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Review article

Preconception health as a target for improved pregnancy outcomes: Where do we go from here?

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ABSTRACT

Preconception health status, especially of women, but also of men, is known to influence pregnancy outcomes. Despite knowledge of the growing importance of preconception health, numerous challenges remain for conducting research in this population and delivering appropriate clinical care. The 2023 Global Pregnancy Collaboration annual workshop focused on exploring preconception health as it relates to adverse pregnancy outcomes. Here we summarize the proceedings and the current state of the science. We particularly focus on quantifying the exposome as a rich target for investigation of factors that increase the risk for and/ or contribute to preeclampsia and other adverse pregnancy outcomes. We conclude with recommendations for the scientific and clinical community to address knowledge gaps regarding the links between preconception health and adverse pregnancy outcomes.

1. Introduction

It has become evident that environmental exposures, behaviors, and physiologic state prior to pregnancy can have a substantial influence on pregnancy outcomes. The influences of the preconception state on the course and outcome of pregnancy were the topic of the September 2023 Global Pregnancy Collaboration annual workshop. In this manuscript, we will provide an update and overview of the proceedings and discuss the state of available information on the impact of the preconceptional state on pregnancy outcomes.

2. Pre-pregnancy physiology and pregnancy outcomes

Dr. Ira Bernstein provided an overview of the relationship between pre-pregnancy physiology and pregnancy outcomes. From a clinical care perspective, it has long been recognized that preexisting medical conditions like diabetes, autoimmune conditions, and hypertension contribute to risk for pregnancy complications, particularly preeclampsia. [1] Dr. Bernstein presented data that suggests it is not only the presence of overt disease that is associated with risk for pregnancy complications, but subclinical cardiometabolic indices prior to

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pregnancy are also associated with preeclampsia. [2–5] Dr. Bernstein and his team previously found evidence of greater vascular stiffness prior to pregnancy in women who go on to develop preeclampsia vs those who remain normotensive. [6] Furthermore, they found evidence that among nulligravids, women with a family history of myocardial infarction or hypertension had greater evidence of arterial stiffness. [7] They hypothesized that pre-pregnancy arterial stiffness may be a risk factor for preeclampsia.

When exploring the possible reason for greater pre-pregnancy vascular stiffness, his team found that individuals who developed preeclampsia, especially preterm preeclampsia, had higher body mass index (BMI), blood pressure, C-reactive protein (CRP), HOMA-IR, and cholesterol prior to conception compared to those who did not develop preterm preeclampsia. [5,8] Additionally, body composition metrics beyond BMI were different between those who developed preeclampsia and those who remained normotensive. Bone mineral density was lower in those who developed preeclampsia. Examining biomarkers of bone formation and bone resorption, they found lower levels of PINP (procollagen I Intact N-Terminal), a marker of bone formation, in preeclampsia cases when measured prior to conception. [9] Dr. Bernstein and colleagues concluded that insulin resistance, inflammation, and bone turnover are potential pre-pregnancy targets that may be contributing to arterial stiffness and ultimately preeclampsia.

3. The exposome and preconception health

Dr. McKenzie Jancsura emphasized the impact of lifetime experiences, behaviors, and exposures on pregnancy outcomes. Dr. Jancsura presented the concept of the exposome, coined in 2005 by Dr. Christopher Wild, [10] which provides a framework for understanding how the culmination of external factors across the lifespan impact health and disease (Fig. 1). [10,11] The exposome is a term to mirror other omics terms such as genomics, epigenomics, proteomics, to reflect the impact of exposures across the lifespan for example diet, sleep, smoking, climate, traffic, social capital (referred to as the specific and general external environment) on cellular processes (referred to as the internal environment) that ultimately leads to health and disease risk. [10,12] The exposome paradigm offers a framework to investigate the mechanisms by which factors such as stress, environmental factors, and dietary factors may contribute to adverse pregnancy outcomes. [11,12].

