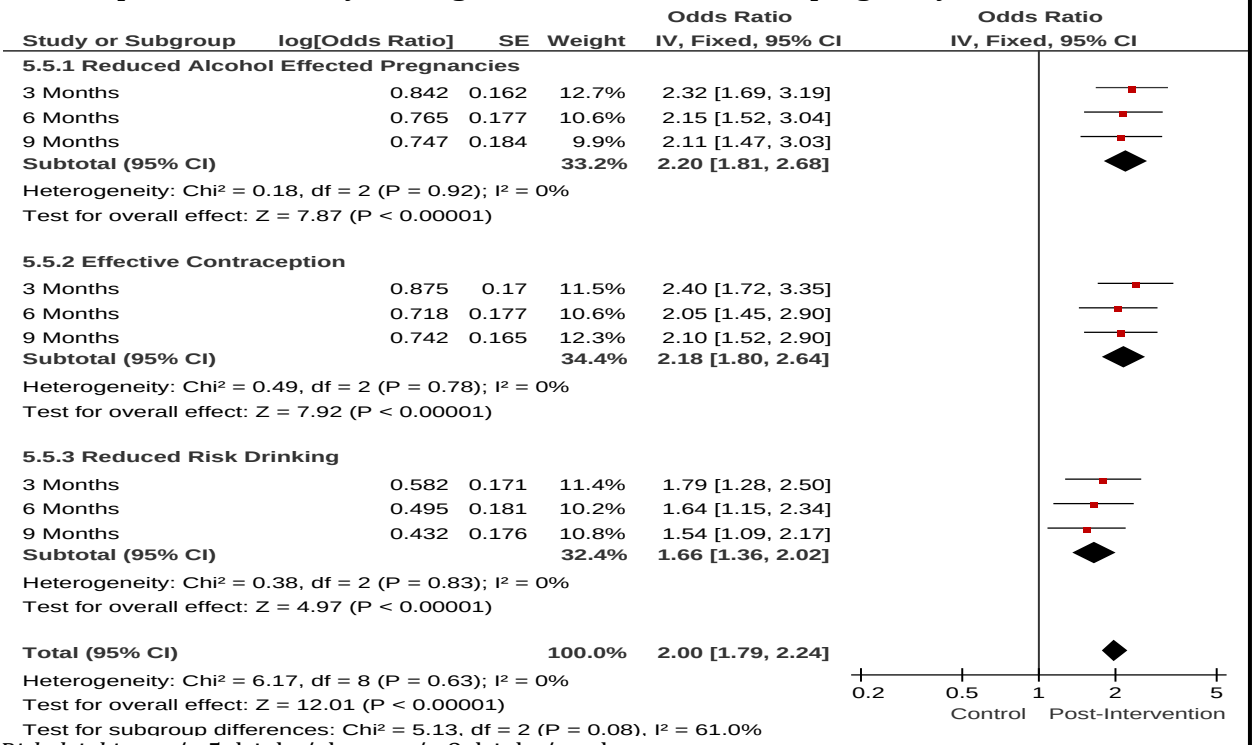
Citation for the above study
Harrison 2009[70]

Figure 10.2.9: Preconception counseling and reduction in risk drinking and drinking habits



Citation to the included study
Elsinga 2008[71]

Figure 10.2.10: Post intervention reduction in risk drinking and improvement in effective contraception use, thereby leading to a reduction in Alcohol pregnancy



Risk drinking: =/> 5 drinks/ day or =/> 8 drinks/week

Ineffective contraception: vaginal intercourse when contraception was either not used or was used ineffectively (deviated from the published guidelines for use of a method)

Reduced risk of "Alcohol Effected Pregnancy": effective contraception, no risky drinking or both.

Citation to the included study:

Floyd 2007[61]

Table 10.2.1. Interventions for alcohol

	Intervention	Results
Floyd 2007[61]	Participants were randomized to receive information plus a brief motivational intervention (*n*=416) or to receive information only (*n*=414). The brief motivational intervention consisted of four counseling sessions and one contraception consultation and services visit. Women consuming more than five drinks on any day or more than eight drinks per week on average, were considered risk drinkers; women who had intercourse without effective contraception were considered at risk of pregnancy. Reversing either or both risk conditions resulted in reduced risk of an AEP.	
Ingersoll 2003[62]	Project CHOICES- The intervention consisted of 4 Motivational Interviewing (MI) sessions and 1 contraceptive counseling session. The goal of MI is to provide personalized feedback of risk, motivate the woman to change 1 or both of the target behaviors (reduction of alcohol use and	Among women who completed the 6-month follow-up, 68.5% were no longer at risk of having an alcohol-exposed pregnancy; 12.6% of women who completed the program reduced drinking only; 23.1% used effective contraception

Table 10.2.1. Interventions for alcohol		
	Intervention	**Results**
	improved contraception), decrease her temptation to engage in risk behavior and increase her confidence to avoid it, facilitate goal setting, develop change plans, and encourage her to attend the contraceptive counseling visit. A woman was considered not to be at risk for having an AEP at the 6-month follow-up contact if she was not at risk for pregnancy (reported abstaining from sexual intercourse or consistent use of effective contraception during the 6 months since the last MI counseling session) or if she reported drinking below risk levels (</= 7 drinks per week in the past 3 months and no more than 4 drinks on any day in the past 6 months), or both.	only; and 32.9% reported both. Results were consistent across the 6 diverse high-risk settings.
Ingersoll 2005[63]	Risk for AEP was defined as having sexual intercourse with a man in the past 90 days while using contraception ineffectively (no use, incorrect use of an effective method, or use of an ineffective method only); drinking at risky levels was defined as engaging in at least one binge in the past 90 days or consuming an average of eight standard drinks per week.	At 1-month follow-up, 15% of the control subjects and 25% of the intervention women reported no risk drinking, a significant difference favoring the intervention group. Significantly fewer control subjects (48%) used effective contraception at 1-month follow-up as compared with intervention women (64%), $\chi 2$ (1) = 5.1, $p < .03$. Significantly more intervention women (74%) were no longer at risk for AEP at 1 month as compared with control subjects (54%), $\chi 2(1) = 8.15$, $p < .005$.
Manwell 2000 (adolescents)[72]	Project TrEAT was conducted in the offices of 64 primary care, community-based physicians. The intervention consisted of two 15 min, physician-delivered counseling visits that included advice, education, and contracting by using a scripted workbook. Subjects assigned to the control group received a booklet on general health issues and were instructed to address any health concerns in their usual manner.Of 5979 female patients ages 18 to 40 who were screened for problem drinking, 205 were randomized into an experimental group (n= 103) or control group (n= 102).	The trial found a significant treatment effect in reducing both 7day alcohol use (p = 0.0039) and binge drinking episodes (j=~ 0.0 021) over the 48month follow-up period. Women in the experimental group who became pregnant during the follow-up period had the most dramatic decreases in alcohol use. A logistic regression model based on a 20% or greater reduction in drinking found an odds ratio of 1.93 (confidence interval 1.07-3.46) in the sample exposed to physician intervention
		Frequency, drinks/month: Mean (SD), number. IMI: baseline 3.4 (1.6), 63; 3 months 2.2 (1.7), 56; 6 months 2.4 (1.8), 53; 12 months 2.5 (1.7), 47 IMI + FCU: baseline 3.4 (1.7), 62; 3 months 1.8 (1.5), 41; 6 months 2.1 (1.5), 39; 12 months 2.6 (2.1) 36 Quantity, per occasion: Mean (SD), number. IMI: baseline 5.2 (1.6) 63; 3 months 2.7

Table 10.2.1. Interventions for alcohol		
	Intervention	**Results**
		(2.3) 56; 6 months 3.0 (2.3) 53; 12 months 3.4 (2.4) 47 IMI + FCU: baseline 5.4 (1.8) 62; 3 months 2.1 (1.9) 41; 6 months 2.4 (2.0) 39; 12 months 3.1 (2.5) 36 High-volume drinking, drinks/month: Mean (SD), number. IMI: baseline 2.7 (1.5) 63; 3 months 1.9 (1.6) 56; 6 months 2.0 (1.7) 53; 12 months 2.0 (1.4) 47 IMI + FCU: baseline 2.5 (1.6) 62; 3 months 1.6 (1.6) 41; 6 months 1.7 (1.6) 39; 12 months 2.4 (2.1) 36

Conclusion

In summary alcohol consumption before or around the time of conception is linked to multiple adverse fetal outcomes including spontaneous abortion, gastrointestinal malformations and neural tube defects. None of these associations reach a level of statistical significance. Pre-pregnancy alcohol consumption is also correlated with maternal depression. Both preconception counselling as well as behavioural interventions have led to a significant improvement in drinking behaviour and thus pregnancies affected by alcohol. What is needed now is to use this important information to upgrade these interventions to have stronger, longer-lasting and more widespread effects.

Key messages

- Pre and periconception alcohol exposure is non-significantly associated with a 30% increase in spontaneous abortion, 24% increase in NTDs and 20% increase in gastrointestinal anomalies.
- Binge episodes during the preconception period lead to a greater incidence of NTDs
- Preconception counselling greatly reduces alcohol intake during the 1st trimester.
- Behavioural interventions lead to a reduction in risk drinking that is highest in the 3 months post-intervention

10.3. Smoking cessation

Background

Smoking during pregnancy has serious effects on the mother and deleterious consequences on the health and well being of the baby at birth as well as during early development. Fetal effects of exposure to maternal smoking include intrauterine growth retardation, prematurity, low birth weight, congenital malformations[80-85] and sudden infant death syndrome (SIDS).[86] Maternal complications include premature rupture of membranes, placenta previa, placental abruption, ectopic pregnancy and spontaneous abortion.[87] In the past two decades many clinical trials have demonstrated the effectiveness of smoking cessation interventions early in the pregnancy.[88] It has been concluded that smoking cessation during pregnancy would reduce infant deaths by 5% and reduce the proportion of low birth-weight singleton births by 10%.

Table 10.2.2: Summary impact estimates for Preconception alcohol consumption				
	Maternal	**Pregnancy**	**Newborn**	**Infant**
Preconception alcohol intake	**<u>Unwanted pregnancy:</u>** Women with unintended pregnancies were significantly more likely to report binge drinking in the preconception period compared with women with intended pregnancies (16.3% vs. 11.9%; OR: 1.43; 95% CI: 1.13–1.54. [Naimi 2003][58] 60% of pregnancies were unintended among women who reported 4 or more binge episodes in the preconception period, compared with 40% among women who reported no binge drinking episodes (OR: 2.3; 95% CI: 2.12–2.57). [Naimi 2003][58]		**<u>Spontaneous abortion:</u>** The adjusted OR for spontaneous abortion in women drinking >13 alcoholic drinks per week was 1.28 (95% CI: 0.76, 2.51) compared with women drinking less than one drink per week [Tolstrup 2003][29] Spontaneous abortion RR of 1.25 (95% CI: 1.02-1.54) with each additional ounce (about two drinks) of absolute alcohol consumed per day before pregnancy.[Russell 1988][49] Adjusted OR was 1.5 [95% CI: 0.7-3.2]. [windham 1997][41] Consumption of alcohol was also clearly associated with elevated risk; OR increased on average by a factor of 1.26 (1.19-1.33) for each drink per day. [Armstrong 1992][37] **<u>NTDs:</u>** Preconception alcohol >1 drink/day OR 1.10 [0.61, 1.98] Preconception alcohol >5 drinks/day OR 1.30 [0.91, 1.85] [Shaw 1996][50] **<u>EA+/-TEF:</u>** EA +/- TEF: ORs were near unity for all EA +/- TEF cases combined and any periconceptional exposure to alcohol (OR 5 1.2; CI 5 0.8, 1.8). (periconception is 1 month before to end of 1st trimester) [Gibbons 2008][64] **<u>Congenital Diagphramatic Hernia:</u>** For periconceptional alcohol exposure, the aORs were near unity for all phenotypes and CDH subtypes. [Caspers 2010][68]	Childhood cancers: Maternal consumption before the relevant pregnancy RR 0.8 (0.7–1.0). Paternal consumption before relevant pregnancy RR 1.0 (0.9–1.3) [Sorahan 1995][75] Leukemia: Maternal consumption of alcohol in the month prior to pregnancy OR 1.3 (1.0–1.7). paternal consumption OR 1.1 (0.7–1.5). [Shu 1996][76] Maternal consumption in the year

Table 10.2.2: Summary impact estimates for Preconception alcohol consumption				
	Maternal	**Pregnancy**	**Newborn**	**Infant**
			<u>Preterm birth:</u> High consumption (>20 units/week) was associated with very preterm birth (<32 weeks gestation) even after controlling for socio-demographic factors, adjusted aOR 3.15 (95% CI 1.26-7.88). Only three cases of Fetal Alcohol Syndrome were recorded (0.05 per 1000 total births), one each in the low, moderate and high consumption groups. Preterm birth (<37 weeks): Low intake (0-5 units/week) aOR 0.77 (0.69-0.85) moderate intake (6-20 units/week) aOR 0.71 (0.60-0.83) High intake (>20 units/week) aOR 1.00 (0.53-1.87) Very preterm birth: Low intake (0-5 units/week) aOR 0.88 (0.70-1.11) moderate intake (6-20 units/week) aOR 0.95 (0.66-1.37) High intake (>20 units/week) aOR 3.15 (1.26-7.88) **<u>LBW</u>**: Low intake (0-5 units/week) aOR 0.69 (0.61-0.78) moderate intake (6-20 units/week) aOR 0.71 (0.58-0.87) High intake (>20 units/week) aOR 1.15 (0.60-2.22) **<u>Perinatal death</u>**: Low intake (0-5 units/week) aOR 0.65 (0.47-0.90) moderate intake (6-20 units/week) aOR 0.72 (0.44-1.18) High intake (>20 units/week) aOR 1.56 (0.33-7.44)	prior to pregnancy OR 1.1 (0.4–2.6). [Arangure 2003][77] ALL: Maternal alcohol consumption in the year before pregnancy OR 1.2 (0.9–1.5). [Steensel-Moll 1985][78] Maternal consumption in the month prior to pregnancy OR 1.1 (0.8–1.6). [Shu 1996][76] Maternal consumption in the month prior to

Table 10.2.2: Summary impact estimates for Preconception alcohol consumption				
	Maternal	**Pregnancy**	**Newborn**	**Infant**
			<u>Low APGAR (<7 at 5 minutes</u>): Low intake (0-5 units/week) aOR 0.67 (0.53-0.85) moderate intake (6-20 units/week) aOR 0.62 (0.42-0.92) High intake (>20 units/week) aOR 1.09 (0.25-4.73) **<u>Congenital anomaly (any</u>**): Low intake (0-5 units/week) aOR 1.01 (0.71-1.44) moderate intake (6-20 units/week) aOR 1.01 (0.82-1.27) High intake (>20 units/week) aOR 0.56 (0.17-1.88). [Mullally 2011 Coh][69] **<u>Neurological status:</u>** Of the 665 infant responses to 25 Einstein Neonatal Behavioral Assessment Schedule (ENBAS) items, only tonus showed a small but significant relationship to pre-pregnancy maternal alcohol intake. The authors conclude that low to moderate maternal alcohol intake has no significant effect on newborn neurological status. [Walpole 1991][73] **<u>CHDs:</u>** relative to non-consumers, women who consumed alcohol less than once a week had a 1.3-fold increased risk of delivering infants with a conotruncal heart defect (95%CI 1.0, 1.9), and women who consumed alcohol once a week or more had a 1.9-fold increased risk (95% CI 1.0, 3.4). The risks associated with consuming five or more drinks per drinking occasion were 1.6 (95% CI 0.8, 3.2) for less than once a week, and 2.4 for once a week or	pregnancy OR 0.8 (0.6–1.1). [Infante-Rivard 2002][79]

Table 10.2.2: Summary impact estimates for Preconception alcohol consumption				
	Maternal	**Pregnancy**	**Newborn**	**Infant**
			more (95% CI 0.6, 9.7). conotruncal defects: >1/week (case vs controls) – 20/207 vs 29/481; none (cases vs controls) 105/207 vs 284/481. TGA: >1/week – cases vs controls 8 vs 29; None 40 vs 284. TOF: : >1/week – cases vs controls 6 vs 29; None 45 284 [Carmichael 2003]**[66] Maternal alcohol use No- cases vs controls 1904 (62.08) 2399 (60.78) Reference Yes- cases vs controls 1141 (37.2) 1532 (38.81) 0.93 (0.85–1.03). [Malik 2008]**[65] **<u>Orofacial defects:</u>** Any periconception drinking (i.e. any alcohol intake between 1 month preconception till the end of the 1st trimester) 695/2275 vs 1054/3568. (However, it was unclear whether these figures correlated with a positive drinking status in the month before conception in all cases. [Romitti 2007][74]	
Preconception alcohol intervention	**<u>Alcohol effected pregnancy (AEP):</u>** ORs were 2.32 (95% CI=1.69–3.20) at 3 months, 2.15 (95% CI=1.52–3.06) at 6 months, and 2.11 (95% CI=1.47–3.03) at 9 Months. [Floyd 2007][61] OR's for intervention participants predictor variables- Attended at least 3 MI counseling sessions OR=0.445 CI 0.191-1.038; Attended 4 MI counseling sessions OR=0.534 CI 0.250-1.140. [Ingersoll 2003][62]			

Table 10.2.2: Summary impact estimates for Preconception alcohol consumption				
	Maternal	**Pregnancy**	**Newborn**	**Infant**
	AEP risk [*n* (%)] No: control 57/105 (54.3) vs. intervention 68/94 (73.9); Yes: control 48/105 (45.7) vs. intervention 24/94 (26.1. [Ingersoll 2005][63] **<u>Alcohol consumption:</u>** Women in the intervention group at the 9-month follow-up were more likely to reduce alcohol consumption to below risk levels at an OR of 1.5 (95% CI 1.1–2.2). [Floyd 2007][61] **<u>Alcohol use:</u>** Trial found a significant treatment effect in reducing both 7 day alcohol use (p = 0.0039) and binge drinking episodes (j=> 0.0 021) over the 48 month follow-up period. [man well 2000][72] **Contraception:** Women in the intervention group at the 9-month follow-up were more likely to use effective contraception at an OR of 2.4 (95% CI 1.7–3.4). [Floyd 2007][61]			
Preconception counseling: alcohol	**<u>Behavior change:</u>** Compared with women receiving standard care, fewer of these women used alcohol in the first 3 months of pregnancy (32% vs. 45%; unadjusted OR, 1.68 [95% CI, 1.03–2.75]). After adjustment for possible confounders, changes in behavior remainedstatistically significant for not drinking alcohol in the first 3 months of pregnancy OR, 1.79 [95% CI, 1.08–2.97]). [Elsinga 2008][71]			

**Periconceptional period- 1 month before conception to end of 1st trimester

Periconception smoking has been shown to be associated with preterm birth,[89] congenital heart defects,[65, 90] neural tube defects,[50] orofacial defects[67] and gastrointestinal malformations.[64] The defects being more strongly associated with heavy smoking.

A study on smoking behaviour of women who want to get pregnant[91] showed that whereas women with the intention to conceive display a greater level of awareness regarding the association between periconception smoking and congenital anomalies, this knowledge and attitude fails to get translated into practice. Preconception counselling resulted in a greater percentage of women having quit smoking before pregnancy compared with those receiving standard care.[71]

Scope of intervention

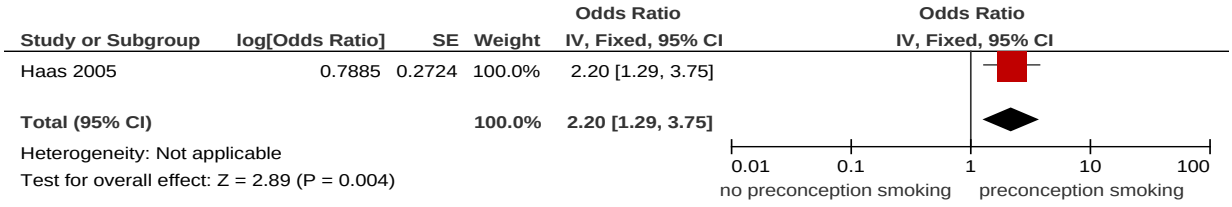
Most mothers (97%) who smoked in the month before pregnancy continued during at least the first part of pregnancy,[67, 91] a period where majority of the congenital anomalies have already originated. Hence what is important is to motivate women of reproductive age to quit smoking before they conceive. Substantial research literature exists for interventions to increase smoking cessation among adults, women in general and pregnant women, however there is a dearth of clinical studies focusing specifically on non pregnant women of childbearing age.

