Preeclampsia in Low and Middle Income Countries—Health Services Lessons Learned From the PRE-EMPT (PRE-Eclampsia–Eclampsia Monitoring, Prevention & Treatment) Project

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Abstract

The hypertensive disorders of pregnancy, in particular preeclampsia, matter because adverse events occur in women with preeclampsia and, to a lesser extent, in women with the other hypertensive disorders. These adverse events are maternal, perinatal, and neonatal and can alter the life trajectory of each individual, should that life not be ended by complications. In this review we discuss a number of priorities and dilemmas that we perceive to be facing health services in low and middle income countries as they try to prioritize interventions to reduce the health burden related to preeclampsia. These priorities and dilemmas relate to calcium for preeclampsia prevention, risk stratification, antihypertensive and magnesium sulphate therapy, and mobile health. Significant progress has been made and is being made to reduce the impact of preeclampsia in low and middle income countries, but it remains a priority focus as we attempt to achieve Millennium Development Goal 5.

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Résumé

Les troubles hypertensifs de la grossesse, particulièrement la prééclampsie, ont de l’importance puisque des événements indésirables se manifestent chez des femmes présentant une prééclampsie et, dans une moindre mesure, chez des femmes présentant d’autres troubles hypertensifs. Ces événements indésirables sont de nature maternelle, périmatiale et néonatale, et peuvent modifier la vie des personnes qui les connaissent, lorsque celles-ci surviennent aux complications. Dans cette analyse, nous discutons d’un nombre de priorités et de dilemmes auxquels doivent faire face les services de santé des pays à revenu faible ou moyen au moment de tenter de hiérarchiser les interventions en vue d’atténuer le fardeau de santé lié à la prééclampsie. Ces priorités et ces dilemmes sont liés à l’administration de calcium aux fins de la prévention de la prééclampsie, à la stratification du risque, aux traitements aux antihypertenseurs et au sulfate de magnésium, et à la santé « mobile ». Bien que des progrès significatifs aient été réalisés et continuent d’être réalisés en vue d’atténuer les effets de la prééclampsie au sein des pays à revenu faible ou moyen, cette problématique demeure une priorité dans le cadre de nos tentatives d’atteindre l’objectif 5 du Millénaire pour le développement.
BACKGROUND

Preeclampsia, although commonly defined by the presence of both significant hypertension and heavy proteinuria, is a pregnancy- and placenta-specific form of systemic inflammation with multiple target organs (Figure). As far as we can determine, preeclampsia and eclampsia claim the lives of approximately 72,000 women and 500,000 fetuses and newborns each year—a loss of almost 1,600 lives per day. Over 99% of these losses occur in low and middle income countries, particularly in sub-Saharan Africa and on the Indian subcontinent. In the Americas, preeclampsia and eclampsia are the leading cause of direct maternal mortality.

Currently, the singular way to initiate resolution of the maternal syndrome of preeclampsia is to deliver the placenta. However, the maternal syndrome of preeclampsia may present de novo postpartum and, especially with early-onset preeclampsia, cause transient postpartum deterioration. Therefore, even timely delivery does not necessarily avoid all end-organ complications of the disorder. In addition, the life-altering and life-threatening complications (e.g., stroke, acute renal failure, eclampsia, pulmonary edema, and placental abruption) probably increase the significant health burden of preeclampsia by at least five-fold.

As a group, we believe that the global community (clinicians, researchers, policy makers, governments, health authorities, and other stakeholders) should focus efforts on reducing the excess number of adverse maternal and perinatal events in women whose pregnancies are complicated by preeclampsia, rather than focus solely on the surrogate of these risks, the diagnosis of preeclampsia.

Given that preeclampsia-related maternal and perinatal deaths and permanent sequelae result primarily from delays in diagnosis, triage, transport, and treatment, an important direction for new initiatives related to improving preeclampsia-related outcomes may be to enhance the availability of life-saving interventions in the communities in which vulnerable women reside. Such interventions may vary from improving the status of pregnant women and facilitating timely decision-making when complications arise, to initiating life-saving therapies (e.g., magnesium sulphate and antihypertensive agents) prior to urgent transfer to an effective and adequately resourced emergency obstetric care facility.

