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11

### Pre-eclampsia in low and middle income countries

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Pre-eclampsia and eclampsia are leading causes of maternal and perinatal morbidity and mortality worldwide. The exact prevalence, however, is unknown. The majority of pre-eclampsia related deaths in LMIC occur in the community and therefore, interventions must be focused at this level. There are a number of unique challenges facing LMIC but the principles of care for women with pre-eclampsia remain the same as in well resourced settings. Three primary delays lead to an increased incidence of maternal mortality from pre-eclampsia- delays in triage, transport and treatment. There are a number of other challenges facing LMIC and the health care worker shortage is particularly significant. Task shifting is a potential strategy to address this challenge. Community health care workers, specifically lady health care workers, are an integral part of the health care force in many LMIC and can be employed to provide timely care to women with pre-eclampsia. Prevention strategies should be applied to every pregnant woman since we cannot predict who will develop pre-eclampsia given the limitation in resources. Aspirin and calcium are the only two recommended therapies at this time. Measuring blood pressure and proteinuria is challenging in LMIC due to financial cost and lack of training. A detection tool that is affordable and can be easily applied is needed. Magnesium sulfate is the drug of choice for the prevention and treatment of eclampsia but it is underutilized due to barriers on multiple levels.

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Pregnant women in low and middle income countries [LMIC] are amongst the most vulnerable populations in the world. Worldwide, hemorrhage is the leading cause of maternal death.<sup>1</sup> Pre-eclampsia and eclampsia follows second and cause significant maternal and perinatal morbidity and mortality.<sup>1</sup> Sepsis, obstructed labour and unsafe abortion round up the top five causes of direct maternal death in LMIC.<sup>1</sup> This is in contrast to high income countries where the top five causes are hypertensive disorders of pregnancy, pulmonary embolism, hemorrhage, abortion and ectopic pregnancy respectively.<sup>1</sup> 99% of maternal mortality occurs in LMIC and many of these deaths are preventable.<sup>2</sup> Most of the mortality occurs at the community level and effective community level interventions are lacking.

In 2001, the United Nations Millennium Declaration was translated into eight goals, one of which is to improve maternal health (Millennium Development Goal [MDG] 5).<sup>3</sup> The target for the MDG 5 is to reduce the maternal mortality ratio by three quarters from 1990 to 2015.<sup>3</sup> However, only 23 countries are on track to achieve the MDG 5 by 2015.<sup>4</sup> In light of this, unprecedented high-level attention has been given to maternal health in the last few years. Governments, donor agencies, the private sector, policy makers, international and national civil society organizations, and program managers from governmental and non-governmental organizations have collaborated to assess progress, revise existing strategies, and launch new, innovative approaches to achieving the MDG 5.<sup>5</sup>

One such initiative is PRE-EMPT (PRE-eclampsia-Eclampsia Monitoring, Prevention and Treatment), which has been recently funded by the Bill and Melinda Gates Foundation. PRE-EMPT consists of a number interrelated projects that will be conducted over a four year period in select LMIC in Africa and South Asia. The overarching theme of this initiative is to reduce the maternal and perinatal consequences of pre-eclampsia. The primary goal is to improve community level case ascertainment and interventions as most maternal mortality and morbidity occurs in this setting. The secondary goal is to develop multifaceted international research collaboration and LMIC-oriented pre-eclampsia knowledge translation activities.

The principles of care of women with pre-eclampsia in LMIC are the same as in high resource countries. However, there are special considerations and challenges unique to LMIC. This section will address the relevant issues with a focus on existing gaps and barriers for prevention, diagnosis and treatment of pre-eclampsia. It will emphasize task shifting particularly at the community level and it will highlight the contributions that PRE-EMPT will make in this area. It is worth highlighting that this chapter is intentionally unemotional while acknowledging that maternal health is a human right. The aim of the section is to list the facts relating to the care of women with pre-eclampsia in LMIC.

## **Background**

### *Definition of LMIC*

There are 144 LMIC according to the World Bank classification of countries.<sup>6</sup> Countries are categorized according to income based on the 2009 Gross National Income (GNI) per capita.<sup>6</sup> The groups are: low income, \$995 or less; lower middle income, \$996–\$3,945; upper middle income, \$3,946–\$12,195; and high income, \$12,196 or more.<sup>6</sup> There are 40 low income countries, 56 lower middle income countries and 48 upper middle income countries.