Dr. Jancsura particularly focused on the impacts of stress. Psychosocial stress has been associated with higher risks of developing pregnancy complications, but the mechanisms by which stress contributes to adverse outcomes have been less clear. One hypothesized mechanism by which stress influences health is allostasis and allostatic load. [13,14] Allostasis refers to the body's ability to adapt to complex challenges, i.e., stress, both physiological and psychological. [14] After repeated exposure to stress, the body may have a diminished ability to adapt, leading to dysregulation of the HPA-axis, sympathetic nervous system, and immune system. [14] This diminished capacity is referred to as allostatic load and physiologically manifests as increased cortisol and catecholamine concentrations, insulin resistance, mitochondrial damage, oxidative stress, telomere shortening, epigenetic modification, and early cell senescence. [15] Allostatic load also indicates that we must explore why people exposed to the same stressor have varying health outcomes. For example, while exposure to adverse childhood experiences increases

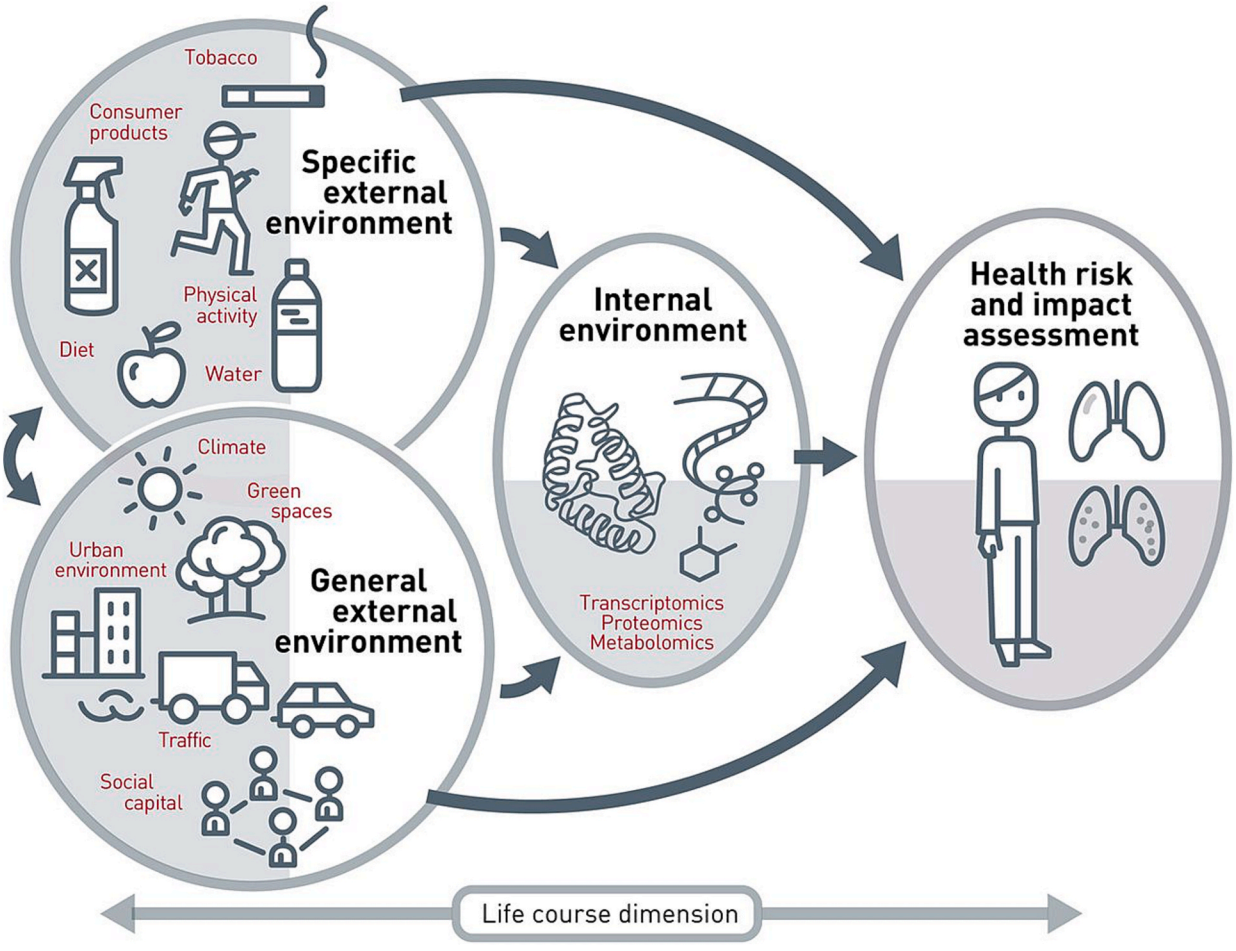

Fig. 1. An overview of the Exposome framework. Reproduced from "The exposome: a new paradigm to study the impact of environment on health", Martine Viriheid, *Thorax 69*, 876–878, 2014 with permission from BMJ Publishing Group Ltd.

risk for anxiety and depression in adulthood, thought to be related to epigenetic modification, not all children exposed to adverse experiences go on to develop anxiety or depression (resilience). [13,16] Similarly not all women who experience adverse childhood experiences, trauma or have high levels of stress develop pregnancy complications. Just as important as studying the associations between stress and adverse pregnancy outcomes is understanding what factors may mitigate this association. Further complicating the association between stress and pregnancy complications is the bidirectional relationship between stress, particularly post-traumatic stress disorder (PTSD), and pregnancy complications. Many women who experience a pregnancy complication, in particular preeclampsia with severe features or HELLP syndrome, experience PTSD. [17,18] Potentially stressful experiences in pregnancy can become another exposure impacting future pregnancies. Several presentations followed Dr. Jancsura's introduction to the exposome to discuss the influences of various modifiable preconception factors on pregnancy outcomes.

4. Environmental exposures