In 2011, the University of British Columbia was awarded the four-year PRE-eclampsia–Eclampsia Monitoring, Prevention & Treatment project grant by the Bill & Melinda Gates Foundation. The overarching theme of this proposal is “reducing the maternal and perinatal consequences of preeclampsia.” Through this grant we aim to determine the impact of this program of research on those outcomes.

The primary objectives of PRE-EMPT are three community-level and primary health centre-level intervention studies tailored to LMIC settings and related to prevention, monitoring, and treatment. The secondary objectives are

1. developing a multifaceted international research collaboration, and
2. LMIC-oriented preeclampsia knowledge translation activities.

We describe here examples of what we have learned to date from these objectives, and the implications derived from our current position for health service decision-making, especially in resource-challenged settings.

PREVENTION

Calcium Supplementation to Reduce the Incidence of Preeclampsia: Should We Provide This to High-Risk Women? If Yes, at What Dose?

In general, preeclampsia is considerably more prevalent in low and middle income communities than in affluent communities. Two striking exceptions have been identified in Ethiopia and in the Mayan Indians of Guatemala, where diets contain high levels of calcium. Subsequent epidemiological, clinical, and laboratory studies linking preeclampsia to calcium deficiency have been outlined in a recent systematic review of calcium supplementation during pregnancy. The conclusion of this systematic review, and that of a parallel meta-analysis, was that supplemental calcium (at least 1 g daily) from mid-pregnancy is associated with a modest reduction in rates of preeclampsia, and a more notable reduction in its severe manifestations, particularly among women at increased risk or with low dietary calcium intake. However, we have found no report of randomized controlled trials of calcium supplementation commenced before pregnancy.

ABBREVIATIONS

<table>
<thead>
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<tr>
<td>AUC ROC</td>
<td>area under the receiver-operator characteristic curve</td>
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<td>BP</td>
<td>blood pressure</td>
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<td>EPIC</td>
<td>European Prospective Investigation into Cancer and Nutrition study</td>
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<tr>
<td>HR</td>
<td>hazard ratio</td>
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<td>LMIC</td>
<td>low and middle income countries</td>
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<td>MDG</td>
<td>Millennium Development Goal</td>
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<td>PIERS</td>
<td>Pre-eclampsia Integrated Estimate of Risk</td>
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<td>PRE-EMPT</td>
<td>Pre-eclampsia–Eclampsia Monitoring, Prevention &amp; Treatment</td>
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<tr>
<td>RDA</td>
<td>recommended daily allowance</td>
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Hofmeyr and colleagues conducted an RCT nested within the large World Health Organization trial of calcium supplementation (1.5 g daily from at least 20 weeks’ gestation) in pregnant women with low dietary calcium intake; this failed to demonstrate an effect of calcium supplementation on biochemical measures commonly elevated in preeclampsia (serum urate, platelet count, and urine protein/creatinine ratio). The lack of effect on proteinuria is consistent with the findings of the main WHO trial, in which there was a trend towards a reduced risk of preeclampsia (RR 0.92; 95% CI 0.75 to 1.13) and “severe” preeclampsia (RR 0.74; 95% CI 0.48 to 1.15), but no reduction in proteinuria (RR 1.01; 95% CI 0.88 to 1.15). Tentative evidence for an effect on the offspring is the finding of reduced rates of childhood hypertension in the children of participants in RCTs of calcium supplementation.

The origins and consequences of preeclampsia

In this model of the origins of preeclampsia, we describe preeclampsia that arises primarily because of imperfect placentation (early-onset or “placental” preeclampsia) and that arises because of either a lowered maternal threshold or excessive physiological placentation (late-onset or “maternal” preeclampsia). Some aspects of the preeclampsia process are specific to it, while others are shared with normotensive intrauterine growth restriction. A lowered maternal threshold may influence the development of early-onset preeclampsia as well through direct endothelial cell activation. The consequences of the endothelial cell activation that appears consistent between all women who develop preeclampsia include a variable impact on multiple vulnerable organ systems. Disease severity generally correlates with the degree and number of organ dysfunctions.