The content of preconception care for women who smoke includes: screening of all women of child-bearing age using evidence-based guidelines, treatment of dependence before planning a pregnancy, informing women about the adverse pregnancy outcomes associated with tobacco consumption, discussion of possible interventions to assist in quitting (including the use of medications) and referring to intensive counseling services where necessary.

Impact estimates

We found limited evidence on the effect of smoking before conception on individual adverse outcomes. Our analysis showed that preconception smoking was significantly linked to the risk of preterm births (OR 2.2; 95% CI: 1.29-3.75) (**Figure 10.3.1**).

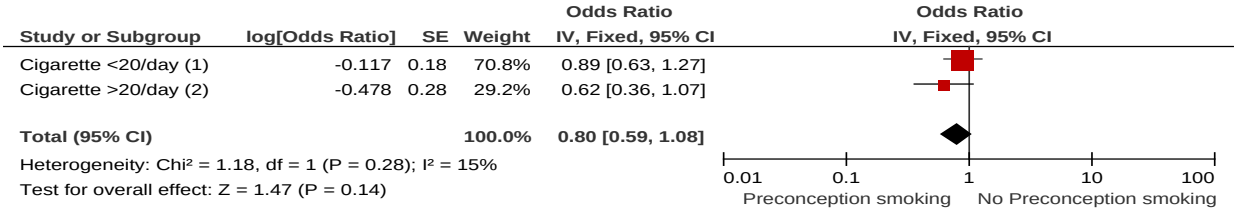
Figure 10.3.1: Preconception smoking and risk of preterm birth



Citations to the included study:
Haas 2005[89]

Preconception smoking showed no significant association with neural tube defects whether the consumption was <20cigarettes/day or >20cigarettes/day (**Figure 10.3.2**) or with orofacial defects. (**figure 10.3.3**)

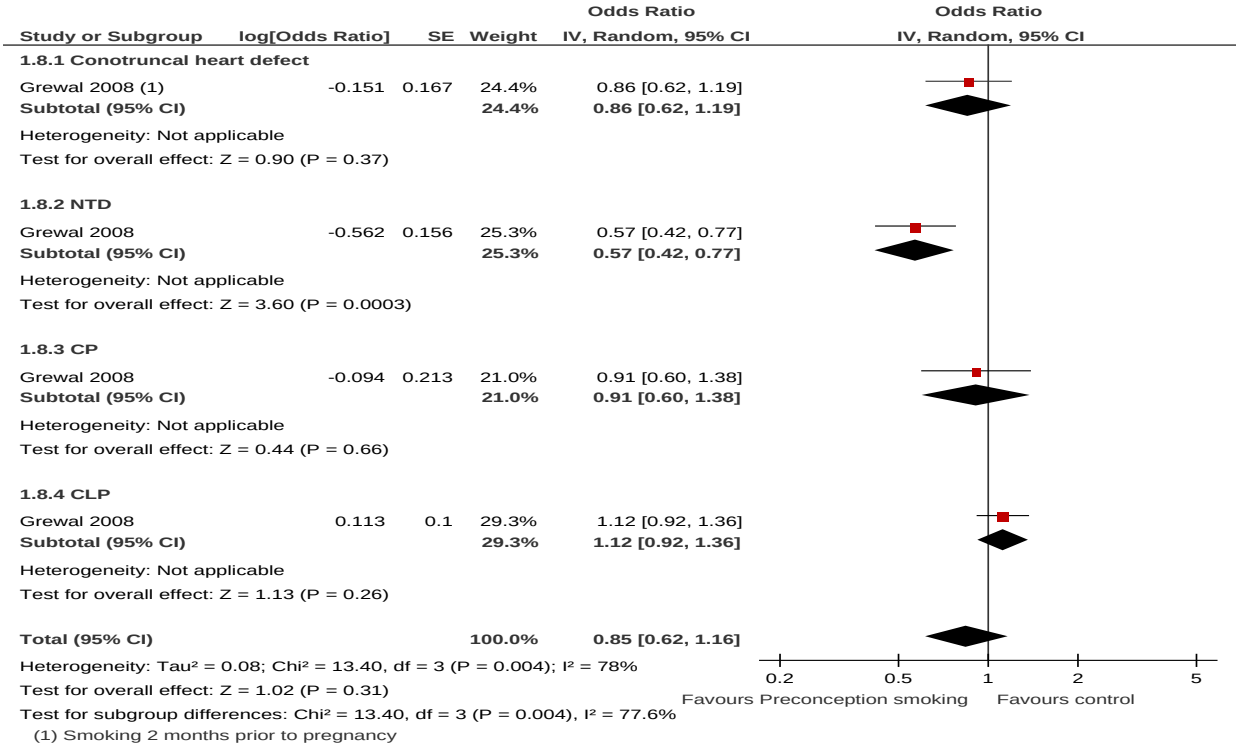
Figure 10.3.2: Preconception smoking and risk of Neural tube defects



(1) Preconception smoking 3 months before conception. Reference: No preconception smoking.
(2) Preconception smoking 3 months before conception. Reference: No preconception smoking.

Citations to the included study:
Shaw 1996[50]

Figure 10.3.2a: Preconception smoking and risk of various congenital anomalies

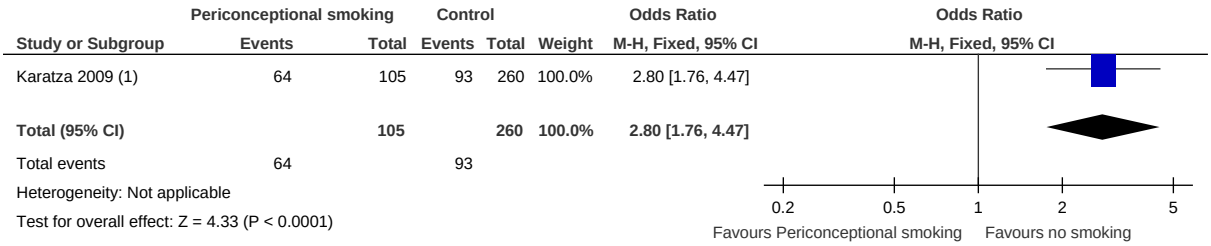


(1) Smoking 2 months prior to pregnancy

Citations to the included study:
Grewal 2008[90]

Periconception studies were analysed separately for different fetal outcomes. Periconception smoking was significantly associated with an almost 3 times increased risk of congenital heart defects (OR 2.80; 95% CI 1.76-4.47) (**figure 10.3.2a**). No significant association was found between exposure and esophageal atresia +/- tracheoesophageal fistula (RR 0.95; 95% CI: 0.76-1.19) (**Figure 10.3.2b**) and congenital diaphragmatic hernia (**Figure 10.3.2c**).

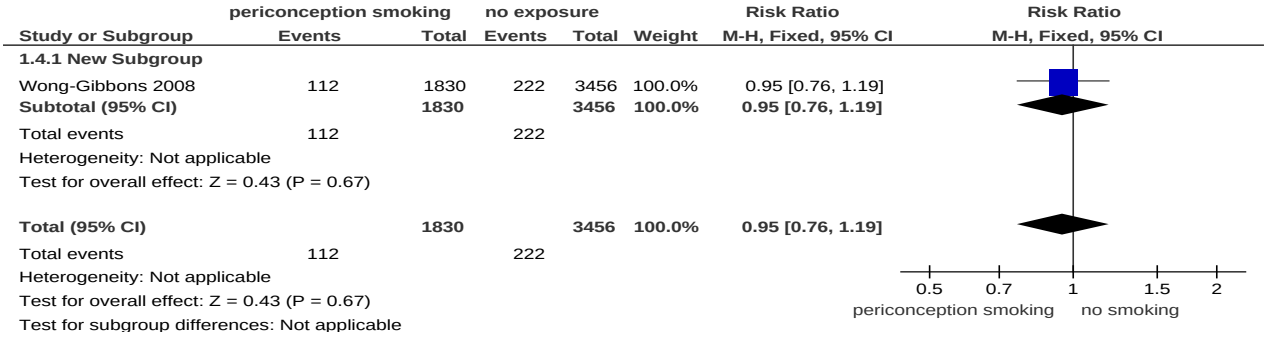
Figure 10.3.2b: Periconception smoking and risk of Congenital heart defect



(1) Periconception period: 1 month before conception till the end of the 1st trimester

Citations to the included study:
Karatza 2009[92]

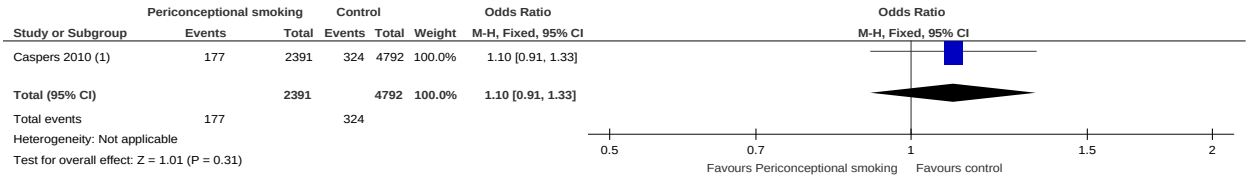
Figure 10.3.2c: Periconception smoking and risk of EA+/- TEF



Citations to the included study:
Wong-sGibbons 2008[64]

**Periconception period: 1 month before pregnancy till the end of the 1st trimester*

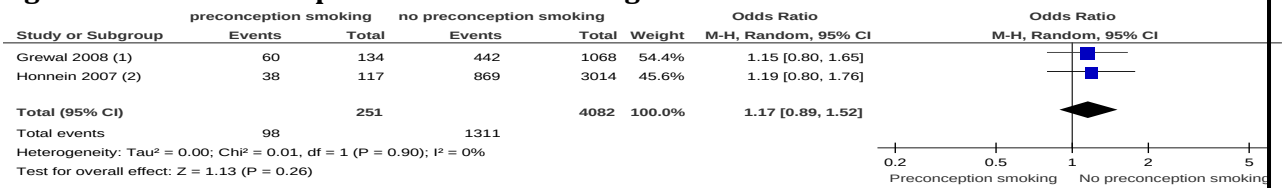
Figure 10.3.3: Periconception maternal smoking and risk of congenital diaphragmatic hernia



(1) Periconceptional period: 1 month before conception till end of 1st trimester. Note: results for type of smoking (active or passive) were not significant. No. of cigarettes/day did not seem to increase the risk of CDH

Citations to the included study:
Caspers 2010[68]

Figure 10.3.4: Preconception maternal smoking and risk of orofacial defects



(1) Smoking 1 month prior to pregnancy
(2) Smoking 1 month prior to pregnancy

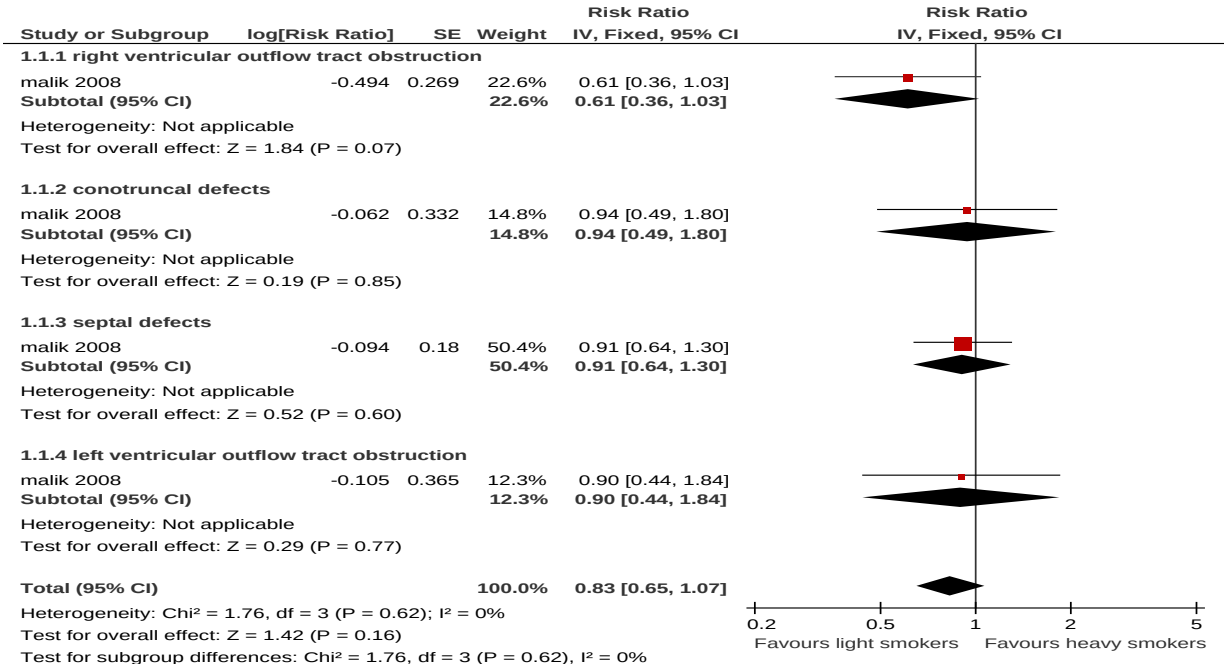
Citations to the included study:
Honein 2007[67], Grewal 2008[90]

When comparing light smoking (< 14 cigarettes/day) versus heavy (>25 cigarettes/day) in the periconception period (1 month before pregnancy till the end of the 1st trimester), light smoking led to a non-significant 17% lower risk of heart defects than heavy. Each

individual heart defect was more common in heavy smokers however; these individual associations were not significant.

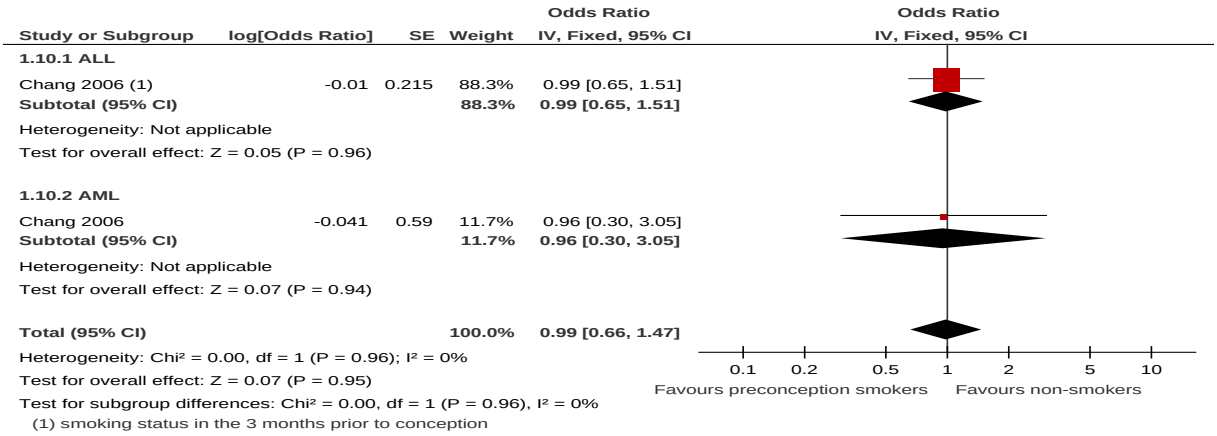
When assessing the effect of preconception parental smoking on the risk of childhood leukemia, it was seen that whereas paternal smoking was significantly associated with a greater risk (**Figure 10.3.5b**) maternal was not (**Figure 10.3.5a**).

Figure 10.3.5: Periconception smoking (light versus heavy) and risk of CHD



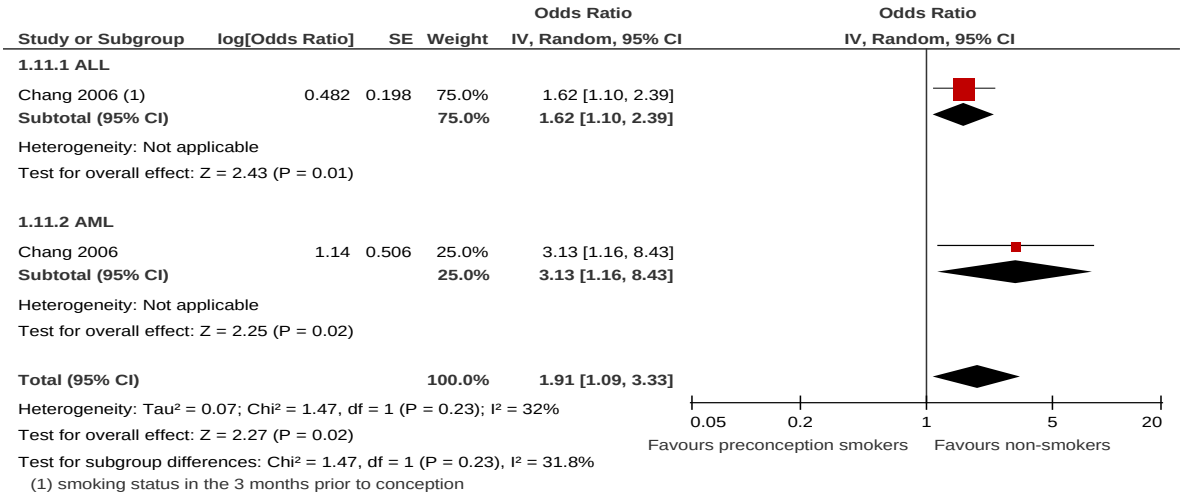
Citations to the included study:
Malik 2008[65]
**Periconception: 1 month before pregnancy to 1st trimester*

Figure 10.2.5a: Preconception maternal smoking and risk of leukemia



Citations to the included study:
Chang 2006[93]

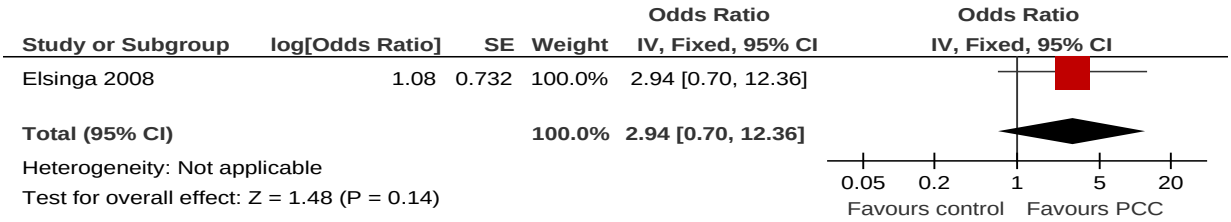
Figure 10.3.5b: Preconception paternal smoking and risk of leukemia



Citations to included study:
Chang 2006[93]

When assessing the effectiveness of a preconception counselling intervention versus standard care, there was an almost 3 times greater likelihood of women quitting smoking in the post-intervention group (2.94; 95% CI: 0.70, 12.36); this finding did not achieve statistical significance. (**Figure 10.3.6**).