### *Epidemiology of pre-eclampsia in LMIC*

Worldwide, pre-eclampsia is the second leading cause of direct maternal death. The exact prevalence of pre-eclampsia and associated mortality and morbidity in LMIC is unknown. Historically, most population level studies and surveys have focused on the prevalence of eclampsia rather pre-eclampsia. The reporting quality of these studies examining causes of maternal mortality has been generally poor; only 50% have included definitions for hypertensive disorders of pregnancy making it difficult to accurately estimate the prevalence of pre-eclampsia.<sup>7</sup>

The World Health Organization (WHO) estimates that at least 16% of maternal deaths in LMIC result from the hypertensive disorders of pregnancy, of which eclampsia is the primary contributor.<sup>1</sup> This global average, however, hides the significant variation in the prevalence between countries. Hypertensive disorders were reported as the cause of 9.1% in each of Africa and Asia, but 25.7% in each of Latin

America and the Caribbean.<sup>1,8</sup> In Mexico, for example, pre-eclampsia is the leading cause of death.<sup>1,8</sup> 2.3% of women with pre-eclampsia progress to developing eclampsia in LMIC as compared to 0.8% of women in high income countries.<sup>9</sup>

In contrast to maternal mortality rate which is underestimated, our current estimates of pre-eclampsia may be an overestimate as they are predominantly derived from facility-based data. Most of the maternal deaths in LMIC occur at the community level and the vast majority of women do not present to a health care facility. In the community setting, verbal autopsy is used to determine the cause of death by retrospectively asking the woman's relatives about symptoms she may have had prior to her death.<sup>10</sup> Although there is a WHO standardised verbal autopsy tool, many countries have adapted it for individual use. The verbal autopsy tool has not been validated for diagnosing pre-eclampsia and pre-eclampsia related death and therefore, its diagnostic accuracy is unknown.

PRE-EMPT will aim to first determine the accuracy of the verbal autopsy questionnaire and then, prospectively determine the prevalence of pre-eclampsia and pre-eclampsia related mortality and morbidity in the community setting. This is in keeping with the mandate that the WHO Director-General, Dr Margaret Chan, has established when she stated that "reliable health data and statistics are the foundation of health policies, strategies, evaluation and monitoring".<sup>11</sup>

### Overview of challenges in LMIC

The Safe Motherhood Initiative, launched in 1987 and targeted towards improving emergency obstetric care, has made access to high quality obstetric care throughout pregnancy and immediately after childbirth, one of its priorities.<sup>12</sup> Despite this, the absence of pre-conception care coupled with a lack of effective and universal antenatal care remains a serious challenge in LMIC. Many women with pre-eclampsia, particularly, at the community level are missed due to the lack of antenatal care. These women are more likely to develop serious complications resulting in maternal and perinatal morbidity and mortality.

Antenatal care utilization is around 68% in LMIC compared to 98% in high resource settings.<sup>13</sup> The region of the world with the lowest levels of use is South Asia, where only 54% of pregnant women have at least one antenatal care visit.<sup>13</sup> In the Middle East and North Africa, use of antenatal care is somewhat higher at 65% of pregnant women.<sup>12</sup> In sub-Saharan Africa, generally the region with the lowest levels of health care use, 68% of women report at least one antenatal visit.<sup>13</sup> These figures, however, show an improvement of around 20% in the last decade.<sup>13</sup>

Not surprisingly, there is marked urban/rural differential in accessing antenatal care in LMIC. Whereas 86% of women in urban settings will have one antenatal visit, only 65% of women rural settings will have the same.<sup>13</sup> For repeated antenatal visits, 61% of women in urban women report four or more antenatal visits compared to 39% of rural women.<sup>13</sup>

When women do access care, there are three primary delays that lead to the increased incidence of maternal mortality due to pre-eclampsia: delays in triage, in transport, and in treatment. These delays occur at the community, primary health center, and hospital facility level respectively. There are a number of factors that lead to these delays: lack of financially feasible and accurate point-of-care diagnostics, inadequate means and/or routes of transportation and unavailability of appropriate treatment due to financial cost or lack of pharmaceutical support including barriers to registration and production.<sup>14</sup>