↑: increased risk of preeclampsia; ↓: decreased risk of preeclampsia; EVT: extravillous trophoblasts; SNP: single nucleotide polymorphism; IUGR: intrauterine growth restriction; DbM: diabetes mellitus; ARDS: acute respiratory distress syndrome; LV: left ventricular; TIA: transient ischemic attack; RIND: reversible ischemic neurological deficit; CVA: cerebrovascular accident; PRES: posterior reversible encephalopathy syndrome; ATN: acute tubular necrosis; ARF: acute renal failure; DIC: disseminated intravascular coagulation
This may also explain an anomaly identified in the systematic review. The incidence of preeclampsia (defined as proteinuric gestational hypertension [blood pressure $\geq 140/90$ mmHg]) was reduced overall by 55% (RR 0.45, 95% CI 0.31 to 0.65) and the composite outcome “maternal death or severe morbidity” was reduced by 20% (RR 0.80; 95% CI 0.65 to 0.97). The observed reduction in “maternal death or severe morbidity” includes severe hypertension, with the outcome that is likely to be modified by the antihypertensive effect of calcium. However, the risk of HELLP syndrome was increased 2.7-fold with calcium supplementation (RR 2.67; 95% CI 1.05 to 6.82).

We believe that these considerations should lead to reflection prior to the programmatic introduction of calcium supplementation to pregnant women in low intake areas. There are four main reasons to pause and reflect. The first is the possible risk associated with calcium supplementation, which should be balanced against the probable benefit; the second is the issue of calcium dose; the third is the timing of the intervention; and the fourth is the issue of mineral balance.

**Calcium: Balancing Potential Risks Against Probable Benefit**

While reducing the incidence of the diagnosis of “preeclampsia” through its antihypertensive effect, calcium supplementation may mask, without altering, the underlying pathology of preeclampsia. Consequently, we suggest that any program of calcium supplementation introduced with the intent of reducing the burden of preeclampsia in a given jurisdiction should be monitored until it is clear that the rate of adverse outcomes (maternal and perinatal severe morbidity and mortality) actually falls, rather than increases. This is particularly relevant in view of the recent findings of the EPIC-Heidelberg observational cohort study that, after an average follow-up time of 11 years, having a moderate total dietary and dairy calcium intake significantly reduced the risk of developing a myocardial infarction (HR 0.69; 95% CI 0.50 to 0.94 and HR 0.68; 95% CI 0.50 to 0.93, respectively). Overall, associations between calcium intake and stroke risk or cardiovascular disease mortality were not found. Users of supplements that included calcium had a significantly higher risk of myocardial infarction (HR 1.86; 95% CI 1.17 to 2.96) than non-users of any supplements, and the risk was more pronounced for users of calcium supplements only (HR 2.39; 95% CI 1.12 to 5.12). This parallels the evidence for a benefit from antioxidants in the prevention of preeclampsia; a diet rich in antioxidants appears to protect against preeclampsia, whereas the ingestion of isolated vitamins C and E does not.

**Calcium: Dietary Replacement Versus Dietary Supplementation**

It appears that dosing studies on calcium replacement or supplementation are required. The current WHO recommendation, derived from meta-analyses, suggests a dose of 1.5 g to 2 g calcium/day, which is 30% to 80% greater than the recommended daily allowance of 1200 mg, in addition to current dietary intake. The study of dietary calcium intake in primiparous women cited above showed a median daily dietary calcium intake of approximately 600 mg. The recommended calcium dose for supplementation during pregnancy has significant cost implications. Ministries of health must consider cost–benefit ratios in their decisions to scale up interventions that may affect health outcomes, and often need to justify their decisions to ministries of finance within their respective regional and federal governments. Without substantive evaluation of the cost–benefit equation for the higher doses, especially in the absence of calcium dosing studies, many countries will be hesitant to scale up this recommendation.

Furthermore, in a placebo-controlled calcium supplementation in pregnant women in The Gambia, women receiving calcium (1500 g/day) had significantly lower hip, lumbar spine and distal radial lower bone mineral content, bone area and bone mineral density throughout lactation than women who received placebo. The authors surmise that such levels of calcium supplementation in pregnant women may disrupt metabolic adaptation to pregnancy and alter bone health.

For women in LMICs, dietary replacement with 500 mg calcium/day would achieve a median daily intake of approximately 1100 mg; this could be achieved with food fortification, and represents the difference in daily calcium intake between high income and low income countries. Higher levels of true supplementation to 1.5 g/day to 2.0 g/day are unacceptable to the palate, are greater than RDA amounts, and are of significant programmatic cost.

