OPTIMIZING CARE AND PATIENT EXPERIENCE OF PREECLAMPSIA IN LOW- AND MIDDLE-INCOME COUNTRIES - THE CASE OF GHANA

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Optimalisering van zorg en patiëntervaringen met zwangerschapsvergiftiging in lage- en midden-inkomenslanden - het geval Ghana

(met een samenvatting in het Nederlands)

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Contents

1

GENERAL INTRODUCTION

Authorship statement

The concept and overall set-up of the general introduction were mine; I conducted the literature search and wrote the general introduction. During the whole process I asked for and implemented input and feedback from my supervisory team.

The burden of hypertensive disorders of pregnancy

Hypertensive disorders in pregnancy (HDPs) continue to contribute significantly to the causes of maternal deaths worldwide with an estimated 11% increase in their global incidence between 1990 and 2019.[1] It is estimated that HDPs account for 14% of maternal deaths.[2]

Hypertension is defined as systolic blood pressure (BP)≥ 140 and/or diastolic BP≥ 90 mm Hg, measured on two occasions at least 4 hours apart.[3–5] Hypertensive disorders in pregnancy have been classified by the International Society for the Study of Hypertension in Pregnancy (ISSHP) to include chronic hypertension, gestational hypertension, transient hypertension, masked hypertension, white coat hypertension, preeclampsia, and eclampsia.[3] The definition of preeclampsia encompasses new-onset hypertension after 20 weeks gestation with the coexistence of either proteinuria or signs of maternal organ damage (renal or liver involvement, neurological or hematological complications, or uteroplacental dysfunction) or both.[3,4] There is some consensus that preeclampsia should be subclassified as preeclampsia with or without severe features rather than mild and severe preeclampsia to ensure institution of appropriate and timely interventions.[3-6] Eclampsia has been redefined as seizures in a woman during pregnancy or up to 14 days postpartum, without any other attributable cause, with at least one of the following signs: Hypertension, Proteinuria, Thrombocytopenia (platelet count of less than 100x109 /L) or raised plasma ALT or AST (twofold the upper limit of normal).[7]

Despite a 30% reduction in deaths due to HDPs over the period globally, low- and middle-income countries (LMICs) continue to bear the brunt of HDPs.[1] This poses a threat to the attainment of Sustainable Development Goal (SDG) 3 as the world counts down to 2030.[8,9] Hypertensive disorders complicate about 10% of pregnancies worldwide[10,11] and are gradually overtaking hemorrhage as the leading cause of maternal mortality in some LMICs. For instance, the age-standardized incidence rates of HDPs were found to be higher in many LMICs.[1] The incidence of preeclampsia and eclampsia and the subsequent maternal and perinatal adverse outcomes, is disproportionately high in poor resource settings (LMICs) compared to high resource countries.[12,13] The global incidence of preeclampsia is estimated at 4.6% but in Africa, it is estimated at 5.6%.[5] In Ghana national data on the incidence of preeclampsia and eclampsia are lacking. A hospital based study estimated the incidence HDPs to be 7.6% and eclampsia and its sequel was shown to be the leading immediate cause of death within HDPs related deaths accounting for 23.8%.[14]

Based on the current understanding of the pathophysiology of preeclampsia and its epidemiologic associations, attempts have been made to predict women who are likely to develop the condition with the aim of prevention.[15,16] In the clinical setting, however, these factors have been shown to predict only 30% of women who develop preeclampsia.[17] Prediction models for predicting the outcome of preeclampsia based on patient clinical

characteristics and laboratory parameters have been developed and some validated externally.[16,18–20] Data on these risk indicators must necessarily originate from LMICs where the incidence of eclampsia is still unacceptably high, but such data is scarce to find. It is therefore important that studies to identify antenatal characteristics of patient with preeclampsia that predict the development of eclampsia be conducted in LMICs to generate data that will form the basis for risk stratification and efficient use of limited resources to optimize the care of patients with HDPs.

Some biomarkers have also been studied and shown to have moderate prediction potential for preeclampsia. These include maternal placental growth factor (PlGF) whose serum concentrations are known to decrease 5 weeks before diagnosis of preeclampsia whereas those of soluble fms-like tyrosine kinase 1 levels are increased[22]. Very recently measurement of cell free RNA has been introduced as a promising biomarker[23].