There is also a current shortage of health care workers. The World Health Organization (WHO) has declared that there are 58 crisis countries facing an acute health care worker crisis.<sup>15</sup> 36 of these countries are in sub-Saharan Africa.<sup>16</sup> In addition to the shortage of health care workers, inappropriate skill-mix is an issue. For example, in Bangladesh, there are around five physicians and two nurses per 10,000 people. The ratio of nurse to physician is only 0.4 to 1.<sup>15</sup> Furthermore, there is an uneven distribution of qualified health care workers in urban settings compared to rural areas.<sup>15</sup>

As in well resourced settings, at the facility level, the introduction and adoption of evidence-based clinical practice remains challenging. Currently, there is no clear policy or country specific standard of care for pre-eclampsia. Access to evidence and guidelines may be limited in LMIC due to financial cost. However, resources such as the WHO Reproductive Health Library (RHL) are free, available online and are particularly targeted for LMIC. RHL takes the best available evidence on sexual and reproductive health from Cochrane systematic reviews and presents it as practical actions for clinicians to take to improve health outcomes.<sup>17</sup>

The adoption of evidence depends on whether the practice is consistent with the values, beliefs and current needs of the local medical team and the population it serves, as well the simplicity of the intervention or treatment, adaptability of the practice to local conditions. Magnesium sulfate (see section titled “*Treatment of Pre-eclampsia*”) is one such example, where despite robust evidence, the uptake of evidence based practice has been low due to multiple systemic barriers.

PRE-EMPT will develop strategies and solutions that are easily adoptable, financially feasible and targeted at the community level where the majority of pre-eclampsia related maternal mortality and morbidity occur. PRE-EMPT has an emphasis on task shifting and will focus on the role of community health workers (CHW) or lady health care workers (as they are known as in many countries) in the care of women with pre-eclampsia. Task shifting is discussed below. The gender of the CHW is very important as women themselves are more comfortable around female health care providers. Furthermore, it may be the societal norm to seek care from females rather than from male health care providers. A 2009 analysis of Demographic and Health Surveys from 41 LMIC found that nearly one quarter of women listed not having a female health provider as a reason that they did not go to a health facility to give birth.<sup>18</sup>

The focus on the community level will also raise awareness and perhaps, counter the existing regional myths, beliefs and misinformation about pre-eclampsia. Most women who survive pre-eclampsia do not champion this issue due to the misconceptions that personal hygiene or sexual infidelities may have been the cause.<sup>14</sup> The lack of champions hinders advocacy for pre-eclampsia.

PRE-EMPT will also collaborate with the WHO to develop, distribute, and implement evidence-based and culturally appropriate knowledge translation tools. This will be critical in reducing the burden of life-ending, life-threatening, and life-altering maternal and perinatal complications of pre-eclampsia and eclampsia. The knowledge translation tools that will be developed will be suitable for use at the community, primary health clinic, and hospital levels to improve evidence based clinical decision-making. Ultimately, these can be used to inform policy making at the professional association, government, and national service health care levels (Table 1).

### The role of task shifting

Given the shortages of the health workforce and skill-mix imbalances, task shifting may be a promising strategy. Task shifting is defined as delegating tasks to existing or new personnel with either less training or narrowly tailored training.<sup>19</sup> The primary objective of task shifting is to increase productivity and efficiency by increasing the number of health care services provided at a given quality and cost, or alternatively, to provide the same level of health care services at a given quality at a lower cost. Another objective of task shifting is to reduce the time needed to scale up the health force, as the personnel performing the shifted tasks require less training.<sup>19</sup>

Tasks can be delegated to non-physician clinicians, medical assistants, nurses and community health care workers. CHW are lay members of communities who work within the local health care system and share ethnicity, language, socioeconomic status and life experiences with the community members they serve.<sup>19</sup> They are an integral part of the health care force in many LMIC where they are employed to provide culturally appropriate health education and information, informal counseling and guidance