**Calcium: Timing the Intervention**

Another issue requiring explanation is the modest effect of calcium supplementation on preeclampsia in contrast to the striking epidemiological differences in populations with good and poor dietary calcium. It is possible that calcium supplementation in the second half of pregnancy is too late to influence the underlying processes of preeclampsia. For example, inadequate placentation occurs in early pregnancy and would not be influenced by an intervention in the second half of pregnancy. While deficient dietary calcium before and during early pregnancy may increase the risk for
preeclampsia, there may be limited potential to reverse this effect by calcium supplementation later in the pregnancy.

Therefore, in response to both the dose and timing issues, the Calcium And Pregnancy RCT is testing the hypothesis that 500 mg of calcium replacement daily (to the RDA), begun before pregnancy in women at high risk of preeclampsia or eclampsia, will reduce the incidence of hypertension and other pregnancy outcomes more effectively than supplementation of 1.5 g/day to 2.0 g/day once pregnancy is diagnosed as currently recommended by the WHO. This RCT is currently recruiting women with low calcium intake in South Africa and Zimbabwe, and, with supplemental funding from the WHO, will recruit in Argentina. In this trial women will be randomized to calcium or placebo from pre-pregnancy until 20 weeks’ gestation, after which time all women will receive open label calcium (1500 mg/d) to supplement calcium intake to WHO-recommended amounts.

Calcium: Mineral Balance

Another explanation for the apparent paradox of the modest effect of calcium supplementation on preeclampsia, in contrast to the striking epidemiological differences in populations with good and poor dietary calcium, is the difference in mineral balance between dietary and supplemental calcium intake. As noted in the EPIC-Heidelberg study, dietary calcium intake appears beneficial in terms of cardiovascular health, whereas supplements do not. It is possible that the balance of minerals (calcium, potassium, and magnesium, in particular) obtained through diet provides health benefits not matched by calcium supplements alone. Other micronutrients (and their balance) present in dairy foods may be important in modulating the consistently observed benefit of adequate calcium intake.

MONITORING

Once a woman has developed preeclampsia or another hypertensive disorder of pregnancy, can her risks be further stratified? We believe that they can.

An initial step towards improved, streamlined, and evidence-based monitoring of women with preeclampsia is to standardize care, including initial clinical and laboratory assessment and ongoing surveillance. At the BC Women’s Hospital and Health Centre we achieved a greater than 80% reduction in the incidence of a combined adverse maternal outcome simply by standardizing assessment and surveillance of women admitted with either gestational hypertension or gestational proteinuria. To test this experience beyond a single tertiary centre in a high resource setting, we repeated this exercise across British Columbia, with the addition of specific advice about items of drug and fluid management, and observed a more than 30% reduction in the incidence of adverse maternal outcomes across the province after a process of active guideline implementation. This latter effect was seen most in smaller units where day-to-day exposure to women with preeclampsia, especially complicated preeclampsia, is infrequent. We presumed that the effect in smaller units was achieved by increasing in-house competence and care provider confidence in those units.

In LMICs, pregnant women often rely on community health professionals, many of whom have under 12 months’ training, to facilitate antenatal and maternity care. These pregnant women are often concentrated in rural areas with inadequate access to comprehensive emergency obstetric care. Therefore, to achieve reductions in adverse outcomes similar to those observed in British Columbia, one must consider cost-effective health care delivery options that will increase the skill level and confidence of community health professionals. Following extensive inquiry, we believe that mobile health (mHealth) technologies have the capacity to strengthen the ability of community-level health professionals to provide evidence-based care (decision-making and initiation of therapies) in a timely fashion and within the household or primary health clinic prior to transport.

The WHO defines mHealth as “mobile technologies as well as advancements in their innovative application to address health priorities.” The mobile phone has become a novel tool to address public health challenges and shift the paradigm of health care access and delivery from traditional facility-based care to community care. The United Nations Millennium Development Goal 8, specifically 8F, calls for the benefits of new technology, particularly information technology, to be made available by increasing the number of mobile phone subscribers.

In 2010, a consortium of international groups called for the use of mobile phones to reduce maternal mortality and achieve MDG 5 by 2015. Mobile phones have been used effectively in a number of capacities for advancing maternal health, including data collection and management, point of care diagnostics and support, capacity strengthening, health promotion, text messaging of prenatal education, automated prenatal care appointment reminders, and access to emergency obstetric care.