Dr. Stefan Hansson and Dr. David Cantonwine discussed the potential impact of environmental exposures. Dr. Hansson's presentation focused on the effects of air pollution, specifically particulate matter less than 2.5 μm in diameter (PM2.5) on placental function. His data indicated that every increase of 5 ug/m3 of PM2.5 is associated with a 2.7 times higher risk for developing preeclampsia. [19] Additionally, the same study showed black carbon exposure is associated with higher risk for preeclampsia and small for gestational age infants. [19] While these data reflect pregnancy exposures, rather than preconception exposures, people tend to have similar exposures over time, thus his team hypothesizes that exposure to air pollution prior to pregnancy increases risk for preeclampsia and other adverse pregnancy outcomes. [20].

To investigate potential mechanisms for how air pollution increases the risk of preeclampsia and small for gestational age, Dr. Hansson and his team conducted a series of experiments. In first trimester trophoblast cells (HTP-8/SV), exposure to particulate matter at levels consistent with air pollution levels in Malmö, Sweden and Prague, Czech Republic resulted in reduced cell growth and altered protein expression in pathways involved with inflammation, endoplasmic reticulum stress, cellular survival, and molecular transport pathways. [21] They further examined DNA methylation in placental samples from preeclampsia cases and normotensive controls with either high or low ambient nitric oxide exposure in the first trimester. Placentas from pregnancies with high nitric oxide (NOx) exposure demonstrated hypomethylation and evidence of placental villous immaturity. [22] Analysis of the sites of DNA methylation suggests potential dysregulation of cell proliferation, differentiation, and migration leading to altered cell signaling. [22] Finally, in ex vivo placenta perfusion experiments, exposure to PM2.5 resulted in swollen mitochondria, dissolved collagen bundles, detached fibroblasts, and shifts in Hofbauer cells towards a pro-inflammatory state. [23,24] These experiments suggest exposure to air pollution leads to several placental alterations, increasing risk for preeclampsia and small for gestational age birthweight. He concluded with anecdotal evidence of the impact of environmental exposures on pregnancy outcomes. After a clinic in Sweden relocated the IVF clinic away from a high-traffic roadway, improved ventilation, replaced filters, and restricted perfumes to reduce environmental exposures in the critical periconceptual setting, successful pregnancy rates increased from 30 % to 40 %.