**Table 1**  
Overview of challenges in LMIC.

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- Limited access to antenatal care [more pronounced in rural settings]
  - Delays in triage, transport and treatment
  - Lack of financially feasible and accurate point-of-care diagnostics
  - Inadequate means and/or routes of transportation
  - Barriers to treatment secondary to financial cost, lack of pharmaceutical support and barriers to registration and production
  - Shortage of health care workers
  - Inappropriate skill-mix
  - Uneven distribution of health care workers in urban vs. rural settings
  - Lack of policy or country specific standard of care for pre-eclampsia
  - Poor uptake of evidence-based guidelines
  - Lack of advocacy
-

on health behaviors. CHW also advocate for individual and community health needs and provide some direct services.<sup>19</sup> For example, in Pakistan, CHW have been trained to promote antenatal care including the use of iron and folate in pregnancy and to promote breastfeeding.<sup>20</sup>

The 2010 State of the World's Mothers report states that female health care workers have a critical role in saving the lives of women, newborns and young children.<sup>16</sup> It further states that relatively modest investments in female health workers can have a measurable impact on survival rates in isolated rural communities.<sup>16</sup> The use of CHW in Nepal has resulted in more women accessing prenatal care, more trained birth attendance and a decline in maternal and perinatal mortality.<sup>16</sup> In India, there is a team of 54,000 women community health volunteers who have been trained to dispense drugs, provide nutrition counseling, manage childhood illnesses, provide essential newborn care and identify danger signs that require prompt referral to a health care facility for proper treatment. This has resulted in reduction of the rural infant mortality rate from 85/1000 to 65/1000 in four years.<sup>16</sup>

Outside of pregnancy, there is high quality evidence demonstrating the potential for task shifting as an important policy option. For example, randomized controlled trials have shown that there were no significant difference in patient assessment, drug recommendation, WHO clinical stage assignment and tuberculosis status assessment in HIV/AIDS patients receiving antiretroviral therapy from CHW in Kenya and Uganda.<sup>21,22</sup>

However, a number of issues have also been raised with task shifting such as quality and safety concerns, professional and institutional resistance, and the need to sustain motivation and performance. One particular concern is that quality of care may decrease if CHW are given complex tasks. However, contextual factors like appropriate leadership, training and workplace infrastructure will be important in addressing this concern and determining the success of a skill-mix policy change.<sup>19</sup>

## **Prevention of pre-eclampsia**

High resource settings have the capability of identifying women at risk (adequate antenatal care and through biomarkers and uterine artery dopplers) and, therefore, applying prevention strategies. In LMIC, prevention strategies should be applied to every pregnant woman since predicting which women will develop the condition is not feasible with current resources. There are only two recommended therapies for the prevention of pre-eclampsia currently: aspirin and calcium.

### *Aspirin*

Aspirin has been studied extensively for the prevention of pre-eclampsia. The role of aspirin is discussed in detail in chapter 3. Aspirin is associated with a 10–19 % reduction in pre-eclampsia risk and a 10–16% decrease perinatal morbidity and mortality.<sup>23,24</sup> This risk reduction was seen in women who were in the 'moderate to high' risk category. Factors such as the woman's personal medical and obstetric history, family history, and ultrasound findings were used to determine risk. This is not feasible in an LMIC setting. Notably, both nulliparity and multiparity as well as young age were identified as risk factors. Based on this alone, a large number of women in LMIC would fall into the risk category. A reduction of 10–19 % in pre-eclampsia risk is significant in an LMIC setting because a large population of women will benefit from therapy especially given the safety profile of aspirin and the low cost of the drug.

### *Calcium*

In most LMIC, pregnant women and women of reproductive age are deficient in calcium.

A number of studies have shown that women in LMIC had mean daily intakes between 236–1084 mg.<sup>25</sup> Interestingly, the WHO/UNICEF multiple micronutrient supplement developed for pregnant and lactating women in crisis areas does not contain calcium.<sup>26</sup>

High quality studies have shown that calcium supplementation of at least 1 gram daily started around mid-pregnancy is associated with a modest reduction in pre-eclampsia and a more notable reduction in its severe manifestations among women with low dietary calcium intake (see chapter 3).<sup>27–29</sup> Calcium supplementation, interestingly, did not effect biochemical measures commonly elevated in pre-eclampsia such as serum urate, platelet count, and proteinuria.<sup>27–29</sup>

To reconcile the apparent contradiction that calcium supplementation reduces the incidence of pre-eclampsia without evidence of an effect on proteinuria and other markers for pre-eclampsia, one hypothesis that has been proposed is that calcium supplementation in the second half of pregnancy reduces blood pressure. This epiphenomenon of blood pressure reduction, therefore, decreases the diagnosis and some of the hypertension-related complications of pre-eclampsia. The effect on other organ systems, particularly the endothelium and platelets, might continue. While deficient dietary calcium before and during early pregnancy may place populations at risk for pre-eclampsia, there may be limited potential to reverse this effect by calcium supplementation later in pregnancy.

