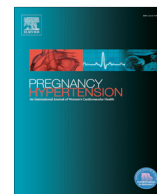




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Guest Editorial

PRE-EMPT (PRE-eclampsia-Eclampsia Monitoring, Prevention and Treatment): A low and middle income country initiative to reduce the global burden of maternal, fetal and infant death and disease related to pre-eclampsia

Pre-eclampsia is associated with an unacceptable burden of death (maternal, fetal and neonatal), disability and health crises throughout the world [1]. However, it is in low and middle income countries (LMICs) that women, their families and their communities bear a disproportionate risk for developing the life-ending, life-threatening, and life-altering complications of pre-eclampsia; it is believed that over 99% of the estimated 70–80,000 annual maternal and 500,000 annual perinatal pre-eclampsia-related deaths occur in LMICs [1]. Many of these complications arise in women who never reach the formal health care system, or who arrive too late to be saved. This disparity in outcomes between women in high income countries and those in LMICs represents a social equity issue [2].

Why are the actuarial risks faced by women with pre-eclampsia in high income countries dramatically lower when compared with women in LMICs? Along with others, we believe that the answer lies, in large part, in (i) the provision of effective routine antenatal care in high income countries, with accelerated visits near and at term (leading to pre-eclampsia detection), (ii) increased awareness of, and responsiveness to, symptoms by women in high income countries (leading to self-referral for assessment), (iii) diagnostic and surveillance capacity in high income countries, (iv) the control of severe pregnancy hypertension (because blood pressure is measured and severe hypertension is diagnosed), (v) the prevention and treatment of eclampsia with MgSO₄ (which is available in all institutions), (vi) timely delivery (given excellent neonatal supportive care), and (vii) maternal organ support (including intensive care and blood transfusion, if necessary) during the recovery phase. The possibility of biological risk factors in LMICs such as dietary deficiencies remains to be proven.

Can key elements of this high income country care be introduced into LMICs in a cost-effective manner and while

engaging key stakeholders to build sustainability? In November 2010, the University of British Columbia received an initial portion of funding from the Bill & Melinda Gates Foundation (BMGF) to establish the PRE-eclampsia-Eclampsia Monitoring, Prevention & Treatment (PRE-EMPT) initiative; in November 2012, a supplemental portion of funding was received. This represents a singular investment in the field of pre-eclampsia research that is focussed on improving outcomes for LMIC women who develop pre-eclampsia in their communities. An important by-product of this scope of activity will be the testing of interventions that may be as applicable in doctors' and midwives' clinics, especially in rural and remote communities, in high income countries.

There are five major components of the PRE-EMPT initiative: prevention of pre-eclampsia, monitoring of women with pre-eclampsia, treatment of women with pre-eclampsia, the 'Co-Laboratory' to maximise the use of existing information and biobanks, and the synthesis and translation of the evidence.

(1) Prevention of pre-eclampsia

The Calcium and Pre-eclampsia (CAP) trial (Principal Investigator [PI]: G. Justus Hofmeyr) is an innovative double blind, placebo-controlled, randomised controlled trial (RCT) that is the first pre- and early pregnancy intervention trial. Data management and technical support are being provided by the WHO Department of Reproductive Health and Research. To test the hypothesis that calcium supplementation commenced before pregnancy will reduce the incidence of pre-eclampsia in populations with calcium-deficient diets more effectively than does supplementation starting at 20 weeks gestation, non-pregnant women with a past history of pre-eclampsia and who are planning another pregnancy are being recruited. Recruited

women are randomised to receive either 500 mg calcium/d (a palatable and less costly dose than 1.5 g/d that for most women in the study population brings the total calcium intake up to the recommended daily allowance of 1–1.2 g/d) or a matched placebo from randomisation, through conception, until 20 + 0 weeks. All women will receive open label calcium (1500 mg/d according to the current WHO recommendation [3]) from 20 + 0 weeks until delivery. The primary outcome is pre-eclampsia, defined as proteinuric gestational hypertension. The secondary outcomes are miscarriage, gestational hypertension, significant proteinuria, serious maternal and perinatal morbidities, Caesarean delivery, perinatal death, birth weight <2500 g, and Apgar score <7 at 5 min. Recruitment commenced in 2011 in South Africa (4 sites) and Zimbabwe (1 site) and, in 2013, in Argentina (the latter 3 sites through additional funds from the WHO); recruitment will continue until a total of 540 women are pregnant (sufficient to show a 15% relative risk reduction for pre-eclampsia). We anticipate that trial recruitment will be completed at the end of October 2014, and the trial will report its findings in late 2015.

As part of the CAP trial we have conducted the first systematic review of low-dose calcium supplementation in pregnancy (submitted), which provides data to support a reduction in the current WHO recommendation of 1500 mg/d, to a logistically more feasible, and possibly safer, dose of 500mg/d.