To provide such an mHealth platform, it is important to develop decision-making tools that can be integrated into a mobile platform, such as a mobile phone, so that clinical
variables (e.g., symptoms and easily observed signs) can be entered and evidence-based, standardized therapeutic advice generated automatically using the software capacity of the mobile device. An example is the phone oximeter, described below.

Over the past decade, we have been developing and validating two risk stratification models to be used in women with clinical preeclampsia (i.e., time of disease, rather than prediction of disease)—the Pre-eclampsia Integrated Estimate of Risk models.28,34–45 The two models are fullPIERS (based on symptoms, signs, and laboratory tests)34 and miniPIERS (based on symptoms and signs).46 Development and internal validation of fullPIERS has been funded by the Canadian Institutes for Health Research, and miniPIERS development and full validation by the PRE-EMPT grant, the WHO, and Canadian Institutes of Health Research.

In the fullPIERS data set (using data from tertiary centres in Canada, New Zealand, Australia, and the United Kingdom), we were able to identify women with preeclampsia who are at increased risk of maternal complications, and we have been able to grade this risk.34 With 2023 women in the fullPIERS database, the AUC ROC is 0.88 (95% CI 0.84 to 0.92), and stratification capacity is robust. The independent predictors of adverse maternal outcome are gestational age at eligibility, chest pain/dyspnea, SpO2, serum creatinine, serum AST, and platelet count. The fullPIERS model assesses risk up to seven days after eligibility (AUC ROC 0.76; 95% CI 0.72 to 0.80). The fullPIERS model requires external validation before it can be advocated for use outside research settings, and will be applicable only to facilities with full laboratory support. A powerful component of the fullPIERS model is pulse oximetry, which has independent power to identify women at risk of adverse outcomes of preeclampsia, including non-cardiorespiratory outcomes.39

The final analytical stages of developing and validating the miniPIERS model are currently being completed. The model will use data derived from women with any hypertensive disorder of pregnancy within 24 hours of admission to academic centres in Brazil, Fiji, Pakistan, South Africa, and Uganda, and will be based on gestational age, parity, symptoms, and signs.47

Once the miniPIERS model has been validated we will transfer the model to an mHealth platform as a mobile phone application, using funding from Saving Lives at Birth and the PRE-EMPT award. This application, PIERS on the Move, will be developed initially for two purposes. The first will be to host miniPIERS on a mobile phone application, with the results of the miniPIERS model guiding care within the context of a planned cluster randomized control trial of community level, community health worker-administered, interventions for preeclampsia that will recruit women in South Asia and sub-Saharan Africa. Funding for the Community-Level Interventions for Pre-eclampsia trial will be obtained from PRE-EMPT.

The second purpose will be to incorporate the phone oximeter, a mobile phone-supported pulse oximeter, into a user-friendly application to guide care, as well as to recalibrate the miniPIERS model to include SpO2.48 Again, we envisage an mHealth application that will both stratify risk and support clinical decision-making, building care provider confidence through integral decision trees that reflect best evidence-based practice and the current WHO recommendations.20

### Monitoring: Removing the Primacy of Proteinuria in Risk Stratification in High Resource Settings

It is a historical accident that proteinuria has achieved a preeminent role in the diagnosis and ongoing surveillance of women with preeclampsia. While significant proteinuria (i.e., 300 mg/24 h, 30 mg protein/mmol creatinine on a random urine collection, or ≥ ++ protein by urinary dipstick) is central to all diagnostic criteria, the presence of hyperuricemia, for example, is as effective for perinatal risk stratification as proteinuria.49 However, there is no clear gold standard for the assessment of proteinuria in pregnancy. Through the PIERS project, we have determined that 24-hour urine collections are vulnerable to both over- and under-collection approximately one half of the time, with under- and over-collection being equally common.50 Similarly, we have identified that the method of protein measurement may alter the quantification performance of proteinuria and albuminuria estimations in dilute urine,51,52 which may explain some of the uncertainties that derive from the literature, especially for albumin/creatinine ratios.53

Once significant proteinuria (however defined) has been observed, is there any further benefit to be derived from ongoing risk stratification including proteinuria? In high resource settings, we have determined that all three methods of proteinuria estimation perform as well (or as poorly) as each other, and none of them have adequate stratification capacity to be used to guide clinical decision-making.54 In the fullPIERS model, measures of proteinuria estimation were displaced from the model by serum creatinine—an observation made previously by Lindheimer and Kanter, as rising serum creatinine is more proximate to the occurrence of an adverse outcome than is the degree of proteinuria.55 The level of dipstick proteinuria will not be a necessary component of the miniPIERS model.
TREATMENT