Currently, there is no report of RCTs of calcium supplementation started before pregnancy. To address this, PRE-EMPT will conduct a double blind placebo controlled trial in two countries where women in the intervention arm will receive calcium from enrolment before pregnancy until 20 weeks gestation. Pregnant women, with a past history of pre-eclampsia/eclampsia, will be supplemented with 500 mg/day of calcium to achieve a mean daily intake of about 1100 mg. Calcium will be provided for 40 weeks prior to conception and the first 20 weeks of pregnancy. The primary outcome will be pre-eclampsia. The secondary outcomes will be gestational hypertension, proteinuria, adverse maternal and perinatal outcomes, maternal ICU admission >24 h, Cesarean section, perinatal death, birth weight <2500 g, or Apgar score <7 at 5 m.

Previously, concern has been raised about the interaction between calcium and iron when taken at the same time. Many pregnant women in LMIC are anemic and therefore, may be taking iron supplements concurrently. 47% of pregnant women in Africa, 39% in Latin America, 80% in Southeast Asia, 65% in the eastern Mediterranean, and 40% in the West Pacific are believed to be anemic.<sup>30</sup> However, this concern has not been borne out in large calcium studies. The accessibility, affordability and acceptability of calcium tablets have also been questioned. There has been some effort made to incorporate calcium into cooking salt in order to fortify food.<sup>31</sup> However, in many LMIC, food is expensive and women tend to eat the least. As calcium tablets are often large and chalky, adherence may be low and alternatives such as “calcium sprinkles” have been explored.<sup>31</sup> However, alternative preparations may be expensive and therefore, a multi-pronged approach to getting calcium to the desired demographic may be most feasible.

## Detection of pre-eclampsia

Pre-eclampsia is classically defined by its most common features: hypertension and proteinuria. The new 2001 WHO antepartum care model calls for blood pressure check in the second antenatal visit in addition to testing for proteinuria but only in nulliparous women or in women with previous pre-eclampsia.<sup>32</sup> However, there are fundamental challenges inherent to this practice in low-resource settings. For example, significant training is needed to accurately measure blood pressure, along with robust and well-maintained equipment. Approximately 50% of women who do not receive antenatal care will not have this test done, and the additional 15 to 30% of women who attend antenatal care do not have their blood pressure taken.<sup>14</sup> Measuring proteinuria can also be challenging in low-resource settings as the cost of urine dipsticks can be prohibitive, and at high-volume sites, boiling urine can be extremely difficult. Table 2 shows the unmet need for blood pressure and proteinuria check in select LMIC.

These challenges result in delays in triage which in turn relates to the presentation of women late in the clinical course of their disease and the failure to have the nature and potential severity of their condition recognized. Getting a triage mechanism into the hands of women and their immediate caregivers is a priority. Immediate care is often given by CHW and therefore, a cost effective, easy to use and accurate triage level that can be used in the community is necessary. Appropriate and timely triage will allow for timely transport. Once women enter the formal health care system, a triage tool to identify those most at risk of adverse outcomes so that they can receive appropriate interventions in the timeliest manner possible is needed.

PRE-EMPT will address this by developing and validating the miniPIERS (Pre-eclampsia Integrated Estimate of RiSk) and genPIERS models (Fig. 1). miniPIERS is solely symptom- and sign-based, and configured for use at the community level in resource-restrained settings. Since CHW will be administering miniPIERS, they will also be trained to take blood pressure and measure proteinuria. Therefore, they will be gaining skills that are critical in the care of women with pre-eclampsia.