(2) Monitoring of women with pre-eclampsia

There are two primary elements of the monitoring component: (i) the miniPIERS (Pre-eclampsia Integrated Estimate of RiSk) model development and its incorporation into the 'PIERS on the Move' platform that includes a phone oximeter, and (ii) development of an integrated mobile health (mHealth) platform for supportive antenatal care in the community and data collection measure the impact on outcomes. This will be used as part of the Community Level interventions for Pre-eclampsia (CLIP) trial (see below).

The miniPIERS model (PI: Peter von Dadelszen) has been developed and validated in women with pre-eclampsia in LMICs (submitted). This model accurately stratifies women by their risk for adverse maternal outcomes at the time of diagnosis of pre-eclampsia. The miniPIERS model is based upon gestational age and maternal symptoms (headache/visual disturbances, chest pain/dyspnoea, or abdominal pain with vaginal bleeding) and signs [systolic blood pressure (sBP) and dipstick proteinuria]; yet, miniPIERS has stratification capacity that approximates that of the symptom-, sign- and laboratory investigation-based fullPIERS model [4]. Funded by Saving Lives at Birth, the PIERS on the Move platform combines miniPIERS with a phone oximeter (co-PIs: J Mark Ansermino, Guy Dumont & Peter von Dadelszen) [5].

The mHealth platform will support antenatal care including supported decision-making by community health care providers (using integrated evidence-based algorithms), data collection through household surveys and verbal autopsies for identified maternal deaths, and

facility surveillance. The explosion of mobile technology in LMICs provides an important opportunity to accelerate improvements in health outcomes for populations that would otherwise be decades away from being 'connected' with the global community; this is particularly relevant to clinical task-shifting to cadres of health workers with insufficient training to make autonomous clinical management decisions, but who are present in women's homes, available to initiate therapy, and keen to actively participate in health care in their communities.

(3) Treatment of women with pre-eclampsia

The treatment of women with pre-eclampsia will be addressed by two trials: (i) CLIP, a cluster RCT of community-level intervention in pre-eclampsia (and associated feasibility study), and (ii) the Gynuity Health Projects Oral Antihypertensive Trial of three different oral antihypertensive therapies for severe hypertension in pregnancy.

Prior to embarking on the CLIP trials, four CLIP Feasibility Studies (co-PIs: Diane Sawchuck & Rahat Qureshi) are being conducted in Ogun State (Nigeria), Maputo Province (Mozambique), Sindh Province (Pakistan) and in Karnataka State (India). The purpose of the CLIP Feasibility Studies is to clarify (i) stakeholder support, (ii) health care system organisation and infrastructure capacity related to antenatal care and pre-eclampsia management, (iii) regulations related to professional scope of practice and/or legal barriers to, and the potential for, task shifting, (iv) provider knowledge and competency related to pre-eclampsia and elements of provider training, (v) community demographics, pre-eclampsia prevalence and rates of associated maternal and perinatal morbidity and mortality, (vi) data collection methods and informational systems for population surveillance, (vii) cultural and/or community beliefs, practices, influences, and attitudes, (viii) specific facilitators and barriers to conducting a RCT, and (ix) RCT cost identification, and the feasibility of remedying identified barriers. The Feasibility Studies use a mixed methods approach based on the normalisation process model [6] in conjunction with literature reviews, target interviews, focus groups, and survey tools. The core approach is similar across the four study sites, but is tailored according to individual setting and cultural context.

In the CLIP cluster RCT (PI: Peter von Dadelszen), we are testing the hypothesis that implementing community-level evidence-based care will reduce pre-eclampsia-related (and all-cause) maternal and perinatal mortality and major morbidity by addressing the 'three delays' in triage, transport, and treatment. Specifically, we seek to reduce that mortality and morbidity by 20% in each of the study sites (listed above), in four individually powered cluster RCTs. In the control clusters, women will receive usual antenatal care, initiation of therapy (usually limited to inpatient facilities), and referral to facility. In the intervention clusters, women will receive the CLIP intervention of (i) community engagement (of community leaders, the women of the communities themselves, and their mothers, husbands, and mothers-in-law) regarding pre-eclampsia and its origins, symptoms, signs, and potential consequences, pre-permissions for maternal transport in the