Figure 10.3.6: Preconception counselling and effect on maternal smoking behaviour



Citations to the included study:
Elsinga 2008[71]

Environmental Tobacco Smoke (ETS) exposure was not associated with either congenital heart defects or gastrointestinal anomalies. (Data not shown)

Conclusion

The number of unplanned pregnancies is on the rise. Women, who are habitual smokers, put their lives and that of their unborn child in jeopardy, as preconception as well as peri-conception smoking significantly increases the threat of preterm births by twice as much and also raises the risks of congenital defects in the fetus. In order to reduce the chances of the adverse effects delineated above, effective interventions for women of reproductive age who smoke should be implemented on a large scale. Although preconception counselling does improve practices in women pertaining to their smoking habits, behavioural interventions in synergy with counselling may play a more significant part.

Table 10.3.1: Summary impact estimates for Preconception smoking					
Intervention	**Maternal**	**Pregnancy**	**Newborn**	**Infant**	**Others**
Periconception smoking		**Preterm birth:** smoking before pregnancy (OR, 2.20; CI, 1.29-3.75) was associated with an increased risk of preterm delivery [Haas 2005][89] **Down's pregnancy**: Maternal smoking during the peri-conceptional period (within 3 months of conception) was not associated with risk of recognized Down syndrome (OR = 1.04; 95% CI: 0.79, 1.37). [Torfs 2000][36]	**CHDs:** Conotruncal defects (Grewal 2008)[243] but data only given for 1st month of pregnancy. Indirectly deduced from data for smoking 2 months prior to pregnancy:- Conotruncal defects: smokers vs non-smokers 28/102 vs 295/921. NTD: smokers vs non-smokers 29/103 vs 308/934 CP: smokers vs non-smokers 19/93 vs 180/806 CLP: smokers vs non-smokers 63/137 vs 439/1065. Stronger association for septal defects in infants exposed to medium and heavy smoking compared with light smoking exposure (OR for septal defects in heavy smokers: 2.06; 95% CI: 1.20–3.54). (Smoking levels are as follows: light, less than half a pack per day, 1 to 14 cigarettes per day; medium, 1 pack per day, 15 to 24 cigarettes per day; heavy, 25 cigarettes per day) [Malik 2008][65] Logistic regression analysis with pregestational diabetes, history of influenza-like illness in the first trimester, therapeutic drug exposure in pregnancy, maternal age, parity, family history of CHD, infant gender, prematurity and paternal smoking, as potential confounding factors showed that periconceptional tobacco smoking was associated with increased risk of CHD in the offspring (OR=2.750, 95% CI=1.659–4.476, p=0.00001). The incidence of neonatal heart disease in women who were non-smokers or		For infertile women, basic information describing the impact of smoking on fertility, along with exhaled CO monitoring and a more intensive intervention were both highly effective. The rate of maintained cessation rose significantly from 4% to 24% over twelve months, with a mean delta "stage-of-change" 0.28. [Hughes 2000][94] **Childhood cancer**: nonsignificant trends of increasing risk with number of cigarettes smoked for paternal preconception smoking and non-significant trends of decreasing risk for maternal preconception smoking (all P-values for trend 40.05). Among the diagnostic subgroups, a statistically significant increased

Table 10.3.1: Summary impact estimates for Preconception smoking					
Intervention	**Maternal**	**Pregnancy**	**Newborn**	**Infant**	**Others**
			smoked 1–10 and ≥11 cigarettes per day increased with the level of fetal tobacco exposure (35.8% versus 55.3% versus 64.3%, x2-test=20.303, p=0.000), suggesting a dose effect. [Karatza 2009][92] **NTDs**: [Shaw 1996][50] Preconception (3 months) cigarette consumption of <20/day OR 0.89 [0.63, 1.27] Preconception (3 months) cigarette consumption of >20/day OR 0.62 [0.36, 1.07] **EA+/-TEF:** ORs were near unity for all EA +/- TEF cases combined and any periconceptional exposure to cigarette smoking (OR 5 1.1; CI 5 0.8,1.6) (periconception is 1 month before to end of 1st trimester) [Gibbons 2008][64] **Congential diaphragmatic hernia:** For all CDH combined, odds of any periconceptional cigarette smoking were elevated, but not significantly 1.10 [0.91, 1.33] [Caspers 2010][68] **Orofacial defects:** >15 cigarettes/day vs no smoking- 150/406 vs 1311/4606. [Romitti 2007][74] Maternal smoking in the periconceptional period was associated with CLP (adjusted odds ratio aOR_=1.3; 95% confidence interval CI=		risk of developing hepatoblastoma was found in children whose mothers smoked preconceptionally (OR=2.68, P=0.02) and strongest (relative to neither parent smoking) for both parents smoking (OR=4.74, P=0.003). [Pang 2003][95]

Table 10.3.1: Summary impact estimates for Preconception smoking					
Intervention	**Maternal**	**Pregnancy**	**Newborn**	**Infant**	**Others**
			1.0 –1.6). Periconceptional smoking was only weakly associated with CPO (1.2; 0.9– 1.5). Mothers who smoked heavily in the periconceptional period were about twice as likely to have an infant with any orofacial cleft (1.8; 95% CI 1.1–2.9) than were women who did not smoke during this period. [Honein 2007][67]		
Periconception (1 month before conception till 1st trimester) Environmental Tobacco Smoke Exposure			**CHDs:** No association with CHDs was seen for mothers exposed to ETS at home or in the workplace [Malik 2008][65] **EA+/-TEF:** exposure to any ETS at home or work in the periconceptional period was not associated overall with either CLP or CPO RR 1.04 [0.92, 1.18] [Honein 2007][67]		
Preconception smoking (3 months before conception)	Unintended pregnancy: In the preconception period, those with unintended pregnancies were more likely to smoke. ORs: white respondents 1.46 CI (1.34–1.59)* vs. Black respondents 0.95 (0.78–1.16) [Naimi 2003][58]				**Childhood leukemia**: Maternal smoking was not associated with an increased risk of childhood leukemia. Paternal preconception smoking was significantly associated with an increased risk of AML (OR = 3.84, 95 % CI: 1.04, 14.17), although this risk was based on only 16

Table 10.3.1: Summary impact estimates for Preconception smoking					
Intervention	**Maternal**	**Pregnancy**	**Newborn**	**Infant**	**Others**
					exposed cases and eight exposed controls. A positive association between paternal preconception smoking and ALL was suggestive but not statistically significant by use of a binary smoking exposure variable (OR =1.32, 95% CI: 0.86, 2.04). [Chang 2006][93]
Preconception counseling for smoking	**Behavior change:** Compared with women receiving standard care, more women with PCC quit smoking before pregnancy (10% vs. 18%; unadjusted OR, 3.04 [95% CI, 0.95–9.69]). [Elsinga 2008][71]				
Partner support intervention	To review if interventions to enhance partner support help smoking cessation when added as an adjunct to a smoking cessation				

Table 10.3.1: Summary impact estimates for Preconception smoking					
Intervention	**Maternal**	**Pregnancy**	**Newborn**	**Infant**	**Others**
	programs. The odds ratio for self-reported abstinence at 6-9 months was 1.08 (CI 95%, 0.81 -1.44); and at 12 months post-treatment was 1.0 (CI 95%, 0.75 - 1.34). Park 2004 (Cochrane)				

Although literature was limited, no association was found between periconceptional ETS exposure and congenital malformations.

Key messages

- Preconception smoking increases the risk of preterm births by more than 2 folds
- Pre/peri conception smoking is not significantly associated with congenital defects.
- Preconception couseling leads to an almost 3 fold increase in women quitting smoking before pregnancy.
- ETS exposure was not associated with either congenital heart defects or gastrointestinal anomalies.

10.4. Reducing illicit drugs consumption

Background

Maternal substance abuse is associated with pregnancy complications, low birth weight, an increased risk of infant mortality, neonatal abstinence syndrome, ineffective parenting techniques, child abuse and neglect, and possible human immunodeficiency virus (HIV) transmission. Substance abuse also is often associated with other social and health problems that affect both the mother and infant, including domestic violence, poverty, homelessness, sexual abuse, psychiatric disorders, and poor health care.[96]

Scope of intervention

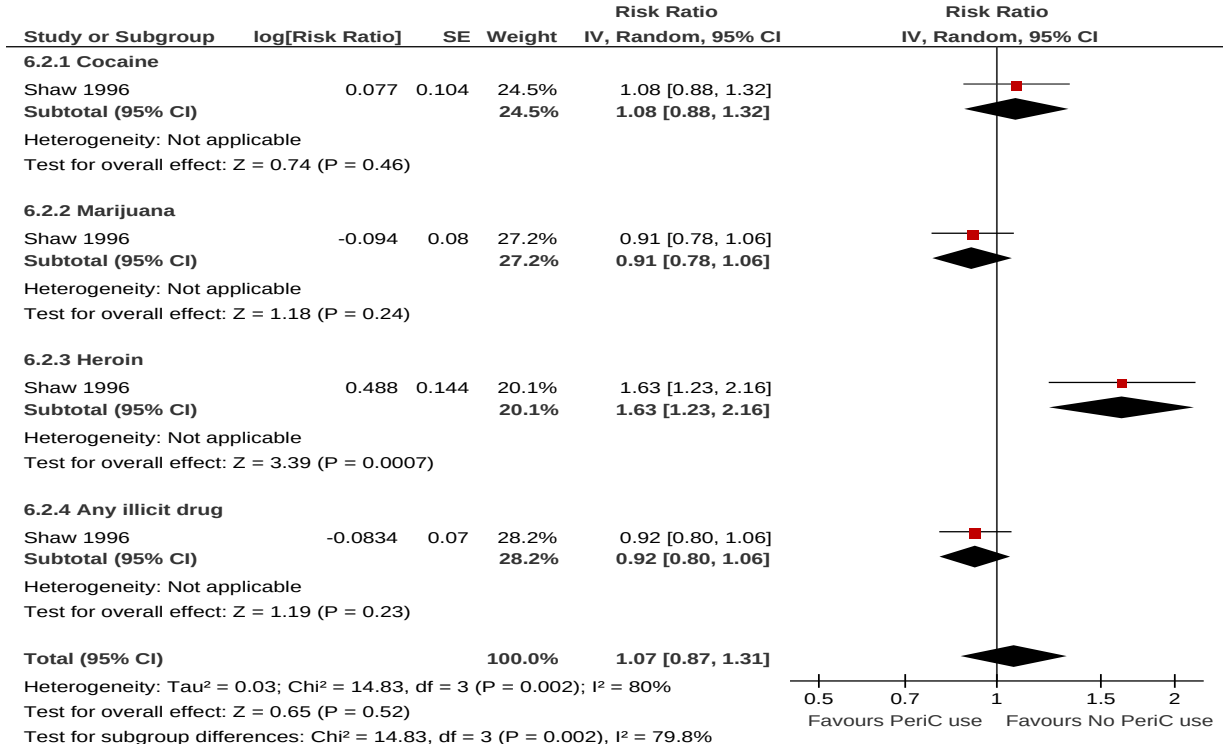
We aimed to assess the effects of preconception abuse of illicit drugs and possible interventions to reduce the level of abuse in this population. Studies reporting peri-conception use and its effects were also looked into. In this section we report evidence for specifically illicit drugs including cocaine, marijuana, heroin etc. Alcohol and smoking are dealt with in their respective sections.

Preconception care for women who use illicit drugs includes identification of women who are consuming it, counseling on the risks associated with preconception use of various drugs (lowbirth weight, prematurity, perinataldeath, abruptio placenta, and small forgestational age births), informing about programs that support abstinence and treatment and promoting the importance of contraception until in control of this unhealthy habit.

Impact estimates

We found a limited number of risk aversion studies concerned with the MNCH effects of periconception substance abuse. Paternal and maternal consumptions were analyzed separately. Paternal periconception use of illicit drugs did not have an association with the risk of neural tube defects (RR 1.07; 95% CI: 0.87-1.31). When looking at the effect of individual drugs, the only significant association with a greater risk of NTDs was that of heroin use in the periconception period (RR 1.63; 95% CI: 1.23-2.16) (**Figure 10.4.1)**.

Figure 10.4.1: Paternal periconception consumption of illicit drugs and risk of NTDs



Citations to the included study:
Shaw 1996[50]

Maternal use of recreational drugs during the periconception period did not lead to an increasedincidence of occurrence of NTDs (RR 0.91; 95% CI: 0.77-1.07) (**Figure 10.4.2)**.

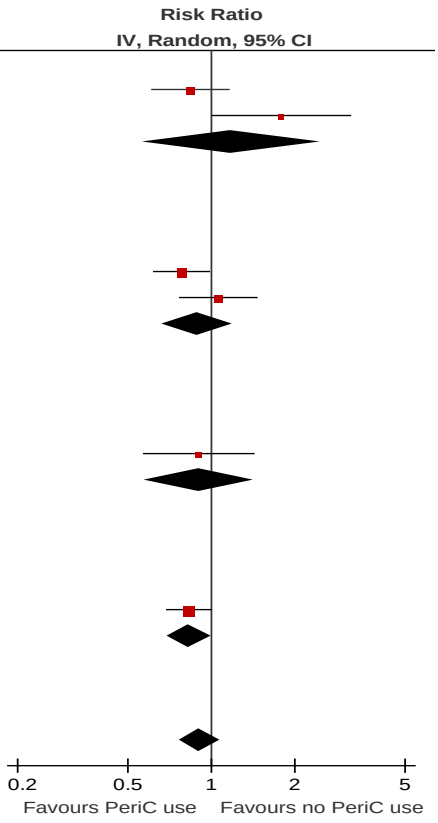
Comparing parental use (combined or individual) with no use did not yield any significant association with NTD risk (**Figure 10.4.3)**.

A strong association was found between recreational drug use in the month in which conception occurred and incidence of gastroschisis, although this evidence came from a single case-control study (**Figure 10.4.4)**. There was no significant association between substance abuse before pregnancy and maternal depression (**Figure 10.4.5)**.

Two interventional studies on reducing illicit drug abuse were cited. One studied the helath seeking behavior of substance-abusing women using the 'Steps of Change' model (Brown 2000)[4]. The other studied the effects of Behavioural Couples therapy vs Individual-Based therapy amongst substance-abusing men on the incidence of partner violence (Stewart 2002)[5]. It reported that post-intervention, male-to-female aggression in the BCT group was lower than in the IBT group (17% vs 43%). Also husbands in the BCT reported fewer days of drug use, longer episodes of abstinence, less drug-related hospitalizations or arrests than husbands receiving individual-based treatment only.

Figure 10.4.2: Maternal periconception consumption of illicit drugs and risk of NTDs

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
7.1.1 Cocaine				
Shaw 1996	-0.174	0.163	16.3%	0.84 [0.61, 1.16]
Van Gelder 2009	0.582	0.292	6.9%	1.79 [1.01, 3.17]
Subtotal (95% CI)			**23.2%**	**1.18 [0.56, 2.46]**
Heterogeneity: Tau² = 0.23; Chi² = 5.11, df = 1 (P = 0.02); I² = 80%				
Test for overall effect: Z = 0.44 (P = 0.66)				
7.1.2 Marijuana				
Shaw 1996	-0.248	0.117	23.1%	0.78 [0.62, 0.98]
Van Gelder 2009	0.058	0.163	16.3%	1.06 [0.77, 1.46]
Subtotal (95% CI)			**39.4%**	**0.89 [0.66, 1.20]**
Heterogeneity: Tau² = 0.03; Chi² = 2.33, df = 1 (P = 0.13); I² = 57%				
Test for overall effect: Z = 0.77 (P = 0.44)				
7.1.3 Heroin etc				
Shaw 1996	-0.105	0.233	10.0%	0.90 [0.57, 1.42]
Subtotal (95% CI)			**10.0%**	**0.90 [0.57, 1.42]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.45 (P = 0.65)				
7.1.4 Any drugs				
Shaw 1996 (1)	-0.186	0.094	27.4%	0.83 [0.69, 1.00]
Subtotal (95% CI)			**27.4%**	**0.83 [0.69, 1.00]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.98 (P = 0.05)				
Total (95% CI)			**100.0%**	**0.91 [0.77, 1.07]**
Heterogeneity: Tau² = 0.02; Chi² = 8.73, df = 5 (P = 0.12); I² = 43%				
Test for overall effect: Z = 1.15 (P = 0.25)				
Test for subgroup differences: Chi² = 0.94, df = 3 (P = 0.82), I² = 0%				

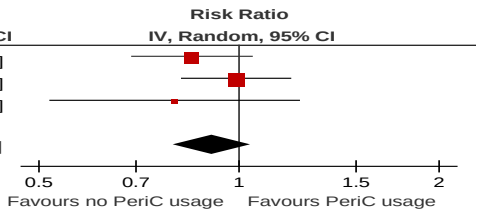


(1) Periconception period: Shaw 1996 3 months pre to 3 months post. Gelder 2009 1 month pre to 3 months post.

Citations to the included studies:
Shaw 1996[50], Van Gelder 2009[97]

Figure 10.4.3- Parental versus maternal periconception consumption of illicit drugs and risk of NTDs

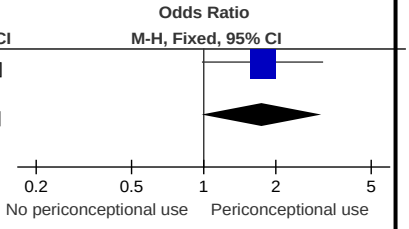
Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Both parents used	-0.163	0.106	40.8%	0.85 [0.69, 1.05]
Only Father used	-0.0101	0.096	49.7%	0.99 [0.82, 1.19]
Only Mother used	-0.223	0.22	9.5%	0.80 [0.52, 1.23]
Total (95% CI)			**100.0%**	**0.91 [0.80, 1.04]**
Heterogeneity: Tau² = 0.00; Chi² = 1.53, df = 2 (P = 0.47); I² = 0%				
Test for overall effect: Z = 1.37 (P = 0.17)				



Citations to the included study:
Shaw 1996[50]

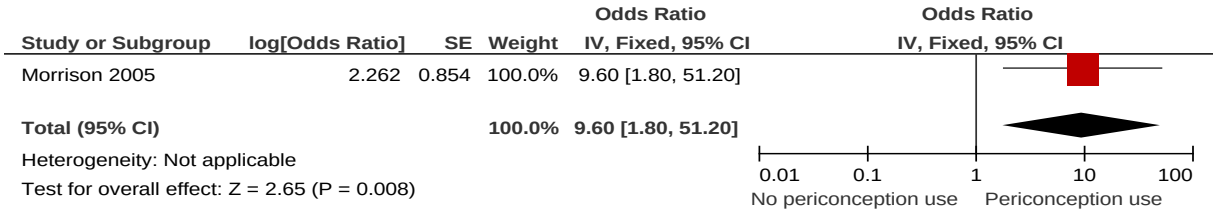
Figure 10.4.4: Maternal periconception consumption of illicit drugs and depression

Study or Subgroup	Periconceptional use Events	Total	no periconceptional use Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Harrison 2009	17	76	113	803	100.0%	1.76 [0.99, 3.13]
Total (95% CI)		**76**		**803**	**100.0%**	**1.76 [0.99, 3.13]**
Total events	17		113			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.93 (P = 0.05)						



Citation to the included study:
Harrison 2009[70]

Figure 10.4.5: Maternal periconception consumption of illicit drugs and risk of Gastroschisis



Citation to the included study:
Morrison 2005[98]

Table 10.4.1: Impact estimates of Illicit drug use

Maternal	Pregnancy	Newborn	Infant
Depression: For depression, the highest rates were seen among alcohol users, alone or in combination with drugs [Harrison 2009][70]		**NTDs:** adjusted risk estimate for paternal periconception (3 months before pregnancy – 1st trimester) heroin use was reduced to 2.3 (95 percent CI 0.42-12.3). [Shaws 1996] [50] for maternal periconception (3 months before pregnancy – 1st trimester) use, elevated risks were not found for any of the investigated substances [Shaws 1996] [50] Analyses restricted to the circumstance where both the mother and the father used at least one drug (other than cigarettes and alcohol) or where either parent used at least one drug did not show increased risks relative to those pregnancies where neither parent used [Shaws 1996][50] Gastroschisis: Incidence of recreational drug use in the peri-conceptional/first trimester periods in cases of fetal gastroschisis was 18%. [Morrison 2005][98]	

Table 10.4.2 - Interventions for reducing illicit drug abuse

Study/yr	Intervention	Results
Brown 2000[99]	4 intervention programs for substance abuse: • 12-step group program • Detoxification program • outpatient drug abuse treatment program • residential substance abuse treatment program	Readiness to seek help for substance abuse behaviors had a statistically significant effect on entry into 12-step groups, x2=4.31, *p*< .05. Injection drug use (IDU) significantly predicted entry into detoxification programs, with IDUs more than four times as likely to enter detox as non-IDUs. only substance abuse treatment readiness significantly predicted entry into drug detoxification, x2=9.62, *p<0* .01. Collectively, client characteristics were significantly related to entry into an outpatient treatment program, x2=14.94, *p=0*.01. Readiness to seek emotional or mental health counseling significantly predicted the receipt of outpatient substance abuse treatment services, x2=5.98,

		p=0.01. IDUs were approximately twice as likely as non-IDUs to enter residential treatment; crack users were almost six times as likely as non-crack users to do so. Readiness to change domestic violence also predicted entry into residential treatment, x2=16.14, *p*<0.001. Readiness to seek substance abuse treatment significantly predicted actual entry into residential treatment, x2=49.69, *p*<0 .001, as did readiness to seek emotional counseling at the final step in this analysis, x2=7.52, *p*<0.01.
Stewart 2002[100]	Individual Based treatment vs Couples Behavioural Treatment. The male partner was the only partner in the IBTcondition who received treatment provided by the clinics.He met with a therapist for two 60-minute individualtherapy sessions and one 90-minute therapy group eachweek. The goal of this treatment was to help these malepartners develop coping skills that would help them remainabstinent from drugs and alcohol. Male partners in the BCT condition received one60-minute weekly individual session and one 90-minuteweekly drug abuse counseling therapy group (both of whichemphasized cognitive-behavioral coping skills training asdescribed for male partners in the IBT condition). Additionally,male partners receiving BCT and their female partnersmet conjointly with a therapist once per week over a12-week period for 60-minute BCT sessions.	Percent days alcohol and drug use BCT vs IBT mean (SD), F-value- Pretreatment: 68.7 (38.6) vs 71.8 (34.4), 2.02 Posttreatment: 19.0 (26.9) vs 29.7 (26.1), 7.78. p <0.01 A smaller proportion of couples in the BCT condition reported male-to-female physical aggression during the yearafter treatment (n = 7, 18%) than those in the IBT condition (n = 17, 43%).

