

RESULTS FROM SYSTEMATIC LITERATURE REVIEW ON PE/E IN BANGLADESH

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BACKGROUND AND INTRODUCTION

Hypertensive disorders of pregnancy are major causes of severe morbidity, long-term disability, and deaths of mothers and their babies. About 10 percent of women experience increased blood pressure during pregnancy and 8 percent of pregnancies develop pre-eclampsia. Among pre-eclampsia patients, about 10 percent develop eclampsia. Globally, about 10 to 20 percent maternal deaths are associated with eclampsia.

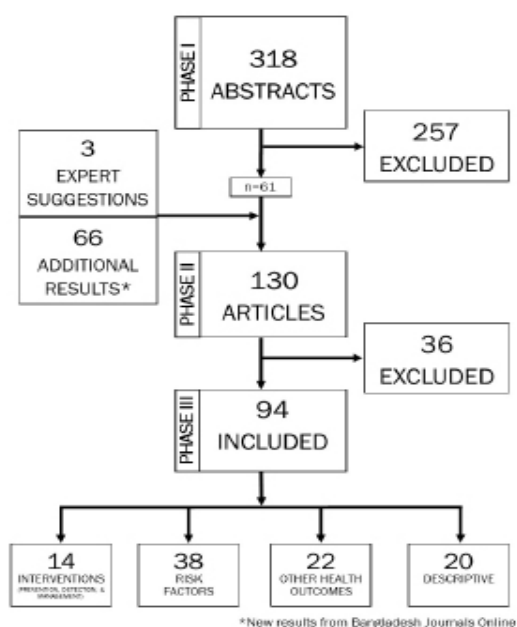
By 2015, at the conclusion of the Millenium Development Goals, Bangladesh had achieved a reduction in maternal death from 550 per 100,000 live births in 1990, to 170 maternal deaths per 100,000 live births in 2015. Despite this progress, there are still between 5,000 and 6,000 maternal deaths every year in Bangladesh, where 20 percent are the result of pre-eclampsia and eclampsia (PE/E).

This systematic review of peer-reviewed literature published between January 2000 and July 2016 identified interventions adopted to manage PE/E throughout Bangladesh. Specifically, it looked at issues around quality of care, gaps in the evidence, and barriers to accessing PE/E services.

APPROACH

The research team developed two sets of key search terms linking various aspects of the diagnosis, treatment, and prevention of PE/E and other hypertensive disorders of pregnancy. The team limited searches to peer-reviewed articles published between January 2000 and July 2016, and ran the articles in PubMed and ScienceDirect. Two independent reviewers excluded any duplicate or non-English citations or citations without relevant titles prior to Phase I. The reviewers then imported the titles and abstracts for the articles into an Excel spreadsheet for independent review. They then read and evaluated the results in three phases: Abstract and title review, full text review, and categorization of papers (Figure 1).

FIGURE 1: Flow chart of review process



PE/E in Brief

- Pre-eclampsia is a condition in pregnant women marked by an increase in blood pressure and protein in urine after 20 weeks gestation.
- Providing high quality antenatal care improves the prevention and early detection of pre-eclampsia and can prevent its progression to eclampsia.
- Eclampsia is a life-threatening condition characterized by convulsions in women with PE.
- Women in developing countries are 300 times more likely to die from eclampsia than women in developed countries.
- Prescribing low-dose aspirin and calcium to at-risk women can prevent pre-eclampsia and eclampsia.
- Pre-eclampsia and eclampsia can be managed by administering anti-hypertensive drugs and magnesium sulphate (MgSO₄).
- MgSO₄ is the safest and most effective treatment for severe PE/E, and is one of 13 UN Life-Saving Commodities for Women and Children.
- PE/E and other hypertensive disorders in pregnancy increase the risk of pre-term births, which can lead to low birth weight, anemia, and stunting.
- Improved prevention, increased detection, and effective treatment of PE/E can prevent unnecessary maternal and newborn deaths.

The Ending Eclampsia project seeks to expand access to proven, underutilized interventions and commodities for the prevention, early detection, and treatment of pre-eclampsia and eclampsia and strengthen global partnerships.

THEMES

From the literature, the reviewers identified several themes, ranging from treatment and prevention strategies, risk factors, and health outcomes for women and babies.