**Table 2**Unmet need for blood pressure and proteinuria check in select LMIC.<sup>33</sup>

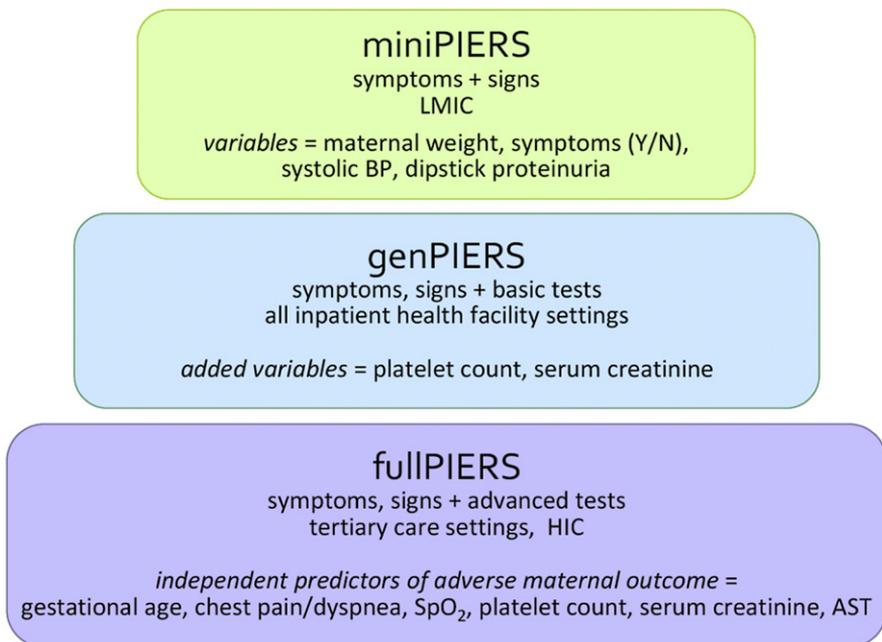
Country	%Unmet need for BP check	%Unmet need for proteinuria check
Bangladesh	53.1%	70.5%
Bolivia	24.5%	50.9%
DRC	38.8%	57.8%
India	52.5%	56.8%
Indonesia	13.9%	63.0%
Kenya	22.8%	38.9%
Malawi	28.6%	81.3%
Mozambique	48.7%	73.9%
Nepal	43.8%	77.7%
Zimbabwe	14.0%	39.8%

genPIERS will include, in addition to symptoms and signs, few laboratory tests (e.g. platelet count and serum creatinine) and will be used at the facility level. The miniPIERS and genPIERS models should aid in case identification, diagnosis, and risk stratification, thereby, accelerating triage and transport from the community to facilities (miniPIERS) and to institute surveillance at the facility level (genPIERS). Effective care will avert the adverse maternal and perinatal consequences of pre-eclampsia. In time, this process of risk stratification will guide use of evidence-based treatment.

### Treatment of pre-eclampsia

#### Antihypertensives

Once a woman is diagnosed with hypertension, treatment with antihypertensives may be warranted. It is unclear how to best manage women with non-severe non-proteinuric pre-existing hypertension or gestational hypertension remote from term. Based on current evidence, arguments can be made both for

**Fig. 1.** The PIERS model.

and against allowing for tighter and 'less tight' (i.e. allowing higher blood pressure levels). There is insufficient evidence on which to base clinical decisions because of reporting bias and between-trial heterogeneity in outcome. The **Control of Hypertension In Pregnancy Study [CHIPS]** an open label, multi-centre international trial is currently underway to address this clinical question.<sup>34</sup> Although this trial is taking place in high resource countries, the results will be translatable to LMIC.

In contrast to non-severe hypertension, severe hypertension (defined as SBP 160 and/or DBP 110) must be treated. The Confidential Inquiry into Maternal and Child Health (CEMACH) highlighted the importance of treating severe hypertension and demonstrated that failure of antihypertensive therapy was the most common source of sub standard care even in high resource settings.<sup>35</sup> Inadequate treatment resulted in intracranial hemorrhage in several cases. This is a particular concern in the community many women where may remain untreated or treatment may be delayed due to challenges with triage and transport. Many women may die or be irreversibly affected by pre-eclampsia prior to arriving at the inpatient facility.

CLIP (**Community Level Intervention for Pre-eclampsia**), one of PRE-EMPT's initiatives, will focus on improving community case identification (using miniPIERS as a diagnostic and triage aid) and implementing rapid treatment using community and facility level interventions to control severe hypertension and to prevent and treat the eclamptic seizures. Trained and supported CHW will institute therapy prior to referral to an inpatient facility for definitive care. By using a pragmatic approach of implementing a "package of care" CLIP will address the main barriers to effective and life-saving care: delays in triage, transport, and treatment.