Pharmacological agents have been proposed as means of preventing preeclampsia. Aspirin appears to be the most promising with its meta-analysis suggesting a moderate preventive effect (RR 0.90, 95% CI 0.84–0.97)[24]. This is amongst other preventive interventions, such as calcium, vitamin D and life style interventions.[25]

Within the spectrum of HDPs, preeclampsia and eclampsia are associated with the most significant adverse maternal, fetal, and neonatal outcomes.[26–28] This thesis therefore focuses on addressing the knowledge gaps in preeclampsia with severe features, such as eclampsia in resource limited settings to improve pregnancy outcomes.

Eclampsia

Preeclampsia may not be entirely preventable, however, quality antenatal care services, prompt diagnosis and its effective management have nearly prevented the development of all cases of eclampsia in most high resource settings.[29] The global incidence of eclampsia is estimated as 0.28%, but at the region level, the incidence is between 0 and 0.1% in Europe [5,10,30], and about 1.5% across the African continent.[31,32] Wide national variations exist in the incidence of eclampsia. Whiles in Brazil it is estimated as 0.6%, it is up to 1.1% in Nigeria.[33,,28]

The wide variations in the incidence of preeclampsia and eclampsia across the globe may be explained by the differences in registration methods, the nature of studies used in the estimation, in the quality of antenatal care and access to healthcare services. In LMICs, lack of access to quality antenatal services has been shown to be a major risk for the development of eclampsia.[34,35] Lack of availability of essential preventive medicines in LMICs may also play a role. The availability and therapeutic use of magnesium sulphate

has also played a significant role in preventing the progression of preeclampsia to eclampsia. The use of magnesium sulphate has been shown to reduce the incidence of eclampsia by more than 50%.[36] In addition, some studies suggest that for women with preeclampsia with severe disease who do not receive anti-seizure prophylaxis, the prevalence of eclampsia may be as high as 2 to 3 % and in women with non-severe features of preeclampsia the incidence is up to 0.6 %.[37]

Management outcomes of pre-eclampsia with severe features and eclampsia in low resource settings

Associated with the disproportionally high burden of HDPs in LMICs is an even higher burden of undesirable outcomes of these pregnancies such as maternal and fetal/neonatal morbidity and mortality, and 99% of adverse outcomes of HDPs occur in LMICs. Whereas globally HDPs account for 14% of maternal deaths, in sub-Saharan Africa it accounts for 22.1% maternal deaths.[38,39] Preeclampsia and eclampsia also predispose mothers to emergency caesarean section[27], which further increases the risk of maternal morbidity and mortality in the near and far future. In addition to the adverse maternal morbidity and mortality attributable to preeclampsia and eclampsia, numerous adverse fetal outcomes such as preterm delivery, small gestational age, intrauterine growth restriction, stillbirths, and neonatal death have been reported.[26,27] The leading primary obstetric cause of perinatal mortality is preeclampsia and eclampsia and it accounts for 25% of perinatal deaths.[40] There is paucity of data characterizing these adverse neonatal events of preeclampsia and eclampsia in the West African subregion with most reports emanating from high income countries. Data on neonatal outcomes of pregnancies complicated with preeclampsia and eclampsia in this setting could facilitate the development of appropriate clinical protocols that is contextualized to the resource availability in LMICs to improve fetal survival.

Eclampsia is a serious complication of HPDs and in 75% of patients with eclampsia, prior diagnosis of HDPs has been documented.[41] Identifying the patient factors that increase the risk of progression from preeclampsia to eclampsia is a critical step in the prevention of eclampsia to improve pregnancy outcomes.