Strategies for prevention and treatment

The papers that examined hypotheses for improving PE/E prevention, detection, and management of examined strategies for prevention, approaches to improve detection and new mechanisms for PE/E management, and delivery mode. Prevention strategies looked at dietary calcium supplementation, plus conjugated linoleic acid (CLA), and methods of calcium supplementation, and concluded that calcium+CLA impacted the reduction of “vascular endothelial dysfunction”vascular endothelial dysfunction in pregnant women at high risk of hypertensive disorders of pregnancy.

To improve detection of pre-eclampsia, one intervention used village theater to increase community knowledge on eclampsia and another improved detection of pre-eclampsia by testing the accuracy of a 12-hour urine sample compared to 24-hour sample. Also according to the literature, community health workers (CHWs) can provide maternity care with referral services for obstetric emergencies, which increase care seeking behaviors for life-threatening conditions during pregnancy.

New mechanisms for PE/E management included a new protocol for administering antihypertensive drugs to pregnant women. Reduced time between onset of symptoms and administration of the loading dose of $MgSO_4$ at a patient’s home, rather than waiting until she arrives in a facility; and another reduced the overall dosage of $MgSO_4$ and prolonging pregnancy by conservatively managing PE/E cases. None of the studies identified in this review used the global standard of care, the Pritchard Regimen, but instead used a lower 10g dose and one used 8g IV dose. These studies indicate that there is likely a lower effective dose than the globally-accepted 14g dose.

For women with PE/E, delivering via cesarean section appeared safer than vaginal delivery, and spinal anesthesia is as safe as general anesthesia for cesarean deliveries.

Demonstrated and potential risk factors

Many studies identified risk factors associated with PE/E. In the 38 reviewed journal articles, two primary themes emerged: Micronutrient deficiencies among pregnant women and a woman’s past medical history with autoimmune disorders like diabetes, and hypertension, or obesity. Other articles discussed elevated enzyme or hormone levels, birth spacing, health-seeking behaviors, maternal age, and poor-quality antenatal care. Levels of serum homocysteine, serum beta-human chorionic gonadotropin, plasma neuropeptide Y concentration levels, serum total bilirubin and alanine aminotransferase, and serum C reactive protein were found to be higher in

1. *Vascular endothelial dysfunction is a key event in cardiovascular and renal disease. It affects the lining of the blood vessels.*

women with PE/E and selenium levels and platelet counts were lower, compared to normal pregnancies.

The role of micronutrient deficiencies in the development of PE/E was a major focus in the literature. Specifically, researchers examined the connection between PE/E and calcium in pregnant women and found that calcium intake was lower among women with PE/E than normotensive pregnant women. Vitamin D insufficiency showed a 3-5 fold increase in risk for developing PE/E. From the literature, zinc and magnesium deficiencies also play a role in the pathogenesis of PE/E. Another micronutrient examined was serum magnesium, which was low in mild pre-eclampsia, and even lower in severe PE. One study found that pre-eclamptic women had lower levels of zinc, copper, manganese, ferritin, and iron, while others found high levels of iron and ferritin in mild and severe PE cases.

Researchers also looked at pregnant women’s history of diabetes, high BMI, cholesterol concentration, abnormal thyroid function, and hypertension to further understand what puts a woman at risk of developing the disorder. and potentially, as may be the case for diabetes, if it increases preterm birth, and low birth weight.

Other maternal health outcomes

Health consequences that follow, or are associated with, PE/E can negatively affect maternal, fetal, newborn, or child health outcomes. Maternal health outcomes associated with PE/E often include increased rates of cesarean section, reduced organ function, HELLP syndrome, and ocular changes. Additional results from the literature show that reduced placental size and weight, pulmonary edema, postpartum hemorrhage, cardiovascular accident, and obstetric shock also appeared as other health outcomes associated with PE/E.

For newborns and children of women with PE/E, health outcomes that emerged from the literature were stillbirth, perinatal and neonatal mortality, low birth weight, preterm birth, intrauterine growth retardation (IUGR), respiratory distress, and potentially include cerebral palsy.

LOOKING FORWARD

Despite the wealth of information in the literature on PE/E in Bangladesh, there are still gaps that require further research. These gaps include the need for clearer clinical guidelines and definitions, dosage variations, community awareness and the most appropriate, effective mechanisms for reducing micronutrient deficiencies.