Overcoming the Reductionist View of the Management of Severe Pregnancy Hypertension

While eclampsia is the most commonly recognized and visible cause of death associated with preeclampsia, the specific causes of death for women with preeclampsia or eclampsia in LMIC have not been well studied. Although the prevalence and burden of illness of severe hypertension of preeclampsia or eclampsia is not accurately documented in LMIC, data from well-resourced settings indicate that failure to treat sustained severe hypertension adequately is an important contributor to maternal mortality in preeclampsia or eclampsia. These findings are supplemented by the institutional data that contribute to the Fourth Report on Confidential Enquiries into Maternal Deaths in South Africa, in which 45% of maternal deaths attributed to preeclampsia were secondary to “cerebral complications” other than eclampsia.

Severe hypertension is defined as a systolic blood pressure ≥ 160 mmHg and/or a diastolic BP ≥ 110 mmHg. The Confidential Enquiries into Maternal Deaths in the United Kingdom have shown that failure to initiate effective antihypertensive therapy for sustained severe hypertension was the most common source of substandard care in the management of women with preeclampsia or eclampsia.56–58 In the recent reports, the majority of women who died from preeclampsia had either intracerebral hemorrhage or cerebral infarction secondary to inadequately-controlled severe hypertension.56–57 Therefore, sustained severe maternal hypertension is considered an obstetric “near miss,” a potentially lethal complication that women survive, due either to excellent medical care or to chance alone.61 It is widely accepted in all international pregnancy hypertension guidelines that women with severe hypertension are at increased risk of stroke and other central nervous system complications, and would therefore benefit from blood pressure reduction.20,60,62–65 The relevant WHO guidelines rate as “strong” the recommendation to treat severe hypertension with antihypertensive therapy.20

The Priority Medicines for Mothers and Children was published in March 2011 by the WHO, United Nations Population Fund, and the United Nations Children’s Fund.66 The New York Times has described Priority Medicines for Mothers and Children as “the top 30 medicines to save mothers and children.”67 These medicines have been taken from the WHO Essential Medicines List.68 Priority Medicines specifically lists eight drugs for management of the three leading causes of maternal morbidity and mortality (postpartum hemorrhage, maternal sepsis, and preeclampsia/eclampsia), as well as for sexually transmitted infections and HIV.68 In theory, medicines on this list should be available within functioning health systems at all times, in adequate amounts, in the appropriate dosage forms, with assured quality and adequate information, and at a price that the individual and the community can afford. Although the reality in each LMIC may be different, the Priority Medicines for Mothers and Children is designed to be an advocacy tool.

The current Priority Medicines for Mothers and Children lists only magnesium sulphate (and calcium gluconate for treatment of magnesium toxicity) as a priority medicine for management of severe preeclampsia or eclampsia.66 The presence of magnesium sulphate on the list is entirely appropriate, because it reduces, by at least 50%, both the incidence and recurrence of eclampsia; in addition, it probably reduces maternal mortality.69–72 However, magnesium sulphate is not an effective antihypertensive agent.74 There is limited observational evidence describing no or transient decreases in BP; a transient decrease in BP may occur 30 minutes after the administration of 2 g to 5 g of magnesium sulphate, but sustained reductions in BP cannot be expected.75

However, as there have been no RCTs of antihypertensive therapy for severe pregnancy hypertension, some have viewed this absence of RCT evidence as a lack of evidence. This apparently reductionist view (that no RCT evidence equates to no evidence) may be the reason that antihypertensive agents have neither been prioritized in LMIC efforts in preeclampsia or eclampsia management nor included in the Priority Medicines for Mothers and Children, and may have led to the avoidable burden of maternal mortality related to uncontrolled severe pregnancy hypertension observed in the United Kingdom and elsewhere.56–58