Magnesium sulfate regimens for seizure prophylaxis in pre-eclampsia with severe features and eclampsia

Generally, good clinical efficacy has been reported with the use of $MgSO_4$ for seizure prophylaxis in preeclampsia despite wide disparities in the dosing regimens and routes of administration.[36,42–44] The international multi-centre collaborative (Magpie trial involving 10,141 women, 175 hospitals, 33 countries including Ghana, demonstrated conclusively that compared to placebo, magnesium sulfate ($MgSO_4$) is clinically efficacious in preventing

eclampsia.[36] This trial demonstrated a 58% lower risk of eclampsia compared to placebo, although, the composite side effect prevalence was higher, 24% in treatment group compared to placebo of 5%[36]. The successful implementation of the regimen used in the trial in some LMICs has been hampered by supply challenges and the intolerable side effects profile. Other reported barriers have been unavailability of magnesium sulfate or pain at injection sites.[36]

$MgSO_4$ also has severe side effects such respiratory arrest and cardiac arrest and theses are dose dependent.[45] This necessitates skilled staff for its administration at higher doses. This has led to a search for the optimal duration magnesium sulfate with several studies being conducted to evaluate the clinical effectiveness of varying durations of treatment in women with preeclampsia and eclampsia. In one study by Ascarelli and co-workers using clinical parameters to determine the duration of therapy in women with mild and severe preeclampsia, it was observed that in women with mild preeclampsia, the mean duration of treatment was 9.5 ± 4.2 hours without the need to re-initiate therapy.[46] Similarly, for those with severe preeclampsia, chronic hypertension with superimposed preeclampsia and HELLP syndrome, the mean duration of treatments were 16 ± 5.9 hours, 16 ± 5.8 hours, and 20 ± 6.7 hours respectively.[46] In another randomized trial of magnesium sulfate in women with severe preeclampsia using diuresis as a clinical parameter to determine the duration of postpartum therapy, it was observed that where diuresis was used to terminate treatment, the mean duration of treatment was 8.45 ± 8hrs compared to 24.03± 2.63hrs in the standard treatment group.[47] A study from Egypt compared the loading dose only versus 12-hour versus 24-hour treatment doses in preeclampsia with severe features. Though this study was under powered to detect eclampsia as a primary outcome, it demonstrated some comparable clinical efficacy in all three arms with the side effect of flushing occurred in 5%; 15% and 30% in the loading dose, 12-hour and 24-hour treatment dose groups, respectively.[48] This seemed to agree with the 25% composite side effect prevalence in the treatment group compared to placebo from the Magpie trial.[36] Ekele and colleagues demonstrated in Nigeria that recurrence of a fit in women with eclampsia treated with only loading dose magnesium sulfate as per the standard Pritchard regiment was 4%[44], which is very high compared to the less than 1% rate reported for women with eclampsia who receive Magnesium sulfate.[37]

Two main regimens for the administration of magnesium sulfate have been accepted internationally because of proven clinical efficacy and their use in very large trials.[36,49] They are the predominantly intramuscular Pritchard regimen in which a loading dose of 4-g IV and 10-g IM, is administered followed by 5g IM maintenance dose every 4 hours and a purely intravenous Zuspan regimen in which a loading dose of 4-g is given followed by a maintenance dose of 1 g/hour continuous infusion.[36,49] In most low resource settings, the limited access to infusion pumps have restricted most centres to the use of the predominantly intramuscular Pritchard regimen compared to the mainly intravenous Zuspan or its modification, the Sibai regimen.[43,44,50]

This thesis research was conducted in a LMIC where the predominantly intramuscular Pritchard regimen is used and sought to define a new protocol with clinical efficacy, minimal side effects, more acceptable to patients and will ultimately improve care outcomes in HDPs. A clinical audit in a major referral hospital in Ghana confirmed poor adherence of only 45% to the maintenance component of the Pritchard regimen in clinical protocols which required clinicians to continue maintenance dose till 24 hours postpartum.[51]

Compliance with the longer duration of intramuscular regimen such as the Pritchard is challenging due to the discomfort and pain associated with the repeated injections or side effects. There are economic implications of a longer duration regimens on LMICs. Results from the Magpie trial estimated the additional hospital care cost per woman receiving magnesium sulfate in low-income countries as $11.[36] This additional cost could be nearly halved if the 12-hour duration of therapy is found to be optimal and efficacious.

Though the benefits of a shorter duration regimens in resource limited countries are immediately evident and include reduced cost to the health system and patients, shorter period of hospitalization, less side effects and reduced discomfort of repeated injections, sufficient data on the efficacy is required to provide the scientific evidence needed for adoption into practice guidelines.