Since CHW are the primary contact, the need for a treatment regimen that is simple and easy to administer must be emphasized. The antihypertensive agent should ideally be a single dose oral agent. However, there is little literature on the use of oral agents in severe hypertension in pregnancy as much of the data comes from use of IV antihypertensives (see chapter 7).

Most LMIC have adopted individual essential medicines list and there is variability between countries for choice of antihypertensives. The WHO defines essential medicines are those that satisfy the priority health care needs of the population. They are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness.<sup>36</sup> It is worthwhile noting that the WHO model list does not contain some of the more commonly used oral antihypertensives in pregnancy such as nifedipine and labetalol. Therefore, there is a potential for limited options in LMIC. Aside from availability, the choice of antihypertensive therapy will also depend on cost, regional familiarity with its use and effectiveness. The CLIP 'pre-eclampsia boxes' will therefore include a suitable oral agent that meets these criteria. The package will also include magnesium sulfate discussed below.

## Prevention of eclampsia

### *Magnesium sulfate*

Magnesium sulfate is a low cost, effective treatment for preventing and treating eclamptic seizures. The landmark trial, Magpie, conducted in 33 international centers showed that for women with pre-eclampsia (defined in the trial by BP 140/90 and 1 + proteinuria), magnesium sulfate reduced the risk of eclampsia by half (NNT = 100, 95% confidence interval 50–100).<sup>37</sup> Maternal mortality was also lower in women receiving magnesium sulfate (relative risk 0.55, 95% CI 0.26–1.14). Following the trial, magnesium sulfate was placed on the WHO list of essential medicines. Magnesium sulfate has also been found to be more effective than diazepam, phenytoin or lytic cocktail in treating seizures.<sup>38–41</sup> This is discussed in more detail in chapter 7.

Despite its clear effectiveness, low cost and despite being on the essential medicines for most countries, magnesium sulfate continues to be underutilized in many LMIC. 45 of the 52 essentials medicines list that we accessed online contained magnesium sulfate. There still remain numerous barriers on multiple levels to its use in LMIC. In recent years, organizations like MCHIP (**Maternal and Child Health Integrated Program**) and Engenderhealth have held workshops for health care providers from across the world in order to identify the barriers and to initiate discussion about task forces to address the underutilization of magnesium sulfate. At the 2007 Engenderhealth "Workshop on magnesium sulfate for the management of pre-eclampsia and eclampsia", several primary challenges were identified: limited provider knowledge and training, little drug availability, lack of national guidelines and protocols and socio-cultural factors.<sup>2</sup> Other barriers include hesitation to administer the

drug (as many clinicians have historically used other therapeutics), a shortage of trained health care professionals to monitor its use, poor incentives for local production and complex mechanisms of approval, acquisition, and distribution of the drug further hinder utilization.

Strategies identified during the workshop to address these barriers included<sup>2</sup>:

- disseminating the strong evidence base for the effectiveness of magnesium sulfate,
- engaging government to take on increased leadership for scale up,
- increasing training in magnesium sulfate as a core component of reproductive health trainings,
- ensuring a committed group of obstetricians, health ministers, etc., to serve as champions for magnesium sulfate use.

## Summary

Pre-eclampsia remains a significant cause of maternal and perinatal morbidity and mortality in LMIC, although its exact prevalence remains unknown. While the principles of care are the same as in high resource settings, there are a number of challenges that must be considered in an LMIC setting. The main challenges include delays in triage, transport and treatment as well as the shortage of trained health care professionals. In order to address the global burden of pre-eclampsia and its maternal and perinatal consequences, task shifting and community level case ascertainment and treatment are key strategies. PRE-EMPT is a bold initiative that will use these principles to address the main barriers to effective and life-saving care for women with pre-eclampsia in LMIC.