Dr. Cantonwine discussed endocrine-disrupting chemicals, specifically phthalates and bisphenol A (BPA). Data from the LIFECODES birth cohort, a collection of approximately 7,200 women from the greater Boston area, included urinary measurements of numerous chemicals. Their results included pregnancy outcome data indicating that higher urinary concentration of monoethylphthalate (MEP), BPA, and total di [2–59]phthalate (∑DEHP) were associated with a higher risk for preeclampsia, with different patterns of relationships to early-onset and late-onset preeclampsia. [25] Furthermore, BPA and ∑DEHP levels were also associated with an altered Flt-1/PIGF ratio, suggesting that a mechanism by which phthalates may contribute to preeclampsia risk is through angiogenic pathways. [25] Dr. Cantonwine discussed a major limitation of available research. He emphasized the lack of subgroup analysis for different presentations of preeclampsia, and failure to consider the interaction of chronic conditions such as type 2 diabetes, obesity, and high blood pressure preceding pregnancy. His group has work underway to address these limitations.

5. Preconception nutrition

Dr. Keith Godfrey reported the results from the NiPPeR trial (Nutritional Intervention Preconception and During Pregnancy to Maintain Healthy Glucose Metabolism and Offspring Health) to illustrate the importance of vitamin and mineral intake. The NiPPeR trial was a large double-blind randomized control trial in over 1,700 women across three healthcare systems in the UK, Singapore and New Zealand. [26] Women in the control group received standard doses of folic acid, β-carotene, calcium, iron and iodine supplements, while those in the intervention group received additional daily supplements of myo-inositol, vitamin D, vitamin B6, vitamin B12, riboflavin, zinc, and probiotics daily for up to 12 months prior to conception and until delivery. Even in these high-income settings there was an extremely high population prevalence of low or marginal status of one or more B vitamins or vitamin D at baseline preconception, in nine of ten of the NiPPeR trial participants. [27] At the conclusion of the study, those in the intervention group had a lower incidence of micronutrient deficiency during pregnancy. [27] Women in the intervention group also had a reduced frequency of preterm birth and preterm prelabor rupture of membranes, [28] major post-partum hemorrhage and blood loss, [29] and lower child obesity at 2 years of age. [30] The mechanisms involved may include nutritional effects on epigenetic processes. [31] The results illustrate the high prevalence of preconception micronutrient insufficiency in high-income populations and the likely importance of optimal nutritional status before and during pregnancy for improving pregnancy outcomes.

6. Approaches for promoting preconception health

There is consensus that preconception health is important, but how we gain access to this population is uncertain. [32,33] While advances have been made, one barrier to investigating preconception health is the high percentage of unplanned and unintended pregnancies. [34] Dr. Judith Stephenson presented a framework from the UK Preconception Partnership to gather data on the true prevalence of preconception care and identify barriers to its uptake. [33,35] They found that 9 in 10 individuals have at least one behavioral or medical risk factor for an adverse pregnancy outcome that could be addressed in the primary care setting. [33,35] Key areas for immediate action and monitoring include normalizing preconception/ interconnectional planning through public health campaigns and focused efforts from primary care providers during annual health care visits. [36–38] Other targets to improve preconceptional health include coordinating with large employers to provide access to health promotion activities for workers and updating school health curricula to include content for adolescents on the importance of health and healthy behaviors *prior* to pregnancy. [36–39] Importantly, we need better data collection of preconception and pregnancy planning data to assess the efficacy of interventions. [35].