This thesis therefore set out to design a new treatment protocol and conduct a randomized clinical trial (RCT) to compare clinical response between the novel 12-hr duration of treatment regimen with the 24-hr Modified Pritchard regimen. Ultimately it is aimed to introduce into clinical practice a regimen which is acceptable to patients and caregivers and demonstrates clinical efficacy with fewer side effects.

Positive experience of preeclampsia pregnancies: the patient perspective and knowledge

Studies across some LMICs including Ghana assessing knowledge of preeclampsia among pregnant women and patients reveal inadequate knowledge of HDPs.[12,52,53] This is due in part to inadequate counselling by healthcare providers who are sometimes overwhelmed by the high number of patients and the low education status of some patients in LMICs.[12,53,54] The World Health Organization (WHO) recommends strong patient involvement in decision making to promote a positive pregnancy experience.[25,55] Shared decision making thrives on patient having sufficient knowledge of their condition. The lack of appreciation of the clinical significance of preeclampsia and eclampsia by the patient may explain the poor health seeking behavior which could lead to underdiagnosis and delayed presentation. There are concerns that due to the reported increased burden of preeclampsia and eclampsia the consequent adverse pregnancy outcomes in low

resource settings may be higher than the actual estimates because of underreporting.[35] It is estimated that a significant proportions of the population of HDPs are undiagnosed, untreated, or ineffectively treated and these pose a risk of increased cardiovascular disease burden in low resource settings.[35]

Qualitative research that evaluates the patient's perspective and knowledge of HDPs of pregnancy in the West African subregion are scanty. Data from such studies that explore the knowledge of patients of their medical conditions as well as their experience of the clinical care they received for severe conditions such as preeclampsia and eclampsia would provide invaluable resources for patient education and feedback for improving the of the quality of care.

Also, evidence suggests that patient's experience of preeclampsia may influence the timing of their next pregnancy and appropriate health seeking behaviour that could assist in early diagnosis, and prompt and effective therapy.[56] If the perspectives of patients are elicited and their concerns addressed in the management plan, patients may be more likely to seek care early and accept therapeutic interventions to improve their long-term health outcomes after suffering these pathologies. Patients who acquire more knowledge may limit their number of subsequent pregnancies as a risk reduction measure. It is therefore important that research efforts in LMICs be focused on identifying the knowledge gaps of patients and formulate solutions to addressing these gaps.

Thesis objectives

The overarching aim is to optimize the care for patients diagnosed of preeclampsia with severe features and eclampsia in low resource settings.
The specific aims are:

1. To compare 12-hour duration of treatment (the novel regimen) with the 24-hour duration of treatment of MgSO4 for seizure prophylaxis in severe preeclampsia in a randomized controlled trial (RCT)
2. To assess the antenatal risk indicators of eclampsia
3. To evaluate the neonatal outcomes of preeclampsia and eclampsia
4. To explore the patient experience and perspective of surviving preeclampsia and eclampsia in a low resource setting

Outline of the thesis

The thesis is organized into 3 sections to align with the specific objectives. It begins with a general introduction (**chapter 1**), which give a background and the justification for this work. This identifies the knowledge gaps that the research work in the subsequent chapters seek to fill. Section one charts the path for a new paradigm in the therapeutics of severe preeclampsia to address the first objective (**chapters 2 and 3**).

Section two focuses on improving management outcomes of severe preeclampsia and eclampsia in low resource settings to address objective two (an assessment of the antenatal risk factors for eclampsia) in **chapter 4** and objective three (an evaluation of the neonatal outcomes of preeclampsia and eclampsia) in **chapter 5** as well as assesses the impact of ANC on maternal and neonatal outcomes in pregnancies complicated by preeclampsia and eclampsia in **chapter 6**

The third section of the thesis looks at the patient perspective of severe preeclampsia care a tertiary hospital in Ghana to address the fourth objective. This section begins with an assessment of the preeclampsia knowledge among postpartum women managed for preeclampsia and eclampsia at Korle Bu Teaching Hospital in Accra **(chapter 7).** Then self-blame and the perceived causes of preeclampsia in urban Ghana is explored **(chapter 8).** Finally, we explore women's knowledge, attitudes, and experiences with preeclampsia in Ghana **(chapter 9). Chapter 10** discusses the future of preeclampsia care and makes recommendations on how to optimize the care for women whose pregnancies are complicated by severe preeclampsia and eclampsia.