### Practice points

- The Millennium Development Goal [MDG] 5 aims to improve maternal health by reducing maternal mortality ratio by three quarters from 1990 to 2015 and by achieving universal access to reproductive health.
- Pre-eclampsia and eclampsia are leading causes of maternal and perinatal morbidity and mortality in LMIC. The exact prevalence is unknown and there is significant variation in the prevalence of pre-eclampsia and eclampsia between countries.
- Most of the maternal deaths in LMIC occur at the community level.
- The principles of care of women with pre-eclampsia in LMIC are the same as in high resource countries but there are special considerations and challenges unique to LMIC.
- The three primary delays that lead to the increased incidence of maternal mortality due to pre-eclampsia are delays in triage, transport and treatment.
- Other major challenges faced by LMIC include limited access to antenatal care, shortage of health care workers and poor uptake of evidence-based guidelines.
- Task shifting is a potential strategy to address the health care worker crisis and to increase access to timely care. Community health care workers particularly female /lady health care workers play a critical role in task shifting.
- Prevention strategies should be applied to all pregnant women in LMIC as predicting which women will develop pre-eclampsia is not feasible in this setting. Aspirin and calcium remain the only two recommended therapies.
- A triage mechanism that is financially feasible, accurate and that can be administered easily at the community level is lacking.
- Magnesium sulfate is the drug of choice for the prevention and treatment of eclampsia but it is underutilized.
- PRE-EMPT (PRE-eclampsia-Eclampsia Monitoring, Prevention and Treatment) consists of a number interrelated projects that aims to reduce the maternal and perinatal consequences of pre-eclampsia in LMIC. The primary goal is to improve community level case ascertainment and interventions The secondary goal is to develop multifaceted international research collaboration and LMIC-oriented pre-eclampsia knowledge translation activities.

## Research agenda

### WHO: World Health Organization

The ultimate objective of the Improving Maternal and Perinatal Health Team (MPH) is to effectively contribute to the UN Global Strategy for Women's and Children's Health by implementing five major areas of action:

1. Develop new lines of research that will benefit health systems globally
2. Coordinate research efforts from the laboratory to the health system
3. Make research accessible to researchers from low income countries and institutions
4. Stimulate alternative thinking
5. Extend beyond public health to reach politics, society and culture, and the private sector

#### Initiatives

- Angiogenic factors for the screening of pre-eclampsia
- Treatment of mild to moderate hypertension trial
- Pre-eclampsia Integrated Estimate of Risk (PIERS)
- pre-conceptional calcium supplementation trial
- Management of Eclampsia

### MCHIP: Maternal and Child Health Integrated Program

The overall objective is to develop, introduce, and scale up an evidence-based, comprehensive package of interventions to prevent and manage PE/E and to generate evidence on technical and operational issues to facilitate program implementation. The mechanisms to achieve this include technical/global leadership and introduction and expansion of evidence-based interventions at the country level.

#### Initiatives

- To assist USAID and other global partners to find effective approaches to prevent and treat PE/E at global and country levels
- Development of Quality of Care (QOC) Assessment Tool
- Conducted pre-eclampsia/eclampsia QOC Assessments in priority countries
- Intervention research is underway on the use of the anticonvulsant drug magnesium sulfate at the community level by skilled birth attendants

### PRE-EMPT: PRE-Eclampsia- Eclampsia Monitoring, Prevention and Treatment

#### Summary of Initiatives and Projects

1. Long-term calcium supplementation in women at high risk of pre-eclampsia: A randomized, placebo controlled trial
2. Development and validation of the **PIERS** (Pre-eclampsia Integrated Estimate of **RiSk**)
3. The **CLIP** (Community Level Intervention of Pre-eclampsia) feasibility study & CLIP pilot cluster randomized controlled trial
4. Pre-eclampsia CoLaboratory: Integrate data and biological materials from prior or ongoing studies of pre-eclampsia including establishing data and biomarker acquisition tools common to the entire PRE-EMPT project
5. Develop and distribute WHO evidence-based knowledge translation tools for pre-eclampsia, including clinical practice guidance and implementation tools

### CLIP objectives

- Pre-eclampsia/eclampsia prevalence rates, and rates of associated maternal and perinatal morbidity and mortality
- Usual community resources/practices for antenatal pre-eclampsia assessment, triage, and management
- Referral and transport infrastructure
- Perinatal health care system and antenatal care model organization
- Professional scope of practice regulations
- Potential for task shifting by CHW in community settings
- Provider knowledge/competency related to pre-eclampsia
- Resource capacity for provider training
- Clinic and referral facility capacity
- Community demographics
- Data collection methods and informational systems for population surveillance
- Cultural and/or community beliefs/practices/influences and attitudes
- Informational resources

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