Conclusion

Our results show that there is inadequate evidence on the possible deleterious effects of illicit drug use before conception, a practice which is too common in most parts of the world. Our analysis cites no significant paternal or parental association with NTDs but analysis of maternal periconception use of illicit drugs shows an unexpected protective effect that is significant. This may be explained by 1) the lack of literature found on the topic under review and 2) the use of data from observational studies. Maternal periconception use of recreational drugs was found to have a very significant positive

association with the risk of gastroschisis. There was no association between maternal substance abuse and maternal depression.

Key messages

- Our results should be interpreted with caution due to a relative scarcity of data on this subject.
- We found no significant association between paternal periconception use of recreational drugs and NTDs. However a strangely protective effect was seen with maternal usage.
- We found a strong positive relation between maternal periconception substance abuse and the risk of gastroschisis.

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Section XI

11 Ameliorating environmental exposures

11.1.1 Radiation exposure

Background

Ionizing radiation is known to have detrimental effects on the reproductive systems of both males and females.[1] It's one of the few known factors to increase the likelihood of childhood cancers. The danger to the embryo and fetus of intrauterine ionizing radiation exposure is well documented.[2, 3]

While some studies have found a significant association between preconception paternal exposure to ionizing radiation and Non-Hodgkins lymphoma in their children[4-6] others found a weak, non-significant association[7] or no association.[8-12] Dickinson et al.[13] found a non-significantly increased risk of solid tumors among children of radiation workers and a significant 2-fold increase in the risk of leukemia and non-Hodgkin lymphoma among the children of radiation workers.

For women the results are less clear. Studies have shown a significantly elevated risk of childhood cancers in children born to exposed female radiation workers.[5, 6] Doyle et al.[14] reported that the risk of an early miscarriage was raised in women employed and monitored at the time of conception as compared those not employed at that time or not monitored. At the same time studies have also been conducted that show no significantly raised risks of such events occurring.[8, 15, 16]

A bulk of controllable exposures to ionizing radiation comes from X-rays. Shea et al.[17] reported that preconception paternal exposure to Xrays may lead to a reduction in gestational age, fetal growth and birth-weight, although they say later that this decrease was non-significant. Shu et al.[18] after multiple studies finally concluded that preconception paternal abdominal X-rays were marginally associated with acute myelogenous leukemia in their offsprings; no association was reported for maternal Xrays. On the contrary, a higher incidence of malignant neoplasms[19] and leukemias[20] was shown in offsprings of women who had had preconception Xray exposures.

Scope of intervention

We looked at studies examining the effects of paternal/maternal preconception radiation on fetal/neonatal effects and despite it not being a part of our above mentioned objectives, we also looked at long term effects of such an exposure. Ionizing radiation exposure composed of both, occupation-related exposure as well as non-occupational exposure.

The content of preconception care with respect to environmental exposures consists of taking a detailed history of the couple to identify possible sources of radiation exposure, informing women of child-bearing age about the possible deleterious effects

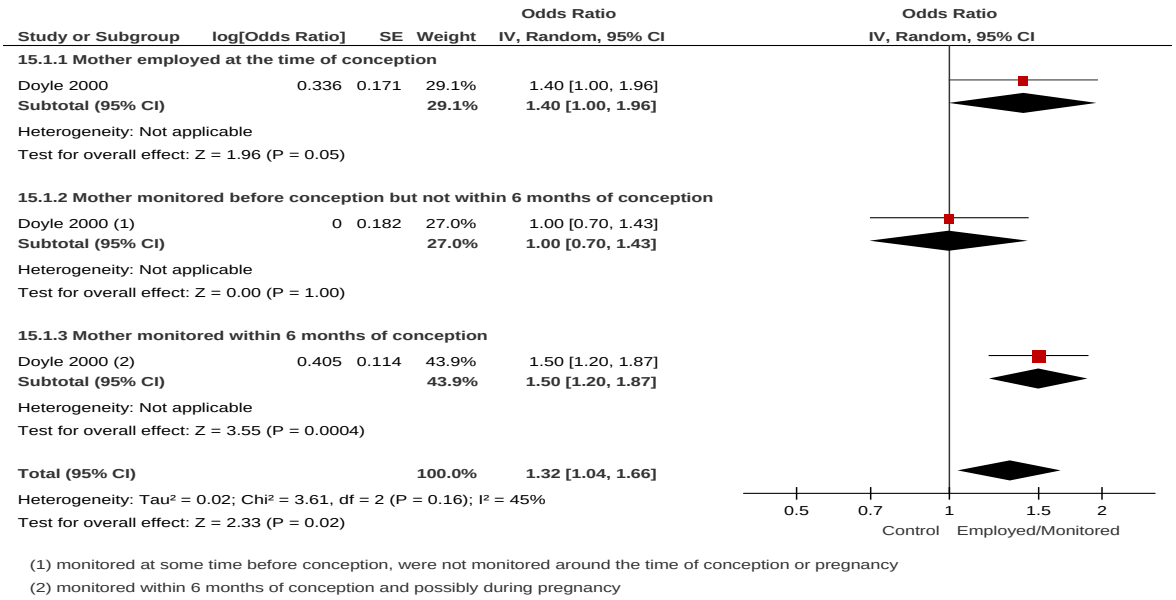
(miscarriage, stillbirths, childhood cancer) of such occupational or non-occupational exposure, on their health as well as that of the fetus, in case of an unknown pregnancy.

Impact estimates

Both occupational and non-occupational radiation exposure were analysed separately. There was only 1 study by Doyle et al[14] reporting evidence on the effect of preconception radiation exposures in women on fetal death. This showed a significant increase in risk of early miscarriage in mothers who had been employed at or before conception [RR 1.32; 95% CI: 1.04-1.66]. This association was stronger in women who were monitored within 6 months of conception (RR 1.50; 95% CI: 1.20-1.87) (**Figure 11.1.1**).

There was also a non-significant association between still births and maternal monitoring before conception (RR 2.30; 95% CI: 0.80-6.62) (**Figure 11.1.2**) and 2nd trimester miscarriage (RR 0.50; 95% CI: 0.20-1.26) (**Figure 11.1.3**).

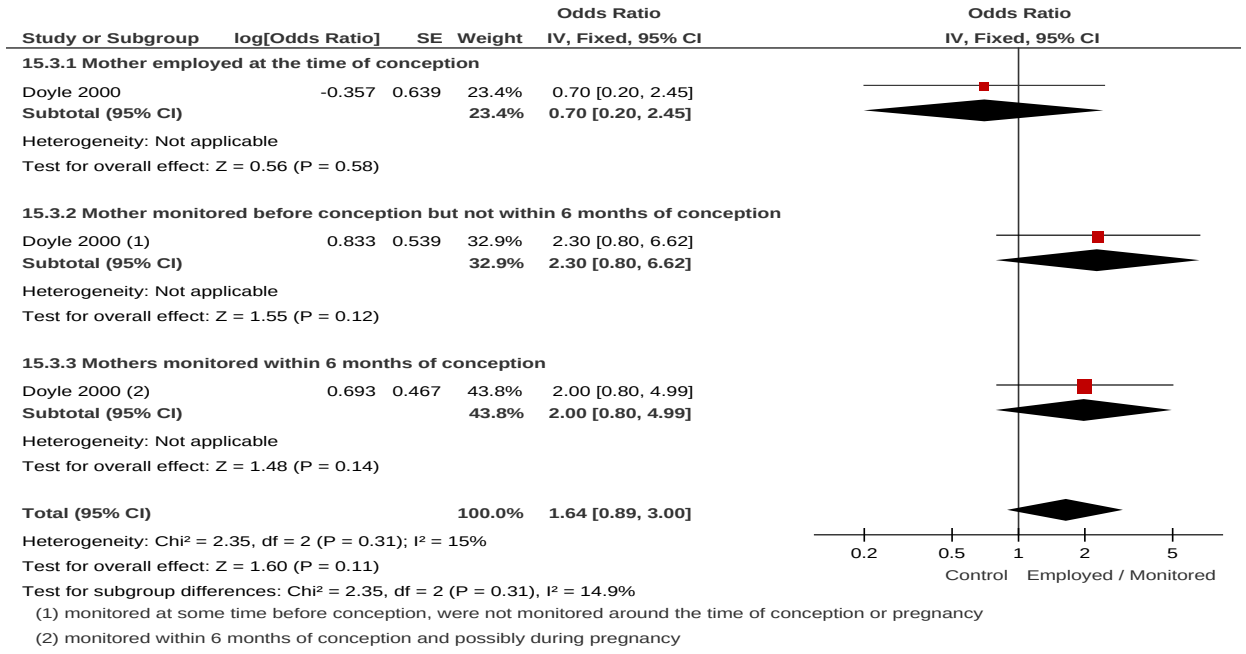
Figure 11.1.1: Women employment status and risk for 1st trimester miscarriage



Citation to included study:
Doyle 2000[14]

Both paternal and maternal exposure to preconception ionizing radiation at work led to an overall greater risk of childhood cancers (RR 1.29; 95%CI: 1.02, 1.63; RR 1.19; 95% CI: 0.92-1.54 respectively) (**Figure 11.1.4** and **Figure 11.1.5**), however this association was only significant for maternal exposure. This finding is not in conjunction with the results of Bunch et al.[16] on the effect of preconception maternal radiation exposure on all childhood cancers (RR 1.90; 95% CI: 0.84-4.58). However pooling this with our respective total proved our initial finding of a significant association between exposure and outcomes (RR 1.33; 95% CI: 1.06-1.67). There was no significant association between individual tumor categories and parental exposure to occupational radiation. Studies looking at the effect of radiation dose on the incidence of childhood hematological malignancies had equivocal results.[5, 7, 12, 15, 21, 22] However, many had samples to small to comment on the significance of their findings.

Figure 11.1.2: Women employment status and risk for stillbirth

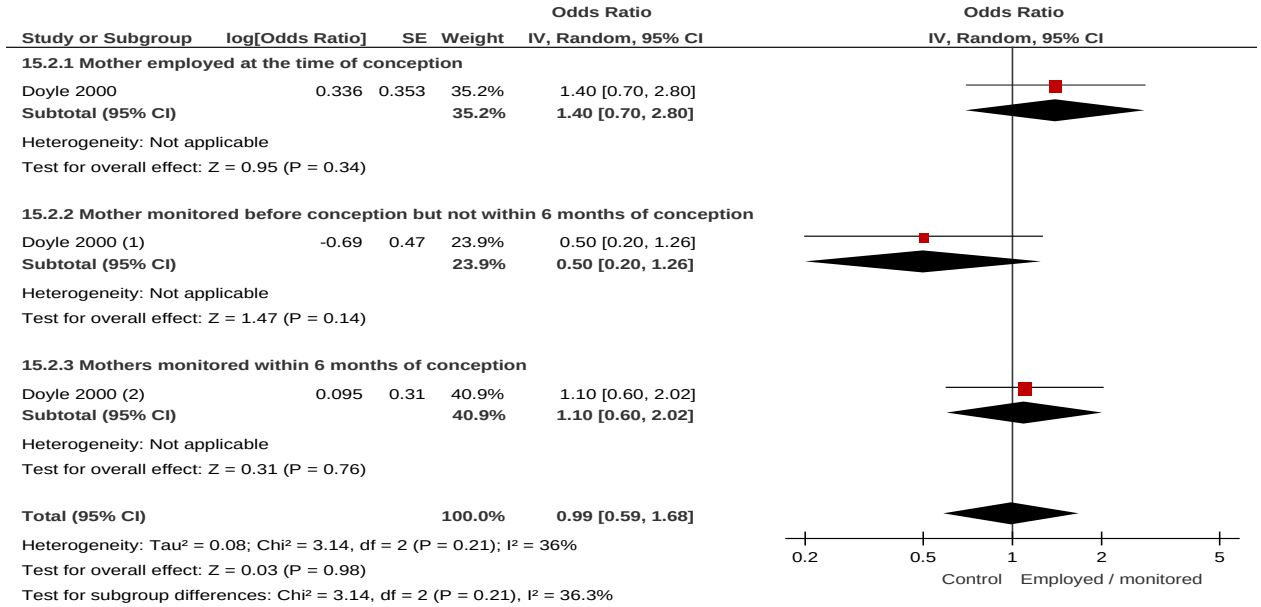


(1) monitored at some time before conception, were not monitored around the time of conception or pregnancy

(2) monitored within 6 months of conception and possibly during pregnancy

Citation to included study:
Doyle 2000[14]

Figure 11.1.3: Women employment status and 2nd trimester miscarriage

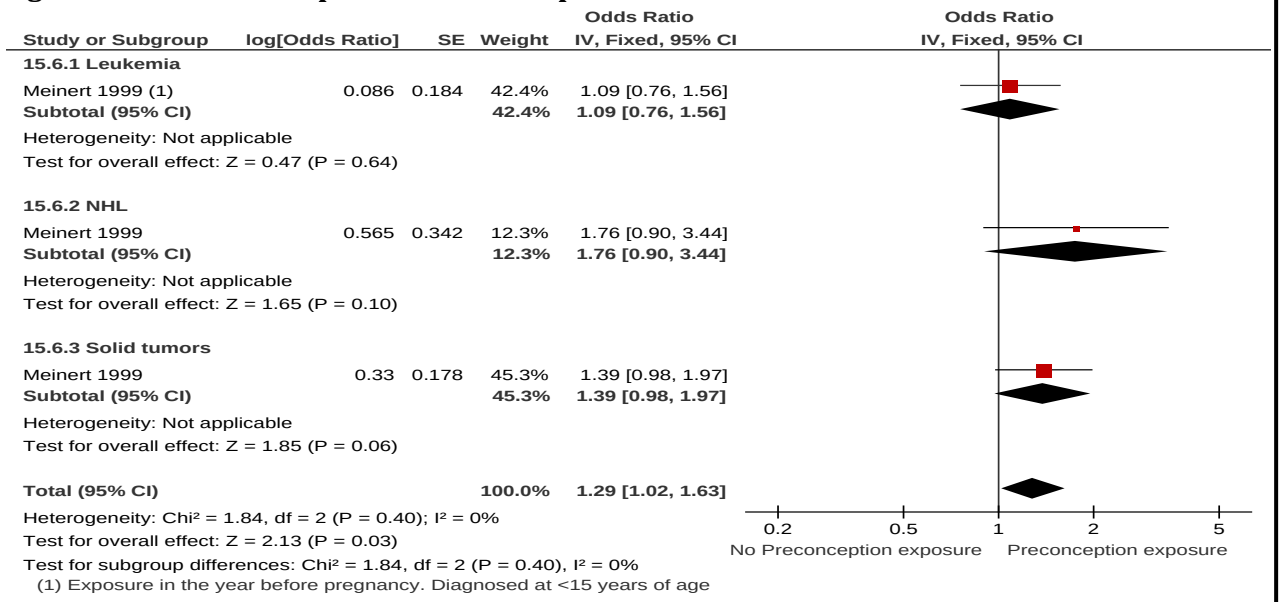


(1) monitored at some time before conception, were not monitored around the time of conception or pregnancy

(2) monitored within 6 months of conception and possibly during pregnancy

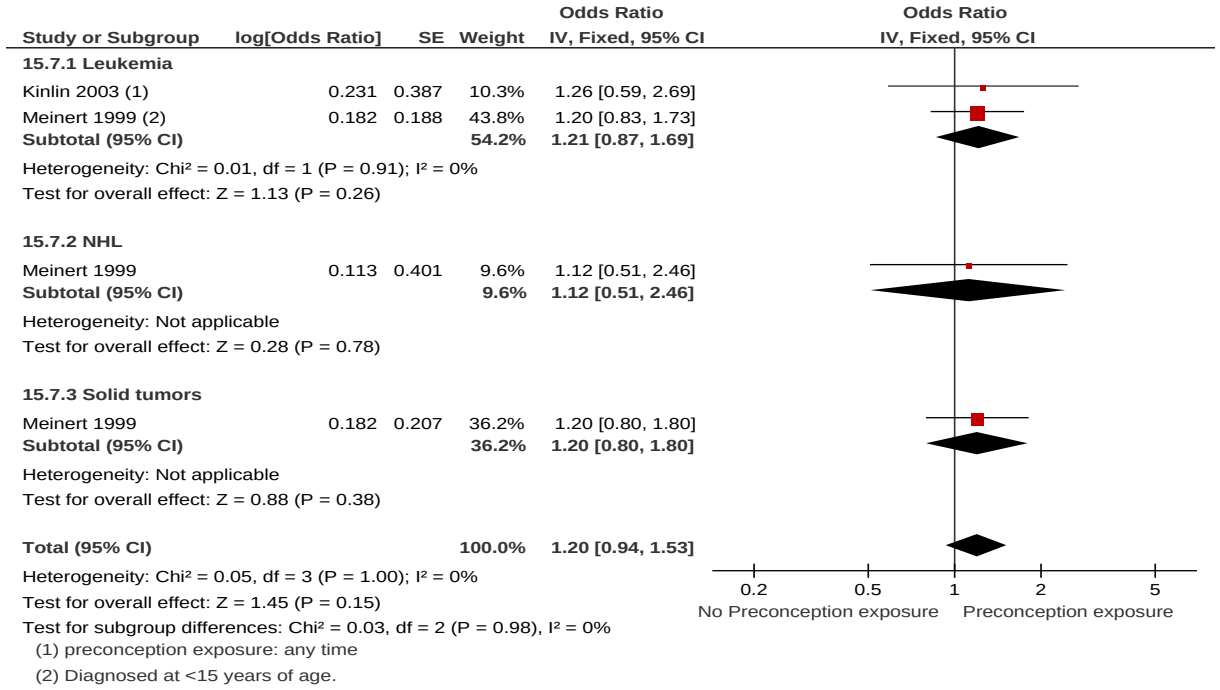
Citation to included study:
Doyle 2000[14]