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2

Open-labeled randomized controlled trial of 12 hours versus 24 hours modified Pritchard regimen in the management of eclampsia and pre-eclampsia in Ghana (MOPEP Study): study protocol

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Authorship statement

I designed the study, performed data management, conducted the data analysis with a statistician, wrote the first draft of the manuscript, and implemented the contribution of the co-authors and external reviewers up to final publication. During the whole process I asked for and implemented input and feedback from the other contributors to this study

ABSTRACT

Introduction

Hypertensive disorders of pregnancy continue to be a major contributor to maternal and perinatal morbidity and mortality. Magnesium sulfate therapy is the standard of care for seizure prophylaxis and treatment for pre-eclampsia and eclampsia respectively, despite wide disparities in dosing regimens and routes of administration. This study compares the clinical efficacy of magnesium sulfate in the reduction of seizure occurrence or recurrence with the 12 hours versus 24 hours modified Pritchard regimens in the management of severe pre-eclampsia and eclampsia.

Methods and analysis

This study is an open labelled randomized controlled trial. The study participants are patients admitted to the Korle Bu Teaching Hospital (KBTH) in Accra, Ghana with a diagnosis of antepartum, intrapartum, or postpartum eclampsia or pre-eclampsia with severe features. All study participants will be administered a loading dose of magnesium sulfate, followed by maintenance dosing. Participants in the control group will receive magnesium sulfate for 24 hours after diagnosis, while those in the treatment group will receive magnesium sulfate for 12 hours after diagnosis. The primary outcome of this study is the occurrence of a seizure any time after the completion of treatment in the assigned group. Secondary outcome measures include maternal health outcomes, magnesium sulfate toxicities and fetal health outcomes. Data collection was started in October 2018 with a target enrolment of 1245 participants with severe pre-eclampsia and 844 participants with eclampsia with a projected study period of 3–2 years.

Ethics and dissemination

Ethical approval was obtained from the KBTH Institutional Review Board (IRB) in Ghana. University of Michigan involvement is limited to protocol development and statistical analysis of de-identified data and has been granted a Not Regulated Determination by the University of Michigan IRB. Results of the study will be shared at clinical forums at the KBTH and will be submitted for publication in an international peer-reviewed journal.

Trial registration number

Pan African Clinical Trial Registry through the South African Medical Research Council (PACTR201811515303983).

Strengths and limitations of this study

- Large randomized controlled trial that addresses duration of administration of magnesium sulfate, which fills an important gap in the literature and has significant implications for management of patients with eclampsia and pre-eclampsia with severe features.
- The study is taking place in a low resource setting with a high incidence of pre-eclampsia and eclampsia and advanced disease at presentation.
- Data collection in a developing country setting with no electronic medical record may contribute to missing information and become a study limitation.
- Lack of blinding of patients and providers to group allocation is a study limitation, however, primary outcome (occurrence of seizure) and secondary outcomes (maternal: clinical toxicities and complications; neonatal: birth outcomes) are objective measures.

Introduction

Hypertensive disorders complicate 10% of pregnancies worldwide[1,2] and pre-eclampsia occurs in 2%-8% of all pregnancies globally.[1] In developing countries, hypertensive disorders account for 10%-15% of maternal deaths.[1,2] In Ghana, the incidence of hypertensive disorders in pregnancy has been estimated from a hospital based study as 7.6%.[3,4] Eclampsi a contributes significantly to maternal mortality in developing countries. In Ghana, a case fatality of 3.9% has been reported, and institutional reports from two major tertiary-level hospitals suggest hypertensive disorders have overtaken haemorrhage as the leading cause of maternal mortality.[3]

While pre-eclampsia may not be preventable, the risk of eclampsia can be significantly reduced with good obstetric management.[5,6] Magnesium sulfate has been used for decades for the management of eclampsia and pre-eclampsia and is the anticonvulsant of choice for the management and prevention of eclamptic seizures.[7,8] Good clinical efficacy has been reported with the use of magnesium sulfate in the management of pre-eclampsia despite wide disparities the dosing regimens and routes of administration.[5,7,9–12]