Therefore, what medication should be selected as the drug of choice for the treatment of severe pregnancy hypertension? Medications in the Priority Medicines for Mothers and Children are chosen on the principles of efficacy, safety, and familiarity at both the national and individual prescriber level.66 There are a number of options for the choice of antihypertensive agent. In RCTs, parenteral labetalol, parenteral hydralazine, and oral nifedipine (intermediate-acting tablets or short-acting capsules) have been evaluated most often. All are reasonable choices for lowering severely elevated BP. Hydralazine may be associated with more maternal hypotension than the other agents.76 Labetalol is not listed in the WHO Essential Medicines List and may therefore not be widely available, and prescribers may not be familiar with its use. Concurrent use of magnesium sulphate and nifedipine may be associated with neuromuscular blockade; however,
a retrospective cohort study and data synthesis found the incidence to be < 1%, and inadvertent magnesium toxicity can be treated effectively by calcium gluconate. Based on this, several national guidelines have accepted that there is no significant interaction. Furthermore, the American Society of Hypertension and WHO guidelines specifically state that there is no interaction between nifedipine and magnesium sulphate.

Although nifedipine is not listed as an antihypertensive agent in the Priority Medicines for Mothers and Children, it is listed for the prevention of preterm birth. As nifedipine is administered orally and there may be limited resources in LMIC for intravenous access, nifedipine may be an ideal medication for treatment of severe hypertension in pregnancy. Also, the oral administration of this medication opens up the possibility of administration in the community setting. However, ultimately, the choice of an antihypertensive agent will depend upon the clinician, regional differences in practice, and availability.

As we believe that the omission of antihypertensive therapy for severe hypertension represented a missed opportunity to advocate for an affordable and effective intervention that may decrease maternal mortality and move us closer to achieving MDG 5, we contacted the WHO Department of Essential Medicines and Health Products. In response to our contact, we have received confirmation from Dr Clive Ondari, Team Coordinator, Medicine Access and Rational Use, Essential Medicines and Health Products, WHO that an antihypertensive for severe pregnancy hypertension (most logically nifedipine) will be added to the updated Priority Medicines for Mothers and Children in 2012.

Once the issue of antihypertensive management for severe pregnancy hypertension has been accepted as a health services priority, in addition to magnesium sulphate, the question then is: at what level of the health system could and should life-saving therapy be initiated?

**CONCLUSION**

The hypertensive disorders of pregnancy, in particular preeclampsia, matter. They matter because adverse events occur in women with preeclampsia and, to a lesser extent, the other hypertensive disorders. These adverse events are maternal, perinatal, and neonatal, and can alter the life trajectory of each individual, if that life is not cut short by complications. The majority of these complications occur in LMICs. The PRE-EMPT project will attempt to address prevention, monitoring, and treatment through three community-level and primary health centre-level intervention studies tailored to LMIC settings. We should not assume that preventing the diagnosis of “preeclampsia” will equate to reduced rates of adverse events. This underlies our hesitancy to recommend programmatic implementation of non-dietary calcium supplementation with the current level of knowledge. Resolving the unsettled questions related to the relationship between calcium and preeclampsia is an urgent research priority. In the interim, it is incumbent on those initiating programs of calcium supplementation to ensure that outcomes improve beyond reduction in the incidence of the diagnosis of “preeclampsia.”

Risk stratification of women with preeclampsia is now possible, so that maternal risks can be balanced against the perinatal risks of prematurity, which are better known to caregivers. Importantly, we suggest that “heavy” proteinuria no longer be an indication to deliver a woman in the absence of either a term pregnancy or other precipitants included in the PIERS models. Mobile health platforms can deliver the PIERS models and PIERS-directed clinical care algorithms into the hands of community health care providers, to whom initiation of lifesaving therapies can be shifted. Such mHealth platforms can be augmented through technology transfer into robust mobile applications, such as the mobile phone oximeter.

We advocate that the management of severe pregnancy hypertension is as important an intervention in women with preeclampsia as the RCT-supported use of magnesium sulphate prevention and treatment of eclampsia. There will never be a randomized placebo-controlled trial of antihypertensives for this indication, nor should there be.

Preeclampsia is a multisystem disorder with a number of biological pathways leading to the clinical syndrome that we recognize. It will be through multisystem interventions (basic and clinical research methodologies, clinical trials, implementation research, health services planning, and programmatic scale-up) and multilevel collaboration (women, their families and communities, clinicians, researchers, policy makers, governments, health authorities, and other stakeholders) that we will reduce the unacceptable personal, family, community and societal burden associated with preeclampsia.

**REFERENCES**