Figure 11.1.4: Preconception maternal exposure to radiation and childhood cancer



Citation to included study:
Meinert 1999[7]

Figure 11.1.5: Preconception paternal exposure to radiation and childhood cancer



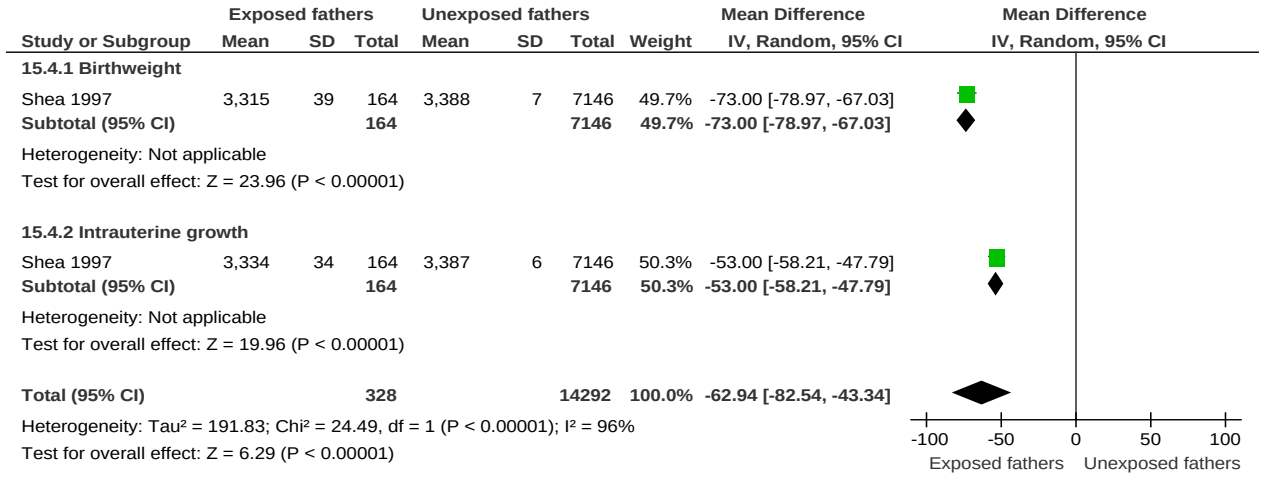
Citation to included study:
Meinert 1999[7], Kinlen 2002[23]

Non-occupational exposure to ionizing radiation via X-rays led to higher rates of adverse fetal and neonatal outcomes. Paternal exposure led to significant decrements in birthweight (MD -73.00; 95% CI: -78.97, -67.03) (**Figure 11.1.6**) and intrauterine growth (MD -53.00; 95% CI: -58.21, -47.79) (**Figure 11.1.7**). There was no data available for possible effects of maternal preconception exposure on these outcomes. Parental Xray exposure before conception showed a weakly significant positive

association with childhood cancers diagnosed in less than 15 years of age, especially between paternal abdominal exposure and leukemia in the offspring.

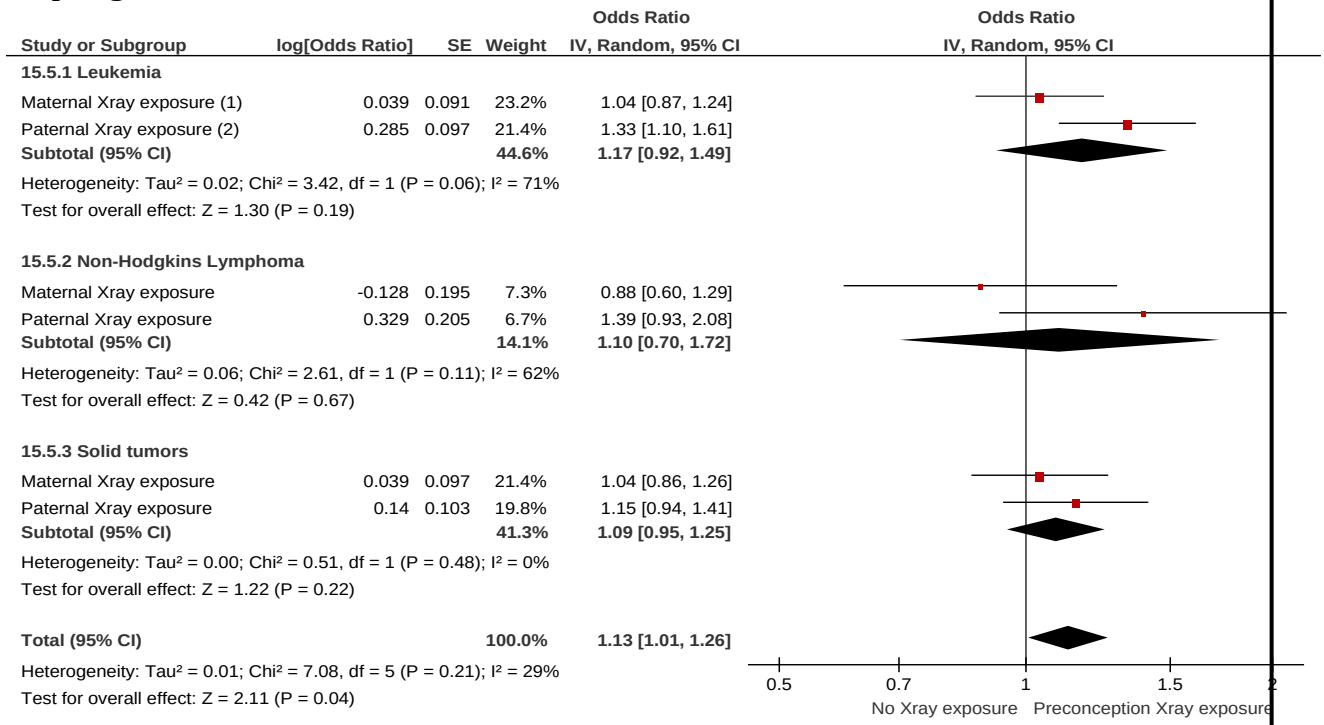
Parental magnetic field exposures in the periconception period were not found to be associated with development of childhood cancers[25,26]

Figure 11.1.6: Paternal preconception exposure to X-rays and Birth-weight and intrauterine growth in their offspring



Citation to included study:
Shea 1997[17]

Figure 11.1.7: Parental preconception exposure to X-rays and malignancies in their offsprings



(1) Diagnostic Xrays of mothers in the 15 months preceding conception. Diagnosed at <15 years of age.
(2) Diagnostic Xrays of fathers in the 2 years preceding conception. Diagnosed at <15 years of age.

Citation to included study:
Meinert 1999[7]

Table 11.1.1: Summary of impact estimates of Radiation exposure				
Maternal /Paternal	**Pregnancy / fetal**	**Newborn**	**Infant**	**Others**
Non-occupational exposure				
Parental exposure	**<u>Intrauterine growth reduction (IUGR):</u>** A similar difference was noted for the mean of intrauterine growth in babies of exposed fathers, 3,374 g exposed versus 3,437 g unexposed (p = 0.078). [Shea 1997][17]	**<u>Birth weight:</u>** The mean birth weight of babies of exposed fathers was 3,358 g compared with a mean of 3,437 g in the unexposed group (p = 0.055). [Shea 1997][17]		**<u>Cancer in offspring:</u>** Diagnostic Xrays of the father in the 2 years preceding birth and the odds of their offspring having-Leukemia: OR=1.33, 95% CI (1.10–1.61); NHL: OR=1.39, 95% CI (0.93–2.08); Solid tumors: OR=1.15, 95% CI (0.94–1.41). A statistically significant association between prenatal paternal X-ray examinations was found with leukemias (OR 5 1.33, 95% CI: 1.10– 1.61; Diagnostic Xrays of mother in the 15 months preceding conception and the odds of their offspring having: Leukemia: OR= 1.04, 95% CI (0.87–1.24); NHL: OR= 0.88, 95% CI (0.60–1.30); Solid tumors: OR= 1.04, 95% CI (0.86–1.25). [Meinert 1999][7] Maternal preconception Xray – Abdominal:- observed/expected 304/307.9, t-value -0.3, RR 0.97 Chest:- observed/expected 926/876.5, t-value +3.0 Extremities:- observed/expected 271/268, t-value +0.3 Paternal preconception Xray – Abdominal:- observed/expected 208/198.0, t-value +1.1, RR 1.12 Chest:- observed/expected 1112/1048.4, t-value +3.9 Extremities:- 557/488.1, t-value +5.1 [Kneale 1980][24] Maternal preconception irradiation: Any exposure No- Control (%) 110 (64), ALL/AML case (%) 108 (69). Yes- Control (%) 63 (36), ALL/AML case (%) 50 (32), OR

Table 11.1.1: Summary of impact estimates of Radiation exposure				
Maternal /Paternal	**Pregnancy / fetal**	**Newborn**	**Infant**	**Others**
				(95% CI) 0.77 (0.48–1.24). Paternal preconception irradiation: Any exposure No- Control(%) 85 (55), ALL/AML case (%)84 (57), Yes- Control (%) 70 (45), ALL/AML case (%) 63 (43), OR (95% CI) 0.92 (0.57–1.47). [Linabery 2006][25]
Occupational exposure				
Paternal exposure				**Cancers**: Children of radiation workers had a non-significantly increased risk of solid tumors (RR=1.5, 95% CI: 0.9–2.4, p = 0:09), determined largely by an increased risk of cancers excluding leukemias, lymphomas, brain, spinal and gender-specific tumors (adjusted RR=1.7, 95% CI: 0.8–3.2, p = 0:50). Within children of radiation workers there was no evidence of an increased risk with increasing paternal preconception dose of external radiation (hazard ratio per 100 move for all solid tumors=0.6, 95% CI: 0.1–1.8, p = 0:52). [Dickinson 2002][13] lack of effect among offspring aged 0–24 years, RR comparing paternal preconceptional radiation =>100 mSv and others=1.5, 95% CI: 0.5–5.0) [Roman 1999][12] For leukaemiaand non-Hodgkin lymphoma, radiation workers overallshowed a relative risk of 1.77 (1.05 to 3.03). Lack of effect among offspring aged 0–14 years, RR comparing paternal preconceptional radiation =>100 mSv and others=1.0, 95% CI: 0.1–13.8. The effect of including the cases in the study ofGardner et al was also examined. The relativerisk of leukaemia and non-Hodgkin lymphoma for atotal preconception dose of

Table 11.1.1: Summary of impact estimates of Radiation exposure				
Maternal /Paternal	**Pregnancy / fetal**	**Newborn**	**Infant**	**Others**
				100 mSv or more was 1.43(0.26 to 7.18). Other relative risks did not differ greatlyfrom those excluding the Gardner cases.When dose was treated as a continuous variable, therelative risk of leukaemia and non-Hodgkinlymphoma for a total preconception dose of 100 mSvwas 2.13 (1.02 to 5.13); this risk was reduced to 1.52(0.71 to 3.76) after radiation worker status was adjustedfor. There were no significant relations between doseand risk for the 6 month and 3 month preconceptiondoses.7 The relative risk for radiation workers irrespective of dose received was 1.83 (1.11 to 3.04) [Draper 1997][5] A case–control study near the Sell afield nuclear plant They found a strong association with preconception radiation exposure in the fathers of the affected children. This study concluded that paternal preconception radiation was a causal factor for childhood leukemia. [Gardner 1990][4] The relative risk for LNHL associated with a total preconception dose of 100 mSv or more was found to be significantly raised at 6.45 (95% CI 1.57, 26.48). [Gardner 1992][21] The relative risk for LNHL associated with a total preconception dose of 100 mSv or more was found to be 0.46 (95% CI 0.01, 5.17), based on one case and four control fathers. [Draper 1997][26] A case control in Germany found a non-significant OR of 1.80 for fathers under dosimetric surveillance; the radiation doses for these fathers were often unknown or below the level of detection and none exceeded 30 mSv.

Table 11.1.1: Summary of impact estimates of Radiation exposure				
Maternal /Paternal	**Pregnancy / fetal**	**Newborn**	**Infant**	**Others**
				[Meinert 1999][7] A study in USA found no association between childhood LNHL and paternal employment at the sites prior to conception. [Sever 1997][8] The estimated paternal doses above the 95th percentile (482 mGy) were associated with a non-significant increased risk of 1.8 (95% CI 0.7–4.6) relative to the reference group, on the basis of six events (two leukemia, two lymphoma, one sarcoma, and one oral cancer case) [Johnson 2008][15] No significant excess of leukemia or of leukemia and non-Hodgkin's lymphoma was found at any radiation level in any preconceptional period OR=1.26 CI (0.59-3.90). [Kinlen 1993][10] Nuclear industry under dosimetric surveillance yielded an OR of 1.80 (95% CI: 0.71–4.58). [Meinert 1999][7] The leukemia rate in children whose fathers had accumulated a preconceptual dose of >100 mSv was 5.8 times that in children conceived before their fathers' employment in the nuclear industry (95% CI 1.3 to 24.8) but this was based on only three exposed cases. [Roman 1999][12] For leukemia, the estimated rate ratio in children whose fathers had a record of monitoring for radiation exposure before their conception was 2.2 (0.8 to 6.1; based on 12 exposed cases). With respect to recorded whole body dose, the rate ratio for leukemia in those whose fathers had

Table 11.1.1: Summary of impact estimates of Radiation exposure				
Maternal /Paternal	**Pregnancy / fetal**	**Newborn**	**Infant**	**Others**
				accumulated a lifetime dose of >100 mSv before their child's conception was 5.8 (1.3 to 24.7). [Roman 1999] [12] For LNHL, statistically significantly raised RRs were found in relation to paternal employment on the date of conception (RR 2.34, 95% CI 1.31, 4.18) and for paternal employment on the date of diagnosis (RR 2.26, 95% CI 1.22, 4.19), when these variables were analysed separately. In contrast, the RR for employment that ceased before conception was close to one (RR 1.04, 95% CI 0.46, 2.35). The simultaneous analysis of all these variables did not yield significantly raised risks for any one of the variables. [Sorahan 2009][27] Relative risk of leukemia as a result of 100 mSv total paternal preconception radiation dose for the offspring of the Sellafield workforce, RR 1.70 (0.81, 3.28). [Little 1995]. Leukaemia cases/controls 3/13 OR (95% CI)1.03 (0.29 to 3.65) ALL cases/controls 3/13 OR (95% CI)1.25 (0.35 to 4.40). [McKinney 2003][28]
Maternal exposure	**Miscarriage**: The risk of early miscarriage was raised in women who were employed at the time of conception compared with the women who were not (p=0·04). With respect to monitoring, the risk of early miscarriage was raised in women who were monitored within 6 months of conception and possibly during	**Malformation:** The overall Prevalence of any major malformation was 23·8 per 1000 pregnancies reported by men and 32·3 per 1000 pregnancies reported by women. For women the risk of any major congenital		**Cancer in offsprings**: No appreciable increased risk or dose–response was observed between maternal preconception exposure and childhood cancer. [Johnson 2008] [15] Likelihood of Maternal exposure in the year before pregnancy and Leukemia in the offspring OR= 1.09 95% CI 0.76–1.55; NHL OR=1.76 CI0.90–3.43 ; Solid tumors OR=1.39 CI 0.98–1.99 [Meinert 1999] [12] For childhood leukaemia and non-Hodgkin lymphoma,

Table 11.1.1: Summary of impact estimates of Radiation exposure				
Maternal /Paternal	**Pregnancy / fetal**	**Newborn**	**Infant**	**Others**
	pregnancy(p0·002), but not in women who, though monitored at some time before conception, were not monitored around the time of conception or pregnancy (p=0·84). Mother employed at time of conception- 1st trimester miscarriage n=331; OR 1·4 (1·0–1·9); 2nd trimester miscarriage n=79 OR 1·4 (0·7–2·7). Mother monitored within 6 months of conception- 1st trimester n=78 OR 1·5 (1·2–1·9); 2nd trimester n= 15 OR 1·1 (0·6–2·2) 7 2·0 (0·8–5·0) [Doyle 2000][14] **Stillbirth**: No evidence of an effect on stillbirth risk of employment in general around the time of conception (within 6 months) (p=0·57). Mother employed at time of conception 331; stillbirth n=25 OR 0·7 (0·2–2·3). Mother monitored within 6 months of conception- Stillbirth n= 7 OR 2·0 (0·8–5·0) [Doyle 2000][14]	malformation was not increased in relation to monitoring status before conception (p=0·17) and there was no significantly increased risk for any specific diagnosis. [Doyle 2000][14]		radiation workers overall showed a non-significantly raised risk of 4.00 (0.40 to 196.5); for other childhood cancers there was a significantly increased relative risk of 5.50 (1.20 to 51.02); for all cancers taken together the relative risk was 5.00 (1.42 to 26.94). [Draper 1997][26] Leukaemia cases/controls 1/7 OR (95% CI)0.63 (0.08 to 5.15) ALL cases/controls 1/7 OR (95% CI)0.76 (0.09 to 6.19). [McKinney 2003]**[28]

**Exposure at periconception was defined as the job held one year prior to the birth of the child and analysis was restricted to natural parents

Table 11.1.2: Summary of impact estimates of magnetic field exposure				
Maternal/paternal	Pregnancy	Newborn	Infant	Others
				Childhood cancers: Frequency-matched conditional logistic regression models revealed no increased cancer risks in children whose fathers were occupationally exposed to magnetic fields above 0.2 lT. The adjusted regression analysis resulted in an odds ratio of 0.85 (95% confidence interval (CI): 0.70, 1.03) for leukemia in children with paternal magnetic field levels above 0.2 lT. The odds ratios for the other types of cancer were based on smaller numbers of exposed cases, and all were close to unity. The analyses revealed no associations between maternal occupational exposure and childhood leukemia (odds ratio (OR) = 0.89, 95% CI: 0.65, 1.23) or central nervous system tumors (OR = 0.88, 95% CI: 0.58, 1.33). [Hug 2009][29] Periconception Electromagnetic fields: Leukaemia - Maternal exposure:- cases/controls 86/452 OR(% 95CI) 0.83 (0.66 to 1.06); paternal exposure:- cases/controls 108/374 OR(% 95CI) 1.23 (1.00 to 1.55). ALL - Maternal exposure:- cases/controls 74/452 OR(% 95CI)0.85 (0.66 to 1.10); paternal exposure:- cases/controls 87/374 OR(% 95CI) 1.16 (0.93 to 1.50). [McKinney 2003]**[28]

**Exposure at periconception was defined as the job held one year prior to the birth of the child and analysis was restricted to natural parents

Conclusion

The current literature available to study the effect of preconception parental exposure to ionizing radiation on MNCH outcomes is limited, especially for fetal and early neonatal effects. Our analyses shows that occupational exposure in female radiation workers before conception leads to a significantly increased risk of early miscarriages but the raise in stillbirths does not attain statistical significance and there is no association with 2nd trimester losses. Such exposure also leads to a significant increase in the not-so-immediate outcomes of childhood cancers. Paternal occupational exposure did not yield an effect on frequency of childhood cancers.