There is lack of consensus in the existing literature about optimal duration and dosing of magnesium sulfate, as well as optimal therapeutic window. Therapeutic failures have been reported for doses considered both high and low.[7,9–12] The narrow therapeutic window widely used in literature is challenged by pharmacokinetic studies which demonstrate that accepted international regimens sometimes fail to reach the minimum therapeutic threshold yet are associated with clinical efficacy.[7,13,14] The duration of treatment has also been questioned, and a wide range of different regimens are currently used in clinical practice. Protocols such as the Sokoto (ultra-short) protocol demonstrated that just the standard loading dose of the Pritchard regimen may be sufficient.[11]

In Korle Bu Teaching Hospital (KBTH) and other centres in Ghana, many patients do not complete the 24 hours maintenance course due to the poor compliance and discomfort associated with the repeated injections, side effects and sometimes financial constraints; yet our observational experience has not demonstrated an increase in disease progression in this cohort of patients. Perhaps, this is secondary to the efficacy demonstrated in shorter regimens like the 12 hours maintenance and ultra-short protocol.[5] The cost to the individual and the healthcare system associated with the 24 hours maintenance course is significant. The determination of the minimum effective duration of treatment with proven clinical efficacy, minimum side effect profile and toxicity is likely to improve compliance, reduce waste and conserve resources in developing countries.

Problem statement

Maternal morbidity and mortality resulting from pre-eclampsia and eclampsia remain high in many middle- to low-income countries. The case fatality of eclampsia is unacceptably

high despite known interventions to reduce the progression to eclampsia. The current dosing regimens are at best empirical with several different regimens being used in clinical practice.

Previous studies comparing clinical efficacy of dosing regimens involved relatively small sample sizes and were not powered to detect clinical differences in toxicity and tolerability. Two small studies have compared outcomes using 12 hours versus 24 hours of magnesium sulfate using an intravenous infusion regimen.[5,12] However, there are no studies that compare 12 hours versus 24 hours of magnesium sulfate using an intramuscular regimen, which is a common method of administration in developing countries, particularly in Africa.[15] Finally, the incidence of the various side effects or toxicities of magnesium sulfate with the Pritchard regimen has not been studied in the Ghanaian population, despite years of utilization of this regimen.

Justification

Magnesium sulfate remains the mainstay of treatment prevention of eclamptic seizures in patients with pre-eclampsia and the prevention of recurrent seizures in patients with eclampsia. The clinical efficacies reported with varying durations and routes of administration necessitates further research to determine the optimum effective duration with demonstrable clinical efficacy and low toxicity which will be cost-efficient to the healthcare system, especially in low-resource countries.

Our study therefore seeks to investigate and compare clinical response between the 12 hours versus 24 hours modified Pritchard regimens. A significant reduction in cost is expected if the reduced duration of treatment proposed by this trial is adopted and there is a need to subject it to a rigorous clinical trial to assure maternal safety.

Aim and objective

Aim

To compare the 12 hours versus 24 hours modified Pritchard regimens of magnesium sulfate in the management of eclampsia and pre-eclampsia with severe features.

Objectives

1. To compare the clinical efficacy of the 12 hours versus 24 hours modified Pritchard regimens in the reduction of seizure occurrence in women with eclampsia and pre-eclampsia with severe features.
2. To compare the side effect profile and toxicity of the 12 hours versus 24 hours modified Pritchard regimens in the management of women with eclampsia and pre-eclampsia with severe features.
3. To compare the neonatal health outcomes following treatment with 12 hours versus 24 hours modified Pritchard regimens in women with eclampsia and pre-eclampsia with severe features.

Hypotheses

H_0: There is no difference in clinical efficacy of magnesium sulfate between the 12 hours versus 24 hours modified Pritchard regimens.

H_1: There is a difference in clinical efficacy of magnesium sulfate between the 12 hours versus 24 hours modified Pritchard regimens.

Methods and analysis

Study design

An open-labelled randomized controlled trial in which the study arm will receive 12 hours of maintenance doses of magnesium sulfate and the control arm will receive 24 hours of maintenance doses of magnesium sulfate. Participants will be enrolled into study groups by simple randomization using a computerized random number generation table.