Definitions

Generally speaking, “toxemia” is an outdated term not frequently used to now classify hypertensive disorders of pregnancy. However, several articles use the term, with only two providing definitions. Definitions for “pre-eclampsia” appeared in many articles, but each set its own standard clinical requirement for diagnosis. The majority include high blood pressure, but with variations of clinical definitions. In low service utilization settings, providers may not encounter cases of PE/E regularly and

may not easily recall the nuanced distinctions between the terms along the spectrum of hypertensive disorders of pregnancy. In order to enable these providers to diagnose and manage PE/E promptly, accurately, and thoroughly, clearer diagnosis guidelines must align with streamlined and precise definitions and management protocols.

Lowest effective dose of MgSO₄

Globally, there are two predominant regimens for administering MgSO₄ to women with severe PE/E: Pritchard and Zuspan. The Pritchard regimen is considered the 'gold standard' treatment method in low resource settings, while the Zuspan regimen requires more medical skills and equipment. While there is evidence to support the effectiveness of both regimens, there is no evidence on whether either regimen provides the lowest effective dosage for controlling convulsions.

The literature forces us to think about the evidence behind the 'standard' regimens requiring massive amounts of MgSO₄. Anecdotally, the small size of Bangladeshi women is cited as the reason why lower doses are adequate, but this requires more research. What characteristics would require a woman to be given a larger dose?

Community awareness and knowledge

Based on the literature, community awareness of danger signs and symptoms is low. Increasing awareness of issues related to pregnancy, specifically PE/E, can lead to improved health-seeking behavior and therefore better health outcomes. As women in these settings are often not the decision makers in a household, it is critical that these health messages target other members of the community, such as husbands and mothers-in-law with the hope that they will recognize dangerous symptoms and encourage pregnant women to access health services, attend early antenatal care visits that include blood pressure measurements.

Micronutrient deficiencies, clinical biomarkers, and trace elements

The most common risk factors discussed in the literature were micronutrient deficiencies, primarily calcium and magnesium, but also iron, zinc, ferritin, and copper. The literature shows that micronutrient deficiencies are a serious matter that needs attention, but it does not discuss the cutoff levels for deficiencies or the most effective, appropriate mechanisms for reducing deficiencies, i.e. dietary supplements and in which form?

Limitations

The published research revealed some gaps for PE/E prevention, detection, and treatment in Bangladesh. The first is the limited understanding of providers' perceptions and working environment. There is a lack of input from the providers at any tier of the health system who are working to reduce maternal and neonatal deaths from PE/E. Most of the research focused on the experiences of PE/E patients and their families, but it did not look at the ways in which facility providers are hindered or prevented in their work to manage hypertensive disorders of pregnancy. Their voice is a powerful one that needs to be heard.

Another limitation was that 76 out of 94 articles focuses on urban settings, with few speaking to the experience of rural women, their families, or providers at primary health care facilities. As urban women are most likely closer to health services, the reviewers felt due to the lack of research focused on rural women, that their unique needs and opportunities for accessing quality services are unclear.

Recommendations

- Determine variables that impact efficacy of lower doses and generate a clear, evidence-based dosing regimen that uses the lowest, effective dose of MgSO₄;
- Simplify terminology used to discuss hypertensive disorders of pregnancy, and establish clear clinical guidelines to define each term for improved diagnosis;
- Work within communities to improve early antenatal care and increase awareness of danger signs in pregnancy;
- Support task shifting initiatives that allow primary health center providers to administer the MgSO₄ loading dose;
- Monitor women for up to one year postpartum to understand the impact of PE/E and extent of follow up women receive;
- Research the most effective, lowest-cost, and least invasive means of administering nutritional supplements that reduce micronutrient deficiencies, and define protocols for analysis during antenatal care check-ups; and
- Learn more about the unique needs of rural woman and their families.

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To read the full report, visit <http://www.endingeclampsia.org/resources/a-systematic-review-of-the-treatment-and-management-of-pre-eclampsia-and-eclampsia-in-bangladesh/>

To learn more about global progress on pre-eclampsia and eclampsia, visit www.endingeclampsia.org.