Paternal Xray exposure in the period before conception caused significantly reduced birth-weights and rates of fetal growth. Paternal Xray was also associated with an increase in resultant cases of childhood cancer. Because diagnostic x-rays will continue to be widely utilized, knowledge of possible detrimental effects on reproductive outcomes is of practical importance. We postulate that these associations would be stronger with exposures closer to the time of conception. Hence future research should be directed at that.

Key messages

- Occupational exposure in women before conception leads to a significant 30% increase in 1st trimester miscarriages
- Occupational exposure in women before conception leads to a significant 29% increase in overall childhood cancers
- Occupational exposure in men before conception leads to a non-significant increase in childhood cancers.
- Paternal X-ray exposure leads to significantly increased rates of fetal growth restriction and decreased birthweights.
- Future research should be targeted at finding the association between exposure closer to the time of conception and MNCH outcomes.

11.2 Chemical exposure

Background

An increasing body of scientific research provides disconcerting verification of the potential impact of environmental toxicants that greatly affect human reproductive health and human development. It is believed that roughly 3% of fetal developmental defects are attributable to chemical exposures.[30] Toxic chemical exposures include organic solvents, metals, pesticides, polychlorinated biphenyl [PCB]. Adverse outcomes associated with chemical exposures include low birth weight;[31] spontaneous abortion, preterm birth, still birth/infant death, congenital anomalies;[32] developmental delays;[33] and childhood cancers.[34]

Scope of intervention

This section was meant to deal with all the environmental exposures other than radiation and ETS which were covered in their respective sections. We intended to review literature for effects of exposure among either parent in the preconception period on the subsequent pregnancy and its outcomes. Early spontaneous abortions

were defined as <12 weeks of gestation; >12 weeks but <20 weeks of gestation was classified as late spontaneous abortion.

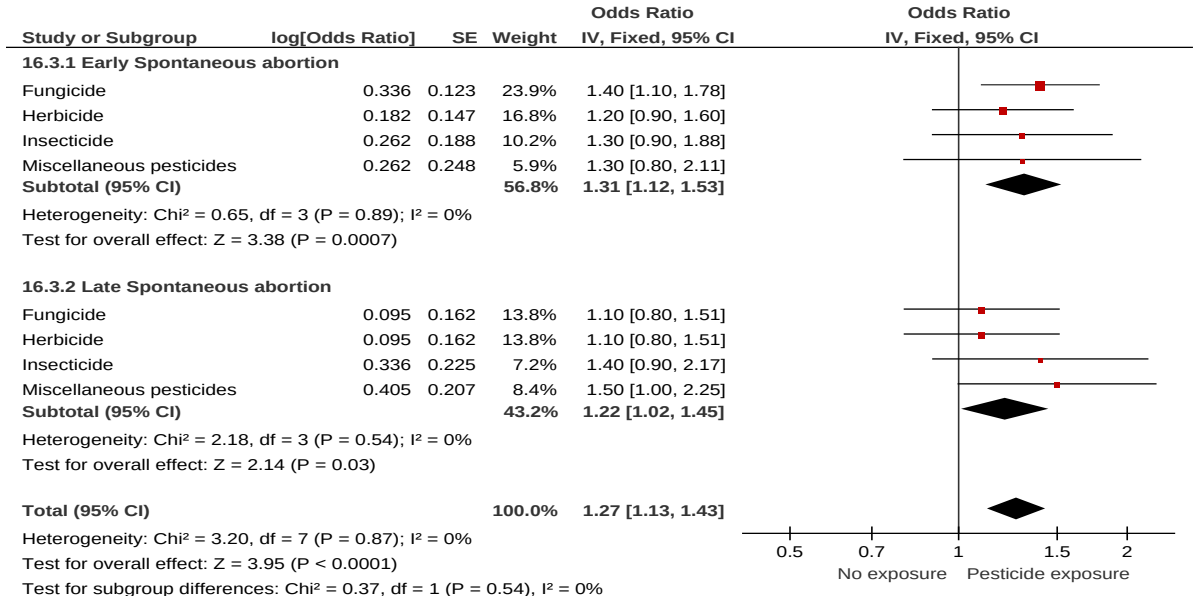
The content of preconception care with respect to environmental exposures consists of taking a detailed history of the couple to identify possible sources of toxic exposure, informing women of child-bearing age about the deleterious effects of such exposure, at home or at the workplace, on their health as well as that of the fetus, in case of an unknown pregnancy status. They should be advised to avoid eatingshark, swordfish, king mackerel, and tile fish to reduce possible exposure to mercury. Women with a history of lead poisoning should be counseled on the risk on the unborn child.

Impact estimates

Parental exposures before conception can result inan array of adverse reproductive effects. We found very limited evidence of toxic forms of exposure and their effects pertaining to MNCH outcomes.

Preconception exposure to pesticides led to a 27% increase in spontaneous abortions (p <0.001); with a 31% increase in early spontaneous abortions (p=0.0007) and a 22% increase in late spontaneous abortions (>12 weeks) (p=0.03) (**Figure 13.2.1**). Fungicides were significantly associated with early spontaneous abortions. Paternal exposure to pesticides in the year before conception also showed significant increase in the rates of hematological malignancies in their offsprings[35,36,37,38, 39.] also reported an increase in childhood leukemias with parental preconception exposure to a multitude of chemicals.

Figure 11.2.1: Preconception exposure to pesticides and spontaneous abortion of fetus



Citation to the included study:
Arbuckle 2001[40]

Analysis of a handful of studies on parental exposure to chemicals like paints, solvents, industrial products etc showed a 10% increase in the risk of ALL in subsequent offsprings with paternal exposure and a 44% increase with maternal exposure; both were significant (p=0.02; p<0.00001 respectively) (**Figure 11.2.2, Figure 11.2.3**).

McKinney et al (2003)[28] also found that exposure to *dermal hydrocarbons andmetal* during the preconception period was linked to a statistically significant increase in leukemia and ALL.

Vinceti 2001[41] reported an excess risk of cardiovascular defects (OR 2.59; 95% CI: 1.68-3.82) in a lead-polluted area.

Women who reported having used of wood to cook during the the acute risk period (ARP- 3months before last period to 1 month after) had more than three times the risk of having infants with an NTD (95%CI=1.70–6.21)[42] another study reported that women who used wood, coal or tires in their home for cooking or heating had twice the odds of having a child with anencephaly compared with women not using this kind of combustible (crude OR 2.04; 95% CI 1.29 to 3.23).[43]

Another area of unavoidable environmental exposure is that of traffic-related particulate air pollution. Perin et al (2010)[44] showed that the risk of early pregnancy loss in women exposed to high levels of ambient particulate matter (>56.72 mg/m3) during the preconceptional period was almost 3-fold higher than expected in the group of women exposed to lower levels.

We also found evidence on the effect of bed-heating devices on the occurrence of certain birth defects (NTDs and orofacial defects), none of which were significant.[45]

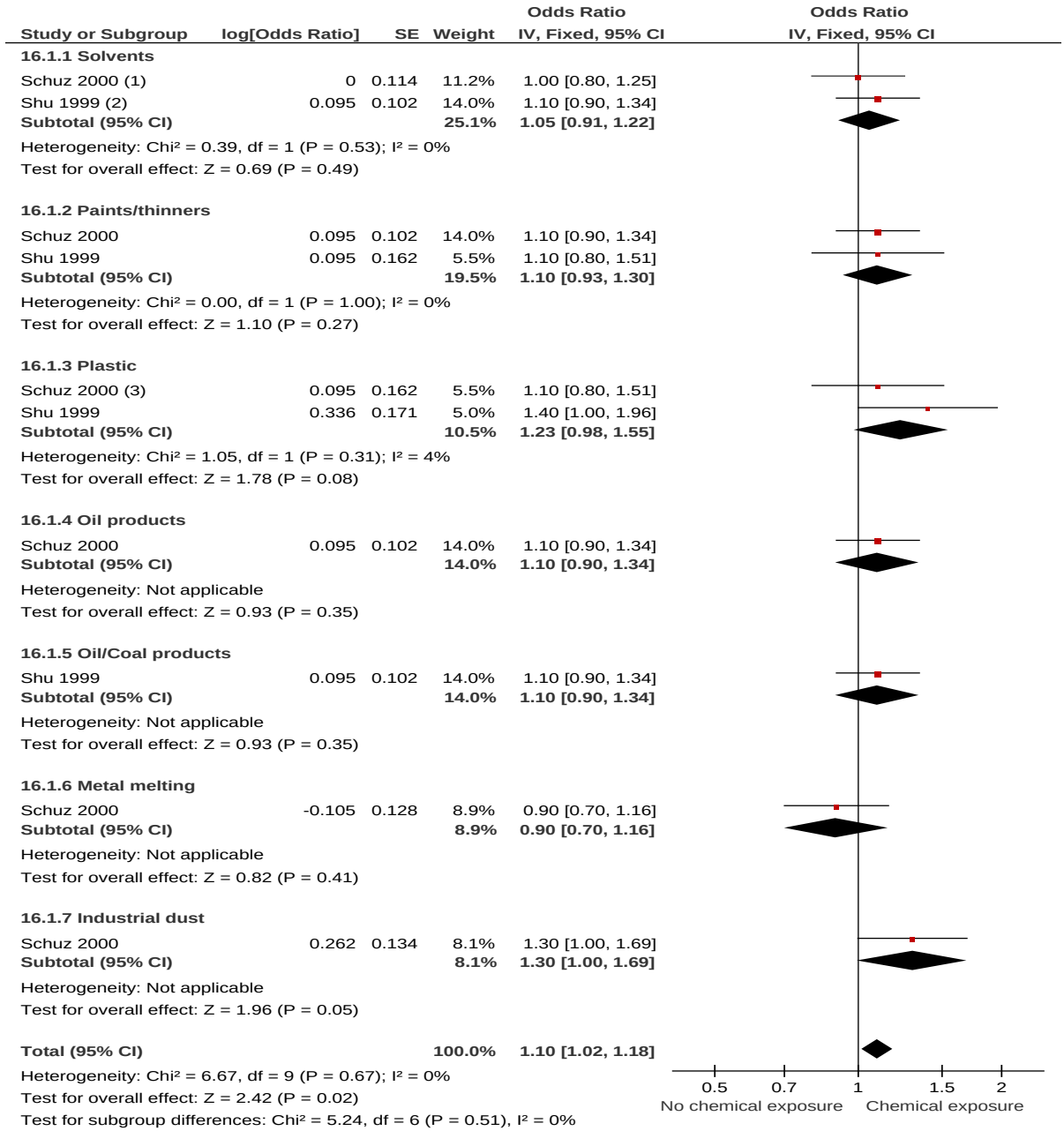
Conclusion

In conclusion, there was a paucity of literature on the MNCH effects of exposure to various environmental agents in the preconception period. Although our data suggests a significant effect of preconception pesticide exposure on all spontaneous abortions and of preconception exposure to other chemicals (solvents, paints, industrial dust etc) on the risk of ALL in their offspring, these results should be interpreted with caution as only a small amount of relevant studies were pooled and analyzed. This clearly delineates the work for future research as countless environmental agents still need to be studied for their effects MNCH outcomes. Only then will comprehensive interventions to reduce exposure be designed and evaluated for a final formation of a sound policy dealing with this topic.

Key messages

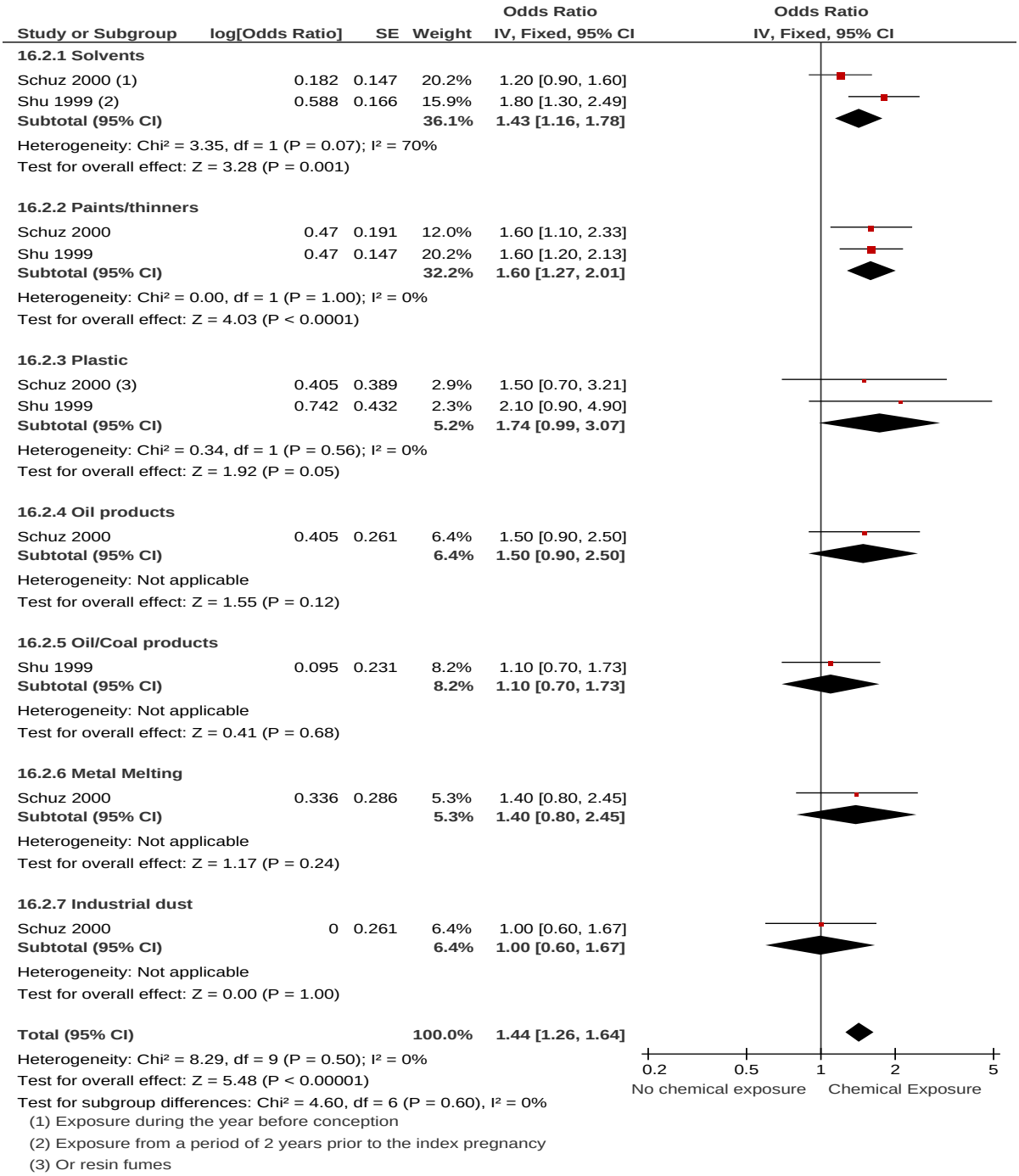
- An absolute deficiency of data exists to assess the possible relation between environmental exposures before conception and subsequent pregnancy outcomes
- Limited data shows a 27% increase in spontaneous abortions in those exposed to pesticides in the preconception period ($p < 0.0001$), especially spontaneous abortions in <12 weeks of gestation
- Limited data links living in a lead-polluted area to a 3-fold increase in congenital heart defects
- Limited data points to a 10% increase in the risk of ALL in offsprings of fathers exposed to various chemicals in the preconception period as compared to 44% when the mother was exposed ($p <0.02$; $p< 0.00001$ respectively)

Figure 11.2.2: Paternal Preconception exposure to Chemicals and ALL



Citation to included studies:
Schuz 2000[46], Shu 1999[47]

Figure 11.2.3: Maternal Preconception exposure to Chemicals and ALL



Citation to included studies:
Schuz 2000[46], Shu 1999[47]

Table 11.2.1: Summary of impact estimates of pesticide exposure				
Maternal /Paternal	**Pregnancy**	**Newborn**	**Infant**	**Others**
	<u>Abortions</u>: Moderate increases in risk of early abortions (< 12 wks) for preconception exposures to phenoxy acetic acid herbicides [OR = 1.5; 95% CI, 1.1–2.1], triazines (OR = 1.4; 95% CI, 1.0–2.0), and any herbicide (OR = 1.4; 95% CI, 1.1–1.9). For late abortions (12-19 wks), preconception exposure to glyphosate (OR = 1.7; 95% CI, 1.0–2.9), thiocarbamates (OR = 1.8; 95% CI, 1.1–3.0), and the miscellaneous class of pesticides (OR = 1.5; 95% CI, 1.0–2.4) was associated with elevated risks. [Arbuckle 2001][40] For most pesticides examined, preconception exposure contributed more to the risk of a spontaneous abortion than exposures during the first trimester. This was especially true for early abortions, as measured by the elevated OR observed when models were constructed with exposure window as the outcome; Preconception vs. post conception exposures- Herbicides: OR 2.3, 95% CI (1.3–3.9), Fungicides: OR 3.9, 95% CI (1.4–10.3), Insecticides: OR 2.6, 95% CI (1.3–5.2). [Arbuckle 2001][40] The estimate of the adjusted odds of clinical spontaneous abortion in the high serum DDT tertilerelative to the low tertile was 1.28(95 % CI: 0.53, 3.10). [Venners 2005][48] **<u>Early pregnancy loss</u>**: Relative to the low serumDDT group(~<20ng/g), the odds of early pregnancy loss in the mediumDDT group (~<28 ng/g) were 1.23 (95 percent CI: 0.72, 2.10) and, for thehigh DDT group (>42ng/g), 2.12 (95 percent CI: 1.26, 3.57) after adjustmentfor important covariates. [Venners 2005][48]	**<u>NTDs:</u>** The children of mothers who worked in agriculture in the ARP had a greater risk of anencephaly (OR = 4.57, 95% CI 1.05 to 19.96). The risk of fathers having a child with anencephaly was greater in those who applied pesticides irrespective of whether it was done in the ARP or the NARP (OR = 2.50, 95% CI 0.73 to 8.64; and OR= 2.03, 95% CI 0.58 to 7.08, respectively). [Lacasana 2006][42]		**<u>Childhood cancer:</u>** Paternal exposure before pregnancy pooled rate ratio 1.41 1.15–1.74. Maternal exposure before pregnancy pooled rate ratio 2.24 1.34–3.72. [Fabry 2010 MA][35] <u>Leukemia:</u> Paternal Preconception (job that ended[1 year prior to birth) exposure, case/controls 4/1 OR 12.17 (1.36–109.21). [Ali 2004][36] Maternal Periconception (job held 1 year prior to birth), cases/controls 5/27, OR 0.81 (0.31–2.12) Paternal periconception exposure, cases/controls 36/185 OR 0.83 (0.58–1.19). [McKinney 2003]**[28] Paternal exposure (1 Year before pregnancy 9/9 OR 1.29 (0.50–3.31)# Maternal exposure (1 Year before pregnancy), cases/controls 4/2 OR 2.59 (0.47–14.30)# [Meinert 1996][50] Paternal exposure (1 Year before pregnancy), cases/controls 62/88 OR 1.50 (1.10–2.20). Maternal exposure (1 Year before pregnancy), cases/controls 19/16 OR 2.10 (1.10–4.20). [Meinert 2000][37]