Dr. Stephenson also highlighted the particular importance of iodine insufficiency from a public health perspective. Previous studies have found that iodine deficiency during pregnancy is associated with lower IQ in childhood, which in turn is linked to lower gross domestic product (GDP) productivity and a greater need for educational support. [40,41] It is estimated that, in the U.K., for every extra IQ point, GDP per capita

would increase by £175, resulting in a £7 billion improvement in GDP in the U.K. alone. [42].

7. mHealth interventions in preconception health

Dr. Régine Steegers-Theunissen presented data from the Rotterdam Periconception cohort and for the implementation of the achieved scientific knowledge, the experiences and data of a mHealth lifestyle behavior program, face-to-face Healthy Pregnancy consultations, and digital- and blended lifestyle care for their ability to improve periconception parental health. In 2012 Dr. Steegers-Theunissen group successfully launched the webapp Smarter Pregnancy (www.slimmerzwanger.nl, https://www.smarterpregnancy.co.uk) a (pre)pregnancy coaching tool to help individuals and couples practice a healthy lifestyle prior to and during pregnancy. [43,44] Coaching is personalized, focused on addressing deficits in folic acid supplement use, improving diet, smoking, drinking, and exercise, and as such achieving improved healthy weight and (mental)health. Data from the Healthy Pregnancy consultations with couples planning pregnancy (two consults within three months) resulted in a thirty percent reduction of risk factors and 65 % enhanced chance of pregnancy even in couples who underwent *in vitro* fertilization treatment. [45,46] Dr. Steegers' team also this information from these consultations to further deploy the Smarter pregnancy webapp based lifestyle intervention for couples. [43,44,47] The effectiveness of Smarter Pregnancy has been demonstrated for general-, hospital-, high risk and obese populations on folic acid supplement, vegetable and fruit intake, and stop smoking. [43] A key finding was that couples that participated in the program together were more likely to comply with the intervention than individuals participating on their own, highlighting the importance of social support. [43].

The app was successful, but less, for couples living in deprived neighborhoods without access to healthy food options. [48] Promising are the demonstrated clinical implications such as a higher chance of pregnancy in (sub)fertile couples, and a history of recurrent miscarriages, a larger size of the embryo, and a slightly lower maternal blood pressure. [49–51] Important for implementation in clinical practice and society is that the cost-effectiveness of Smarter pregnancy has been shown for obese women and in couples who underwent subfertility treatment. [49,52].

8. Interventions to address preconception health in low resource settings

Efforts to address preconception health are not limited to high resource countries. Dr. Shane Norris presented data from the Healthy Life Trajectories Initiative (HeLTI) study in South Africa. The HeLTI study works with young women living in Soweto, South Africa, a community with high rates of preexisting health problems, behavioral, and socioeconomic risk. In the cohort, over half had a BMI indicating overweight, smoked, or misused alcohol or drugs. About a quarter had diabetes, hypertension, anxiety, or depression, a quarter had HIV, and thirty percent had anemia. [53,54] Additionally, the population experiences socioeconomic risk. Forty-three percent were unemployed, 28 % food insecure, and 55 % experienced adverse childhood events and trauma. Typical behavioral change theory suggests that interventions to improve health literacy and improve behavior change intention will change behavior and improve health. However, such theories do not consider the substantial instability faced by individuals who are unemployed, with economic stress, food insecurity, limited social support, or exposure to crime and violence.

Dr. Norris presented an ongoing intervention study working with the Soweto South Africa population that uses community health workers to reduce the impact of socioeconomic instability allowing participants to implement behavior changes to improve health outcomes. [53,55] Baseline data were collected from over 6,000 non-pregnant women aged 19–28 who will be followed through the next few years through future pregnancies. A second study, HeLTI Adolescent, is also underway which seeks to improve BMI (both underweight and overweight) prior to conception to mitigate transgenerational risk for metabolic diseases. [56] This study was possible through intensive coordination between governmental and health agency stakeholders as well as local community leadership. Community health workers are the key contact in the study serving as a bridge between the community and healthcare providers.