face of maternal illness, and fundraising activities around transport and treatment costs; (ii) provision of antenatal care through CLIP visits and use of the CLIP PIERS on the Move tool (for risk stratification); and (iii) for women with a CLIP 'trigger', use (when indicated) of the CLIP package of oral antihypertensive therapy (methyldopa), intramuscular (i.m.) magnesium sulphate, and appropriate referral to an emergency obstetric care (EmOC) facility. Community health care providers (cHCPs; the names of which vary in each country) will assess pregnant women with a target frequency of at least every 4 weeks. They will be trained to: enquire about women's symptoms (using country-specific pictograms), take women's blood pressure (BP) [using sBP as it more closely reflects the risk for hypertensive stroke than does diastolic BP (dBP) [7,8]], and check urine for protein using a dipstick on the first visit or on any subsequent visits if a sBP \geq 140 mmHg is found. These assessments will aid in the diagnosis and risk assessment of women with pre-eclampsia. In addition, these cHCPs will initiate definitive therapy (methyldopa and MgSO₄) close to women's homes and first level clinics as indicated by the PIERS on the Move mHealth application, and then arrange for urgent transport (as applicable) so that women can receive definitive care in a comprehensive EmOC facility. Once the four individually-powered trials are completed, we will conduct an individual patient data (IPD) meta-analysis, in which we will analyse data for women recruited at 20 weeks gestation or beyond, to standardise data to the latest public declaration of pregnancy in the four CLIP countries (i.e., 20 weeks in Pakistan). We anticipate that this analysis will be of data from approximately 100,000 pregnancies. Our hope is that community engagement with enhanced case identification and task-shifting to care in women's homes will combine equally to reduce all cause maternal and perinatal severe morbidity and mortality.

The Gynuity Health Projects Oral Antihypertensive Trial (PI: Hillary Bracken) aims to determine which of the commonly used oral antihypertensive agents is(are) effective for the treatment of severe pregnancy hypertension, defined as a sBP \geq 160 mmHg and/or dBP \geq 110 mmHg. Compared with parenteral agents typically used to treat severe hypertension, oral antihypertensive agents are easy to administer, which may be particularly advantageous in low resource settings. The RCT will test the efficacy and acceptability of three oral regimens for management of severe hypertension in pregnancy. Women will be randomly allocated to receive one of three medications: intermediate-acting 10 mg nifedipine (i.e., the 'PA tablet'), 200 mg labetalol, and 1000 mg methyldopa. The feasibility of the proposed regimens will be evaluated in a pilot study prior to the start of the trial. In the RCT, rates of efficacy, side effects, and maternal and fetal outcomes will be compared between groups. The primary outcome will be a BP within the target range (of 130–150 mmHg systolic and 80–100 mmHg diastolic) at 6 h post-treatment, without a serious adverse maternal or perinatal outcome, defined as hypotension (sBP < 120 mmHg and/or dBP < 70 mmHg and fetal compromise), Caesarean delivery for fetal compromise, severe maternal headache, or eclampsia.

(4) Global pregnancy CoLaboratory

The overarching goal of the CoLaboratory (PI: James Roberts) is to improve the health of women and their infants by facilitating research that addresses adverse pregnancy outcomes. This is being accomplished by: (i) facilitating access to data and biological samples for investigators worldwide, (ii) using the intellectual, data, and biological resources of the CoLaboratory to perform large studies that could not be accomplished by any one centre, and (iii) working to establish data and biological sample resources in LMICs. Initially, the CoLaboratory recruited 20 groups from around the world to participate; the number of participating sites is now 23. Ten projects have been initiated, including a novel meta-synthesis of data related to the role of angiogenic imbalance in the origins of pre-eclampsia and fetal growth restriction using extant datasets and across a variety of commercial platforms. In collaboration with the Global Alliance to Prevent Prematurity and Stillbirth (GAPPS) and the University of Oxford we have developed and are hosting the LINK registry (<http://www.linkregistry.org>), which is a searchable database of pregnancy and birth cohort studies from around the world. The goal is to promote collaboration among researchers by sharing their information about previously conducted and planned studies, in terms of participants, bio-specimens collected, treatments administered, and outcomes measured.

(5) Knowledge translation (KT)

KT (co-PIs: Matthews Mathai & Eleni Tsigas) will be vital to efforts to reduce the burden of life-ending, life-threatening, and life-altering maternal complications of pre-eclampsia/eclampsia. The main achievement of the KT group has been the WHO Recommendations for Prevention and Treatment of Pre-eclampsia and Eclampsia that were published in September 2011 [3]. This document can be used to inform policy making and implementation of best practices at national and sub-national levels, through various channels including ministries of health, professional associations, educational institutions, and civil society organisations. Additional KT activities include the development, dissemination, and implementation of evidence-based and culturally appropriate tools for both well- and under-resourced settings at the level of the community (to facilitate patient self-identification of pre-eclampsia), and primary health centre (PHC) or EmOC facility to improve evidence-informed clinical decision-making and treatment. To date, tools developed for LMICs include culturally appropriate pictograms for each of our CLIP countries, and support of the Preeclampsia Foundation, the North American-based patient advocacy group, in its global outreach efforts, particularly through its high traffic website (<http://www.preeclampsia.org>).

In summary, PRE-EMPT aims to improve the care of women with pre-eclampsia in LMICs, to reduce the associated burden of maternal and perinatal mortality and morbidity. In the post-MDG era, we must maintain our focus on maternal and child health if we are to achieve the ultimate

goal of a 75% reduction in maternal mortality (pre-empt.cfri.ca).

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