	<u>Total pregnancy loss:</u> Relative to the low serumDDT group (~<20ng/g), the adjusted odds of total pregnancy loss in themedium DDT group (~<28 ng/g) were 1.22 (95 percent confidence interval(CI): 0.73, 2.04) and, for the high DDT group(>42ng/g), 2.01 (95 percent CI: 1.23, 3.28). Adjusted relative odds oftotal pregnancy losses for a 10-ng/g increase in serum DDTwere 1.17 (95 percent CI: 1.06, 1.30). [Venners 2005][48] **<u>Stillbirths:</u>** Women who cook with biomass fuels are significantly more likely to have experienced a stillbirth than those who cook with cleaner fuels (OR= 1.44; 95% CI 1.04-1.97). Women who cook with biofuels are twice as likely to have experienced two or more stillbirths as those who cook with cleaner fuels (RRR= 2.01; 95% CI 1.11-3.62). Results were positive but not significant when adjusting for active tobacco smoking [Mishra 2005][49]			<u>Acute leukemia:</u> Paternal exposure (1 Year before conception), 64 cases OR 1.20 (0.90–1.80). Maternal exposure (1 Year before conception) 11 cases OR 2.40 (1.00–5.90). [Monge 2007][51] Paternal exposure (2 Years before conception), cases/controls 7/3 OR 2.91 (0.44–19.23). [Perez-Saldivar 2008][52] <u>ALL</u>: Paternal preconception (2 Years prior to pregnancy) exposure, cases/controls 66/47, RR 1.56 (1.02–2.40). [Infante-Rivard 1999][38] Maternal Periconception (job held 1 year prior to birth) exposure, cases/controls 5/27 OR 0.97 (0.37–2.52). Paternal periconception exposure, cases/controls 31/185 OR 0.85 (0.58–1.24). [McKinney 2003]**[28] Preconception parental exposure to organic solvents/pesticides/other hazardous material (compared with Non-exposed) OR 5.05 (95% CI) 1.52–16.73. [Korek 2006][39]

#Discordant pairs

**Exposure at periconception was defined as the job held one year prior to the birth of the child and analysis was restricted to natural parents

Table 11.2.2: Summary of impact estimates of lead exposure				
Maternal /Paternal	**Pregnancy**	**Newborn**	**Infant**	**Others**
		Malformations: In the lead-polluted area, we observed an excess risk of cardiovascular defects which decreased from 2.59 [95% CI 1.68–3.82] in the first period to 1.18 (95% CI 0.62–2.06) and 0.97 (95% CI 0.57–1.54) in the subsequent periods. We also found an excess risk of oral clefts and musculoskeletal anomalies, with decreasing trends over time. [Vinceti 2001][41]		

Table 11.2.3: Summary of impact estimates of other Chemical exposure				
Maternal/Paternal	**Pregnancy / fetal**	**Newborn**	**Infant**	**Others**
		NTD: occupational exposure to organic solvents in both parents, the couples in which at least one of the parents was occupationally exposed to **organic solvents** compared with couples in which none of the parents were exposed, demonstrated a statistically significant increase in the odds of anencephaly when the exposure was during the peri-conceptional period (ARP) (adjusted OR 2.97; 95% CI 1.36 to 6.52) or when the exposure was at some time during the last		**Acute Lymphoblastic leukemia/ NHL** Paternal exposure- Solvents: OR 1.0 CI (0.8–1.2), Paints: OR 1.1 CI (0.9–1.4), oil products: OR 1.1 CI (0.9–1.3), plastic or resin fumes: OR 1.1 CI (0.8–1.6), industrial dust OR 1.3 CI (1.0–1.6), metal melting: OR 0.9 CI (0.7–1.2). Maternal exposure- Solvents: OR 1.2 CI (0.9–1.7), Paints: OR 1.6 CI (1.1–2.4), oil products: OR 1.5 CI (0.9–2.5), plastic or resin fumes: OR 1.5 CI (0.7–3.0), industrial dust OR 1.4 CI (0.8–2.5), metal melting: OR 1.0 CI (0.6–1.7). [Schuz 2000][46] Maternal exposure to solvents - [(OR), 1.8; 95% (CI), 1.3–2.5] and paints or thinners (OR, 1.6; 95% CI, 1.2–2.2) during the preconception period (OR, 1.6; 95% CI, 1.1–2.3) were related to an increased risk of childhood ALL**.** The elevated risk associated with maternal Exposure to paints or thinners was restricted largely to children diagnosed at 5 years of age or younger, and the

		5 years (adjusted OR 2.77; 95% CI 1.35 to 5.70). Maternal cases (n=157), controls (n=151); paternal exposure (n=129), controls (n=110). Maternal exposure -during last 5 years, Not exposed cases (%)/controls (%) 138 (91.39)/147 (97.35); Exposed cases (%)/controls (%) 13 (8.61)/4 (2.65) aOR 9.22 (1.97 to 43.17). In the acute risk period (ARP- 3months before last period to 1 month after), Not exposed cases(%)/controls(%) 138 (94.52)/147 (100) Exposed cases (%)/ controls (%) 8 (5.48)/ 0 (0). Non-acute risk period (NARP) when the exposure was before the ARP. Not exposed cases/controls 138 (96.50) /147 (97.35) Exposed cases/controls 5 (3.50)/ 4 (2.65) aOR 1.69 (0.25 to 11.41). The odds of having a child with anencephaly was higher if the fathers were exposed to organic solvents during the ARP (aOR 2.08; 95% CI 0.93 to 4.60) or at some time		association with solvents and plastic materials was more pronounced among children older than 5 years at diagnosis. A positive association between ALL and paternal exposure to plastic materials during the preconception period was also found (OR, 1.4; 95% CI, 1.0 –1.9). paternal exposure to solvents (OR, 1.1; 95% CI, 0.9–1.3), paints/thinner OR 1.0; 95% CI, (0.8–1.2), oil/coal products OR 1.1 CI, (0.9–1.3) [Shu 1999][47] Twofold increases in risk were seen for leukaemia and ALL among the children of mothers exposed to *dermal (skin/ epidermal) hydrocarbons* at periconception (leukaemia: OR 2.20, 95% CI 1.23-3.95; ALL: OR 2.16, 95% CI 1.16-4.02). Statistically significant threefold increase in risk was present for children diagnosed with leukaemia and ALL whose mothers had been exposed to *metal* at periconception (leukaemia: OR 3.68, 95% CI 1.59 to 8.55; ALL: OR 3.91, 95% CI 1.64 to 9.32). Statistically significant raised risks were observed for other cancers among the offspring of mothers and fathers exposed to *textile dust* at periconception (mothers: OR 1.81, 95% CI 1.28 to 2.55; fathers: OR 2.02, 95% CI 1.23 to 3.31). [McKinney 2003]**[28] Paternal exposure to:- *Driving*: leukemia cases/controls 121/389, OR (95%CI) 1.36 (1.10 to 1.68). ALL cases/controls 95/389 OR (95%CI) 1.26 (1.00 to 1.59). *Exhaust fumes:* leukemia cases/controls 147/485 1.33 (1.09 to 1.61). ALL cases/controls 118/485 OR (95%CI) 1.26 (1.02 to 1.56). *Inhaled particulate matter*: leukemia cases/controls 115/345 OR (95%CI) 1.48 (1.19 to 1.84). ALL cases/controls 93/345 OR (95%CI) 1.41 (1.11 to 1.79). Cases n=3838, controls n=7629. Statistically significant raised risks were seen for other

		during the last 5 years (adjusted OR 2.16; 95% CI 1.08 to 5.32). [Garduno 2009][43] Thirty-seven case fathers and 44 control fathers were considered to have solvent exposed occupations, revealing an OR = 0.8 [0.5, 1.3] among working fathers. The ORs associated with this potential exposure for anencephaly and spina bifida, respectively, were 0.7 [0.3, 1.3] and 1.0 [0.6, 1.7]. [Shaw 2002]^^[53]		cancers among the children of men working with leather at periconception (OR 4.02, 95% CI 1.39 to 11.63). [McKinney 2003]**[28] **<u>CNS tumors</u>**: <u>Maternal</u>: There is little evidence that any of the maternal exposures were associated with an increased incidence of neuroblastoma in offspring. {self-reported Exposure: Cases (n=537)/controls(n=503), aOR (95%CI)} Halogenated hydrocarbons: 15/19, 0.7 (0.4,1.5) Nonvolatile hydrocarbons: 26/20, 1.2 (0.7, 2.2) Volatile hydrocarbons: 55/40, 1.4 (0.9,2.1) Paints, inks, and pigments: 21/20, 1.00 (0.5,1.9) <u>Paternal</u>: Paternal occupational exposures to several chemicals were associated with increased incidence of neuroblastoma in offspring. Odds ratios for several hydrocarbons were 1.5 or above, including alcohols, benzene, cutting oil, diesel fuel, lacquer thinner, mineral spirits, paint thinner, and turpentine. Odds ratios for the categories of volatile hydrocarbons (odds ratio (OR) _ 1.5; 95 percent confidence interval (CI): 1.0, 2.1) and nonvolatile hydrocarbons (OR _ 1.5; 95% CI: 1.0, 2.2) were elevated as well. {self-reported Exposure: Cases (n=405)/controls(n=302), aOR (95%CI)} Halogenated hydrocarbons:75/48, 1.2 (0.8, 1.7) Nonvolatile hydrocarbons: 130/78, 1.3 (0.9,1.9) Volatile hydrocarbons: 175/114, 1.2 (0.9, 1.7) Paints, inks, and pigments: 52/44, 0.8 (0.5, 1.3) Metals, alloys, and solders: 55/44, 0.9 (0.6, 1.4). [Roos 2001][54] Paternal preconceptional occupational exposure to PAH was associated with increased risks of all childhood brain

				tumors (odds ratio (OR) = 1.3, 95% CI: 1.1, 1.6) and astroglial tumors (OR = 1.4, 95% confidence interval: 1.1, 1.7). Exposed: cases/controls 484/784; non-exposed: cases/controls 560/1174. (Cases n=1098, controls n=2051). When maternal occupational exposure before conception was considered, no increase in risk was observed for any tumor group. [Cordier 2004][55]
Carcinogen exposure				**ALL:** At least one occupation with high exposure in the 2 years period before conception of indexed child cases/n (%) 45/193 (23.3) controls/n 28/193 (14.5) OR 1.79 [1.06, 3.02]; aOR 1.69 [0.98,2.92]. [Saldivar 2007][52]

Table 11.3.4: Summary of impact estimates of other miscellaneous environmental exposures

Fuel exposure		**NTDs:** Maternal use of wood to cook during the ARP cases/n (%) 87/151, (57.62) controls/n (%) 60/151 (39.74), OR (95%CI) 3.25 (1.70–6.21). [Lacasana 2006][42] Women who reported the burning of wood, coal or tires in their home for cooking or heating had twice the odds of having a child with anencephaly compared with women not using this kind of combustible (crude OR 2.04; 95% CI 1.29 to 3.23). [Garduno 2009][43]		
		NTD: [Bed heating device, Neural tube defect cases/, Controls, OR (95% CI), AOR 95% CI]- No device used 417/ 418 (Reference) Electric blanket 54/ 47, 1.1 [0.7–1.8], 1.8 [1.2–2.6]; <daily use 30/ 24, 1.3 [0.7–2.2], 1.7 [1.0–3.1]; Daily use 24/ 23, 1.0 [0.6–1.9], 1.6 [0.8–3.0; Heated water bed 71/ 70, 1.0 [0.7–1.5], 1.2 [0.8–		

		1.8]; <daily use 10/ 5, 2.0 [0.7–5.6], 2.5 [0.8–7.6]; Daily use 61/ 65, 0.9 [0.6–1.4], 1.1[0.7–1.7]. [Shaw 1999]^^[56] [Bed-heating device, Neural tube defect cases/ Controls, OR (95% CI) AOR (95% CI)]- Electric blanket 18/31, 1.1 [0.6–2.0], 1.2 [0.6–2.3]; <daily use 12/ 15, 1.5 [0.7–3.3] 1.6 [0.7–3.6]; Daily use 4 /15, 0.5 [0.2–1.5], 0.6 [0.2–1.8]; <6 hr/day 4/8, 0.9 [0.3–3.1], 1.0 [0.3–3.5]; =>6 hr/day 12/22, 1.0 [0.5–2.1], 1.3 [0.6–2.6]; Low setting 9/18, 0.9 [0.4–2.1], 1.1 [0.5–2.5]; Medium setting 3/9, 0.6 [0.1–2.3], 0.7 [0.2–2.9]; Heated water bed 48/81, 1.1 [0.7–1.6], 1.2 [0.8–1.9]; <daily use 4/ 8 0.9 [0.3–3.1], 0.9 [0.2–3.0]; Daily use 44 /71 1.2 [0.8–1.8], 1.3 [0.8–2.0]; <6 hr/day 4/ 11 0.7 [0.2–2.2], 0.7 [0.2–2.3]; =>6 hr/day 38 /59, 1.2 [0.8–1.9], 1.3 [0.8–2.1]; Mattress pad 5/ 5, 1.9 [0.5–6.5], 2.4 [0.6–9.3]. [Shaw 1999]^*[56] **<u>Orofacial defects</u>**: Isolated CL/P - No device used controls/cases 560/263 (Reference) Electric blanket controls /cases 47/17, OR 0.8 [0.4–1.4], aOR 0.8 [0.5–1.5] Multiple CL/P – no device used cases 68 (Reference) electric device used cases 6, OR 1.1 [0.4–2.6], aOR 1.3 [0.5–3.4]. Isolated CPO - No device used controls/cases 560/ 105 (Reference) Electric blanket controls/cases 47/ 8, OR 0.9 [0.4–2.1], aOR 0.8 [0.4–1.9] Multiple CPO- no device used cases 55		

		(Reference), Electric blanket cases 6, OR 1.3 [0.5–3.2], aOR 1.5 [0.6–3.8]. [Shaw 1999]^*[56]		
Particulate air matter	**<u>Pregnancy loss</u>:** the risk of early pregnancy loss in women exposed to high levels of ambient PM10 (Q4 period: >56.72 mg/m3) during the preconceptional period was 2.72 -fold higher than expected in the group of women exposed to lower levels of ambient PM10(<56.72 mg/m3). [Perin 2010][44]			

**Exposure at periconception was defined as the job held one year prior to the birth of the child and analysis was restricted to natural parents
^^Periconceptional is defined as the 6-month period, 3 months before and 3 months afterconception.
^*Periconceptional is defined as the 4-month period from 1 month before to 3 months after conception.

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CHNRI Process for Prioritizing Research Gaps

The CHNRI Process for Prioritizing Research Gaps in Preconception Care

The systematic priority-setting method developed by CHNRI aims to draw the attention of researchers and investors alike, to research gaps that are important and encompass not just description of disease burden or discovery of new knowledge, but also how to develop and deliver interventions to reach users who have the greatest need. Ninty nine percent (99%) of maternal deaths and 90% of child deaths occur in low-income countries. Currently, however, research investment is largely driven by scientists' own research interests, media coverage and advocacy; and those who will fund and publish the research. The application of a fair, transparent process to systematically enlist and rank competing research options ensures that there is a balance in research investment that will have a large impact on population health in the short- and long-term, and that will improve equity in healthcare.

The CHNRI exercise for preconception care used a clear framework based on multiple endpoints coupled to a systematic process of scoring to determine which research options would make the greatest impact on reducing maternal and child mortality and morbidity from preventable causes. Drawing on the systematic review, the primary team developed sample research questions within the CHNRI matrix, that were circulated to 20 experts in various areas of maternal and child health that related to preconception care. Each technical expert received a summary of findings, including effect sizes, from the primary review, in addition to sample questions, the CHNRI matrix and previously published CHNRI exercises on childhood mortality and stillbirths. In communication with the primary team, these experts were encouraged to develop an exhaustive list of research questions relating to their assigned category of risk/intervention (for example, birth spacing or nutritional supplementation). Five experts were not able to participate due to constraints on their time, and in these cases, we sought another contact person in the same area of expertise. These lists were reviewed and collated by the primary team. The number of questions for each category varied from 6 to 50. The same experts were then asked to serve as primary contacts for others in their field and circulate the materials for scoring, in order to achieve representation of various geographic regions with different disease burdens and priorities in maternal and child health. The criteria used for scoring in this round were the original 5 CHNRI criteria, and although experts received the summary of findings from the main review, many found criterion 4 "maximum potential of disease burden reduction" difficult to score or the research questions disconnected. In all, 130 experts were approached and 60 responded with scores. For a few categories, only one scored sheet was returned, and for others up to 13 experts weighed in. The experts contacted, and those who contributed were mainly from Asia, North America and South America.

The results of the updated review and the preliminary CHNRI exercise were presented at a meeting with 10 international experts representing various specialties relating to maternal and child health. This core group then reviewed the definitions and parameters necessary to define the context for a second round of the CHNRI exercise. The context was set as low- and middle-income countries, with a timeline for development and delivery of interventions in 10 years. A consensus was reached to focus only on these 2 domains in the CHNRI method, and it was agreed that a separate exercise for the domains "description" and "discovery" would follow

shortly thereafter, since the criteria and timelines for these would differ. The questions for each category of preconception risks and interventions were reviewed and amalgamated to better highlight important gaps and not diffuse the focus. It was ensured that no critical research question was missing, and that questions were framed correctly and comprehensively. The criteria were also modified to reflect the context and subject of Preconception Care. The final criteria employed were answerability in an ethical manner; generation of new knowledge and evidence of effect; deliverability, affordability, sustainability; impact on maternal and child mortality and severe morbidity; long-term impact on women and children; and greater equity. Each expert was to score the questions themselves and inculcate a second expert to do the same. In total, 22 scorers out of 30 participated in this round, since the CHNRI exercise reaches saturation with between 20 and 25 scorers, and more participants were from Africa than in the previous round. The scores were not weighted since it was felt that weight applied to CHNRI exercises for stillbirths and childhood diseases would not be suitable, and a separate stakeholder consultation would not be feasible to arrange at this point.

After research priority scores and average expert agreement were computed, the results showed that within the specified context, experts favored research investment into scaling up interventions that already exist, and have to a limited extent, proven efficacy. For example, the topmost ranked question seeks to address the gap in coverage of nutritional interventions, such as supplementation, through integration with other programs. The top half of the ranked priorities scored high on deliverability, impact and equity. These research questions focused on adolescent health, chronic conditions, infectious diseases and contraception, and strongly emphasized the need for research to identify strategies to deliver interventions that are known to improve the health of women and children. In particular, the research options suggest that integration of preconception interventions with other programs and systems, and task-shifting to community health workers, and maximizing uptake by adolescents.

Since research options under the domains “description” and “discovery” were not included at present, the discrimination between the highest and lowest ranked questions was not significantly broad, with the range of Research Priority Scores being from 60.5 to 84.2. The research questions in the bottom half of the ranked list reflected interventions for which there is less evidence of effect, and therefore experts were undecided as to how great their impact on maternal and child outcomes or equity would be. These included questions on the development of effective strategies to promote women’s mental health; reduce coerced sex and intimate partner violence; reduce the risk of chronic conditions and genetic diseases in the community; and prevent harmful exposures such as substance use amongst women of reproductive age. Developing the use of information technologies to improve demand for services was also ranked low because of uncertainty about impact on mortality and severe morbidity.

The results of this exercise, which involved a substantial number of researchers active in maternal and child health, highlighted that research questions can be prioritized very differently depending on the criterion used. Scores for the top questions generally matched for

answerability and deliverability. For evidence of effect and potential impact, the questions ranking the highest were on integration of nutritional interventions, and preventing adolescent pregnancies; however other priorities that appeared frequently regarded increasing contraceptive use; improving the supply chain for interventions; STI/HIV identification and management in preconception care; screening for chronic diseases; developing a package of preconception interventions; and finally, public health measures to reduce exposure to environmental tobacco smoke.

This CHNRI exercise offers an advantage in that it has been vetted twice by a large number of experts, in varied fields relating to maternal and child health and representing many geographic regions. While opportunities to further develop and prioritize the research agenda for preconception care, perhaps through extending this exercise, are being explored by global organizations and partnerships, the results of this process provide key insights that can be used to channel research investment. It is then expected from technical experts, researchers and funding agencies to use the derived scores to perform program budgeting and analysis, to make the results accessible to public, to advocate and implement the identified priorities and to critically evaluate and improve this process.