9. Machine learning and artificial intelligence

Innovative approaches do not only relate to novel interventions, but also novel computational analysis. Dr. Dominik Heider discussed the power of machine learning and artificial intelligence models to improve pregnancy health, highlighting areas of improvement in data collection to optimize their use. He highlighted that all models are limited by the quality and quantity of the input data. Some variables are easily abstracted from a clinical record such as blood pressure, but other potentially useful data like a patient experiencing a visual disturbance are not easily abstractable or interpretable. Particularly for AI-informed models, the amount of data needed is astronomical; more data than can be produced from a single hospital center. The potential for machine learning and AI models will continue to be limited by bureaucratic processes for accessing data and limitations in quantifying critical qualitative data. The ongoing development of this field may improve the utility of advanced computational models for understanding or predicting risk for adverse pregnancy outcomes, such as federated and swarm learning approaches. [57] Cooperation between hospitals, governments, and countries will be necessary to realize the full potential of AI in pregnancy research. [58].

10. Summary and recommendations

It is becoming increasingly evident that events and exposures across the lives of women, that in many cases long antedate pregnancy, have a profound effect on pregnancy outcome. The collective experiences constitute the "exposome" and are recognized as important targets to modify to facilitate successful pregnancy. Growing evidence suggests the importance of physiological differences in women prior to pregnancies complicated by adverse pregnancy outcomes. However, challenges remain for identifying and mitigating such factors. Of particular importance is resolving the question, what is different about women who do or do not respond to the same stress in type and duration in regard to adverse pregnancy outcomes? There are obvious targets: pollution, diet, and unhealthy nutrition and lifestyle behaviors whose ablation requires skillful modifications before pregnancy. However other factors may be contributing to adverse pregnancy outcomes that are not being captured by current research approaches. Additionally, it's important to recognize the intergenerational impact of pregnancy complications, whereby fetal exposures in the uterine environment have lasting consequences. As suggested by the fetal origin of disease, the intrauterine environment is the first exposure that influences health outcomes, which is particularly important for female offspring when considering risks for pregnancy complications. Use of apps to instruct and modify behavior prior to pregnancy have shown encouraging findings to improve outcomes. It is quite likely that there is a myriad of other important components to consider. With the advent of electronic medical records and tools to manage large volumes of data we have the ability to begin to identify more intervention targets to improve outcomes. It is mandatory to strive to modify components of the exposome that we recognize and begin to search for and appropriately modify those we do not to ultimately prevent preeclampsia and other adverse pregnancy outcomes.

11. Recommendations

11.1. Research

1. Reconsider and revise Electronic Medical Record as a source of useful medical information to recognize and evaluate components of the exposome relevant to pregnancy outcome.
2. Increase research directed at recognizing, testing, and modifying exposome factors relevant to pregnancy outcome.
3. Direct attention to resilience, why similar exposures do not affect outcomes in all women.
4. Identify new research techniques to appropriately measure pre-pregnancy health status.

11.2. Clinical

1. Expand preconception counseling into the care of all women and their partners of childbearing age.
2. Promote optimal health behaviors in adolescents and young adults by providing specific information regarding the importance of pre-pregnancy health.

12. Conclusion

Given the increasing occurrence of adverse pregnancy outcomes, particularly preeclampsia, it is imperative that, as a research and clinical community, we improve the preconception health of mothers and fathers to promote the optimal outcomes for mother and infant. The exposome framework provides a unique lens to explore and quantify the individual and collective effects of exposures prior to pregnancy, identifying potential intervention targets to ultimately prevent preeclampsia and other adverse pregnancy outcomes.

Author Contributions

MKJ and JMR drafted the manuscript, critically appraised the manuscript, and revised the manuscript. IB, SRH, DEC, KMG, JS, RST, SN, and DH critically appraised the manuscript. All authors approve of the final submission.

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Declaration of Competing Interest

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