RESEARCH QUESTION	RPS	AEA
How can preconception nutrition interventions, such as diet diversity, micronutrient supplementation/fortification and achieving optimal BMI, be integrated into broader nutrition and/or health programs and delivered in a cost-effective manner?	84.2	0.735
What are the public health approaches to regulate and reduce exposures to environmental tobacco smoke?	81.7	0.672
How can effective interventions to prevent adolescent pregnancy and repeat adolescent pregnancy be delivered at scale?	81.6	0.705
What are the public health approaches to regulate and reduce environmental exposures to smoke stoves?	81.6	0.631
What approaches work to increase the use of effective contraception, especially long-acting methods, particularly in the postnatal and post-abortion time periods?	81.5	0.682
What are effective, affordable and feasible means to screen for hypertension affecting girls and women before conception?	80.7	0.687
What are the most effective strategies to scale up the prevention/ detection/ treatment of malaria and helminthiasis to reduce anemia in women of reproductive age?	80.7	0.679
What effective strategies can be developed to modify individuals' behavior to reduce their environmental exposures to smoke stoves?	80.6	0.634
What effective, affordable strategies could be developed to provide effective STI/HIV identification and management, including early antiretroviral therapy, as part of preconception care, and how could these be adapted to maximize uptake by adolescents?	80.4	0.657
How can task-shifting to community health workers to screen for chronic conditions among women during the preconception period and take appropriate action (such as referring to specialist, counselling, refer to support groups) be effectively enabled?	80.4	0.652
Develop and evaluate the effect and cost of different delivery strategies for an immunization package for girls including rubella and tetanus, and others as appropriate	80.4	0.677
How can the supply chain for commodities for effective preconception services (nutrition, contraception, medications for chronic and infectious diseases) be integrated with other logistical systems so that it is more reliable and effective?	80.3	0.682
What is the effect, cost and feasibility of using cell phones and other information technologies to improve capacities of front-line workers to target and follow-up women of reproductive age for improved preconception health care?	79.2	0.664
What are effective strategies to increase the demand for and supply of contraceptives for women, including multiparas, during their later reproductive years?	79.2	0.659
How can effective interventions (that increase demand, care-seeking and access) to promote adolescent health and nutrition be delivered at scale?	79.2	0.667
What are effective, affordable and feasible means to screen for diabetes affecting girls and women before conception?	78.5	0.672
What alternative delivery approaches can be developed to increase coverage and affordability of preconception interventions among girls and women in different settings (ie. urban, peri-urban and rural)?	78.5	0.644
How can preconception care be most effectively integrated into RMNCH programs for service delivery at scale?	78.1	0.631
What should constitute an essential package of preconception health interventions for all girls and women of reproductive age?	78.0	0.631

How can cell phones and other information technologies be best utilized to improve care-seeking for preconception services and healthy behaviors, especially amongst adolescents?	77.9	0.652
What are the public health approaches to regulate and reduce environmental exposures to lead?	77.7	0.601
How can the quality of and access to comprehensive post-abortion care services, (including contraceptive counseling, provided by different cadres of healthcare workers, and adaptation to maximize uptake by adolescents) be improved?	76.1	0.629
How can a package of promotive and preventive mental health interventions for women and girls be effectively and feasibly provided through community health workers and/or groups, with linkages to the primary healthcare system for treatment?	75.8	0.573
What effective strategies can be developed to modify individuals' behavior to reduce their exposures to environmental tobacco smoke?	75.5	0.591
What are the most effective strategies to involve men in improving preconception health in community and primary healthcare settings?	74.9	0.576
What are the best approaches for ensuring that women avoid tobacco use in the preconception period?	74.5	0.636
What are the most effective approaches for ensuring that women do not consume harmful levels of alcohol (especially binge and heavy drinking) during the preconception period?	74.1	0.588
How can communication channels (mass media, social networking) be used to increase healthy preconception behaviors and demand for preconception services?	74.0	0.609
How can partnerships with other sectors including agriculture, industry, and education be developed to increase the distribution and consumption of nutritious foods and supplements?	73.9	0.586
How can economic incentives and performance-based payments be used to increase healthy preconception behaviors and demand for preconception services?	72.7	0.598
What effective strategies can be developed to modify individuals' behavior to reduce their environmental exposures to lead?	71.5	0.551
What strategies could be developed to promote knowledge of and access to emergency contraception?	70.9	0.563
What are effective, affordable and feasible means to screen for cardiac disease affecting girls and women before conception?	69.6	0.508
What is the effect, cost and feasibility of a package for community-based genetic screening, that includes screening using a complete medical history, basic laboratory investigations, minimum laboratory requirements, counseling and post-screening services (for hemoglobinopathies, or similar genetic diseases)?	67.0	0.533
What effective strategies could be developed to prevent and respond to coerced sex and intimate partner violence in women and girls?	65.5	0.513
What is the feasibility of addressing the risks for consanguinity in a culturally-appropriate manner?	65.0	0.510
What are the principal ethical concerns for implementing genetic screening and bio-banking in the community settings, and what approaches could be developed to address them?	60.5	0.452

*RPS= Research Priority Score, AEA= Average Expert Agreement

Cost Effectiveness Analysis

Cost analysis

Interventions (may have an impact on preconception period) for women of child bearing age

Condition	Intervention	Type	Cost effectiveness USD/DALY	Cost effectiveness estimate (USD)	Cost effectiveness range (USD/DALY)	Number of DALY averted (00)	Number of deaths averted (00)	Quality of CE analysis evidence
Diabetes	ACE inhibitor for blood pressure control Setting: Clinic	Personal	-	620 per QALY (EAP); 830 per QALY (ECA); 1,020 per QALY (LAC); 870 per QALY (MNA); 510 per QALY (SAR); 460 per QALY (SSA)	-	-	-	5
	Annual eye examination Setting: clinic	Personal	-	420 per QALY (EAP); 560 per QALY (ECA); 700 per QALY (LAC); 590 per QALY (MNA); 350 per QALY (SAR); 320 per QALY (SSA)	-	-	-	5
	Diabetes Screening Screening of individuals at increased risk for undiagnosed diabetes Clinic, Local or district hospital	Population	-	5,140 per QALY (EAP); 6,910 per QALY (ECA); 8,550 per QALY (LAC); 7,260 per QALY (MNA); 4,280 per QALY (SAR); 3,870 per QALY (SSA)	-	-	-	5
	Annual screening for microalbuminuria Setting: clinic, local or district hospital	Population	-	3,310 per QALY (EAP); 4,450 per QALY (ECA); 5,510 per QALY (LAC); 4,680 per QALY (MNA); 2,760 per QALY (SAR); 2,500 per QALY (SSA)	-	-	-	5
	Lifestyle intervention (type 2 prevention) Behavioral change for weight reduction by means of a combination of a low-calorie diet and moderate physical activity Setting: Clinic	Population	-	80 per QALY (EAP); 100 per QALY (ECA); 130 per QALY (LAC); 110 per QALY (MNA); 60 per QALY (SAR); 60 per QALY (SSA)	-	-	-	5
	Intensive glucose control to lower the level of glucose in the person with diabetes to a level close to that of a person without diabetes, for people with HbA1c higher than 8 percent, in order to prevent or delay long-term diabetes complications Setting: Clinic	Personal	-	2,410 per QALY (EAP); 3,230 per QALY (ECA); 4,000 per QALY (LAC); 3,400 per QALY (MNA); 2,000 per QALY (SAR); 1,810 per QALY (SSA)	-	-	-	5
	Smoking cessation Personal Counseling and medication such as the nicotine patch	Personal	-	870 per QALY (EAP); 1,170 per QALY (ECA); 1,450 per QALY (LAC); 1,230 per QALY (MNA); 730 per QALY(SAR); 660 per QALY (SSA)	-	-	-	5
	Metformin intervention for preventing type 2 diabetes Setting:	Personal	-	2,180 per QALY (EAP); 2,930 per QALY (ECA); 3,630 per QALY (LAC); 3,080 per QALY (MNA); 1,820 per QALY (SAR); 1,640 per QALY (SSA)	-	-	-	5
	Cholesterol control Setting: clinic	Personal	-	4,420 per QALY (EAP); 5,940 per QALY (ECA); 7,350 per QALY (LAC); 6,240 per QALY (MNA); 3,680 per	-	-	-	5

Condition	Intervention	Type	Cost effectiveness USD/DALY	Cost effectiveness estimate (USD)	Cost effectiveness range (USD/DALY)	Number of DALY averted (00)	Number of deaths averted (00)	Quality of CE analysis evidence
				QALY (SAR); 3,330 per QALY (SSA)				
CHF	ACE inhibitor and beta blocker with diuretics Setting: Local or district hospital	Personal	150	-	27-274	11.59	-	5
MI	Aspirin and beta blocker Setting: clinic, local or district hospital	Personal	14	-	13-15	1.04	-	5
IHD	Aspirin, beta blocker and ACE inhibitor Setting: Local or district hospital or referral hospital	Personal	688	-	451-926	8.4	-	5
Kidney disease	ACE inhibitors for all type I diabetics with macroproteinuria and all type -2 diabetics Setting: clinic	Personal	-	1100-7700 per QALY (USA)	-	-	-	4
Asthma	Education in addition to exercise program Setting: Clinic	Population	-	- 71,500/QALY (High-income countries)	-	-	-	1
	Quick-releavers in addition to inhaled corticosteroids Rapid-acting bronchodilators that act to relieve bronchoconstriction and accompanying acute symptoms of wheeze, chest tightness, and cough, e.g., salbutamol; incremental to inhaled corticosteroid treatment Setting: Clinic, Local or district hospital	Personal	-	10,600-13,900 per QALY (High-income countries)	-	-	-	1
Alcohol abuse	Advertising ban and reduced access to beverage retail Policy level approach	population	404	-	367-441	0.44	-	5
	Brief advice to heavy drinkers by primary health care providers Setting: clinic	Personal	642	-	-	1.75	-	5
	Excise tax. 25 to 50 percent increase in the current excise tax rate on alcoholic beverages Policy level approach	Population	1,377	-	1,249-1,504	0.62	-	5
	Excise tax, advertising ban, with brief advice	Population	631	-	601-661	2.85	-	5
Opioid abuse	Buprenorphine maintenance substitution Setting: clinic	Personal	-	49000 per QALY (high income countries)	-	-	-	1
	Conventional outpatient detoxification Setting: clinic	Personal	-	12,764 per abstinent patient (Australia)	-	-	-	1
	Drug-free treatments Setting: clinic	Personal		7000-13,000a (USA)				1
Tobacco	addiction Taxation causing 33% price increase Population A 33 percent price increase due to tobacco taxes to discourage tobacco use, prevent initiation (and subsequent addiction) among youths, increase the likelihood of cessation among	Population	22	-	-	37.27	1,905.99	5

Condition	Intervention	Type	Cost effectiveness USD/DALY	Cost effectiveness estimate (USD)	Cost effectiveness range (USD/DALY)	Number of DALY averted (00)	Number of deaths averted (00)	Quality of CE analysis evidence
	current users, reduce relapse among former users, and reduce consumption Policy level approach							
	addiction Nicotine replacement therapy Smoking cessation treatments in the form of nicotine replacement therapy Setting: Clinic	Personal	396	-	-	37.14	452.05	5
	Advertising bans on television, radio, and billboards; health information and advertising in the form of health warning labels on tobacco products; interventions to reduce tobacco supply, such as smuggling control; restrictions on smoking Policy level approach	Population	353	-	-	-	-	5
HIV/AIDS	Antiretroviral therapy Setting: clinic	Personal	922 (Sub-Saharan Africa)	-	350-1494 (Sub-Saharan Africa)	-	-	3 (Sub-Saharan Africa)
	Blood and needle safety Setting: community, clinic, referral hospital, local or district hospital	Population	84 (sub-Saharan Africa	-	7-161 (sub-Saharan Africa)	-	-	2 (sub-Saharan Africa)
	Condom promotion and distribution Setting: community, clinic	Population	82 (Sub-Saharan Africa)	-	52-112 (Sub-Saharan Africa)	-	-	1 (Sub-Saharan Africa)
	Peer and education programs for high-risk groups Targeting community members (for example, students or commercial sex workers) to disseminate information and teach specific skills Community personal behavior change	Population	37	-	6-68	-	-	2
Environmental	Control of toxins related to industrial sector interventions include arsenic emissions standards at copper smelters and asbestos ban for brake linings Approach: policy level	Population	-	Less than 45600 per LYS (USA)	-	-	-	-
	Control of toxins related to agriculture and forestry Interventions include targeted pesticide bans and emissions standards at processing facilities Approach: policy level	Population	-	less than 0 per LYS (USA)	-	-	-	-
	Control of toxins related to energy industry Interventions include coal-fired power plant emissions controls, gasoline lead reduction, and desulphuring residual fuel oil Approach: policy level	Population	-	less than 0 per LYS (USA)	-	-	-	-
	Control of toxins related to residential sector	Population	-	5320-7730 per LYS (USA)	-	-	-	-

Condition	Intervention	Type	Cost effectiveness USD/DALY	Cost effectiveness estimate (USD)	Cost effectiveness range (USD/DALY)	Number of DALY averted (00)	Number of deaths averted (00)	Quality of CE analysis evidence
	Interventions include radon remediation and sedimentation, filtration, and chlorination of drinking water Approach: policy level							
Indoor air pollution	Replacement of traditional open stoves with enclosed stoves that are more efficient and/or have flues for ventilation policy level approach	Population	306	605 per healthy year (EAP); 975-1134 per healthy year (LAC); 379-471 per healthy year (MNA): 13-15 per healthy year (SAR); 21-26 per healthy year (SSA)	-	-	-	5
	related illness Improved stove with kerosene or LPG Population Replacement of traditional open stoves with enclosed stoves that use kerosene or LPG Policy policy level approach	Population	26	85 per healthy year (EAP); 522-1416 per healthy year (ECA); 305-784 per healthy year (LAC); 227-624 per healthy year (MNA): 27-182 per healthy year (SAR); 46-304 per healthy year (SSA)	-	-	-	5
	related illness Kerosene Population Substitution of wood, dung, and crop residues with kerosene for cooking and heating Policy policy level approach	Population	12	232 per healthy year (EAP); 172-188 per healthy year (ECA); 109-650 per healthy year (LAC); 98 per healthy year (MNA): 37-65 per healthy year (SAR); 62-87 per healthy year (SSA)	-	-	-	5
	related illness Liquefied petroleum gas Population Substitution of wood, dung, and crop residues with liquefied petroleum gas for cooking and heating policy level approach	Population	103	1746 per healthy year (EAP); 1258-1361 per healthy year (ECA); 806-1447 per healthy year (LAC); 779-785 per healthy year (MNA); 321-558 per healthy year (SA);	534-736 per healthy year (SSA)	-	-	5
Tuberculosis	Directly observed short-course chemotherapy Setting: Clinic	Personal	301	-	84-551	-	-	5
	Directly observed short-course chemotherapy Setting: Clinic	Personal	102	-	15-189	-	-	5
	Isoniazid treatment Personal Isoniazid treatment of latent infection (with or without x-ray exclusion of active cases; nonHIV-infected population) Setting: Local or district hospital	Personal	13,158	-	9,450-16,867	-	-	5
	Management of drug resistance Personal Introduction of resistance testing, second-line drugs, longer treatment regimen (12-18 months), and rigorous bacteriological and clinical monitoring; standardized or individualized regime Setting: Local or district hospital	Personal	318	-	208-429	-	-	5
	Isoniazid treatment Personal Isoniazid treatment of latent infection (x-ray exclusion of active cases; non-HIV-positive population) is conducted for	Personal	197	-	45-348	-	-	5

Condition	Intervention	Type	Cost effectiveness USD/DALY	Cost effectiveness estimate (USD)	Cost effectiveness range (USD/DALY)	Number of DALY averted (00)	Number of deaths averted (00)	Quality of CE analysis evidence
	epidemic tuberculosis Setting: Local or district hospital							
HIV/AIDS Tuberculosis co-infection	prevention and treatment Preventive therapy, short-course chemotherapy, or co-trimoxazole prophylaxis Setting: Clinic	Personal	121 (Sub-Saharan Africa)	-	6-235 (Sub-Saharan Africa)	-	-	2 (Sub-Saharan Africa)
HIV/AIDS Sexually transmitted infection	Sexually transmitted infection screening and treatment promotion to prevent future infection and to identify and treat high risk populations Setting: Clinic	Personal	57 (Sub-Saharan Africa)	-	9-105 (Sub-Saharan Africa)	-	-	2 (Sub-Saharan Africa)
HIV/AIDS	Home care Personal Home visits providing basic care to sick AIDS patients or comprehensive schemes that provide palliative care, nutrition, psychosocial support and counseling, and links Setting: Home	Personal	673 (Sub-Saharan Africa	-	-	-	-	2 (Sub-Saharan Africa)
HIV/AIDS primary prevention, cure	Treatment of opportunistic infections Opportunistic infection prophylaxis; necessary for patients without access to antiretroviral treatment, for immunosuppressed patients waiting for antiretroviral treatment to take effect, for patients who refuse or cannot take antiretroviral treatment Setting: Clinic, Local or district hospital	Personal	156	-	3-310	-	-	3
Malaria	Insecticidetreated bed nets Impregnation of bed nets with deltamethrin, one treatment of permethrin, or two treatments of permethrin, with the bed nets either purchased or subsidized Home control of environmental hazards policy level approach	Population	11 (Sub-Saharan Africa)	-	5-17 (Sub-Saharan Africa)	376.00 (Sub-Saharan Africa)	1,429.60 (Sub-Saharan Africa)	5 (Sub-Saharan Africa)
	Residual household spraying One or two doses of malathion, DDT, deltamethrin, or lambdacyhalothrin applied to household surfaces Home control of environmental hazards policy level approach	Population	17 (Sub-Saharan Africa)	-	9-24 (Sub-Saharan Africa)	376.00 (Sub-Saharan Africa)	1,429.60 (Sub-Saharan Africa)	5 (Sub-Saharan Africa)
Depression	Drugs with optional episodic or maintenance psychosocial treatment Setting: Local or district hospital, Referral hospital	Personal	1,699	-	657-2,741	3.96	-	5
Bipolar disorder	Episodic treatment in a hospital setting with lithium or valproate with or without maintenance or episodic psychosocial treatment disorder Setting: Local or district hospital, Referral hospital	Personal	4,417	-	3,590-5,244	-	-	5
	Episodic treatment of bipolar disorder in a	Personal	3,113	-	2,498-3,728	1.35	-	5

Condition	Intervention	Type	Cost effectiveness USD/DALY	Cost effectiveness estimate (USD)	Cost effectiveness range (USD/DALY)	Number of DALY averted (00)	Number of deaths averted (00)	Quality of CE analysis evidence
	community setting using lithium or valproate with or without maintenance or episodic psychosocial treatment based Setting: Local or district hospital, Referral hospital							
Panic disorder	Drugs with optional psychosocial treatment. Anxiolytic drugs (benzodiazepine), tricyclic antidepressants or selective serotonin reuptake inhibitor used with or without psychosocial treatment Setting: Local or district hospital, Referral hospital	Personal	734	-	384-1,084	0.83	-	5
Unwanted pregnancy	Family-planning programs Intrauterine devices, voluntary sterilization, condoms and other barrier methods, implants, and oral contraceptives Setting: Clinic	Personal	117	-	-	-	-	3
Epilepsy	First line treatment with phenobarbital to treat epilepsy patients Setting: Local or district hospital	Personal	89	-	-	2.99	3.32	5
	Antiepileptic drugs, phenobarbital and lamotrigine, or a combination of phenobarbital and surgery to treat epilepsy patients unresponsive to Phenobarbital Setting: Referral hospital	Personal	3,027	-	2,994-3,060	0.29	0.32	5