Study site

The KBTH is the country's premier teaching hospital and serves as a national referral hospital for the southern half of the country. It is a tertiary hospital with a bed capacity of 2000 and an average daily outpatient department attendance of 1500 patients. The maternity unit conducts about 9500 deliveries per year. Current standard of care at KBTH is a modified Pritchard regimen of magnesium sulfate, with administration of a loading dose followed by 24 hours of maintenance dosing, starting at the time of diagnosis of eclampsia or pre-eclampsia with severe features.

Study population

Accra is a cosmopolitan city with people of varied ethnic backgrounds and social status. It is expected that the sample will represent this diversity and be reflective of the nation. Participants will be patients receiving their prenatal care at KBTH, as well as referral cases from peri-urban and rural communities around Accra.

Inclusion criteria

1. Clinical diagnosis of antepartum, intrapartum, or postpartum eclampsia based on:
    a. Elevated blood pressures of 140/90 mm Hg or higher on two occasions at least 4 hours apart after 20 weeks of pregnancy and
    b. Seizures not attributed to other causes.
2. Clinical diagnosis of pre-eclampsia with severe features (definitions per ACOG Hypertension in Pregnancy Guidelines[16]) based on:
    a. Elevated blood pressures of 160/110 mm Hg or higher on two occasions at least 4 hours apart after 20 weeks of pregnancy, with proteinuria or presence of laboratory values or clinical symptoms indicating end-organ dysfunction or
    b. Elevated blood pressures of 140/90 mm Hg or higher on two occasions at least 4 hours apart after 20 weeks of pregnancy, with presence of laboratory values or clinical symptoms indicating end-organ dysfunction.

3. Patients who receive loading dose of $MgSO_4$ at referral clinics prior to referral will be eligible for randomization if they otherwise meet the inclusion criteria.
4. Age 18 years or older.
5. Exclusion criteria
    1. Eclampsia complicated by acute renal failure, HELLP syndrome (hemolysis, elevated liver enzymes and low platelet count) or pulmonary oedema.
    2. Comorbid maternal diagnosis of renal disease and/or seizure disorder.
    3. Contraindication to $MgSO_4$ (eg, drug hypersensitivity, myasthenia gravis, anuria, or oliguria).
    4. Prior intake of any other anticonvulsant.
    5. Prior exposure within 72 hours to magnesium sulfate which was not a component of the study regimens
    6. Refusal to give consent or unable to give consent (eg, unconscious).
    7. Age 17 or younger.

Sample size estimation

An occurrence of a seizure is the primary outcome. In women with eclampsia, this will be a recurrent seizure and in women with pre-eclampsia with severe features, this will be their initial seizure.

Regarding eclampsia, we assume that the recurrent seizure rate of women receiving 12 hours of magnesium will be halfway between the seizure rate of women receiving 24 hours of magnesium (13.2%) and women receiving no magnesium (27.9%) at 20.6%.[17] To detect a difference between 20.6% recurrent seizure in the 12 hours group and 13.2% recurrent seizure in the 24 hours group, a total sample size of 402) 804 in each group) is needed, assuming a two-sided test, 5% significance level and 80% statistical power.

Regarding pre-eclampsia, in the subgroup analysis of the Magpie Trial, women with severe pre-eclampsia have a 1.1% rate of seizure if treated with 24 hours of magnesium.[10] In our current study, with a high-risk population, we anticipate a 6% rate of seizures in women who receive no magnesium based on study site department data. In absence of data from the literature, we assume that the seizure rate of women receiving 12 hours of magnesium will be halfway between the seizure rate of women receiving 24 hours of magnesium (1.1%) and women receiving no magnesium (6%) at 3.55%. To detect a difference between 3.55% seizures in the 12 hours group and 1.1% seizures in the 24 hours group, a total sample size of 593) 1186 in each group) is needed, assuming a two-sided test, 5% significance level and 80% statistical power.

Assuming 5% lost to follow-up and intervention discontinuation, 844 women with eclampsia (422 in each group) and 1245 women with severe pre-eclampsia (623 in each group) were recruited. See figure 1 for Consolidated Standards of Reporting Trials (CONSORT) flow chart.

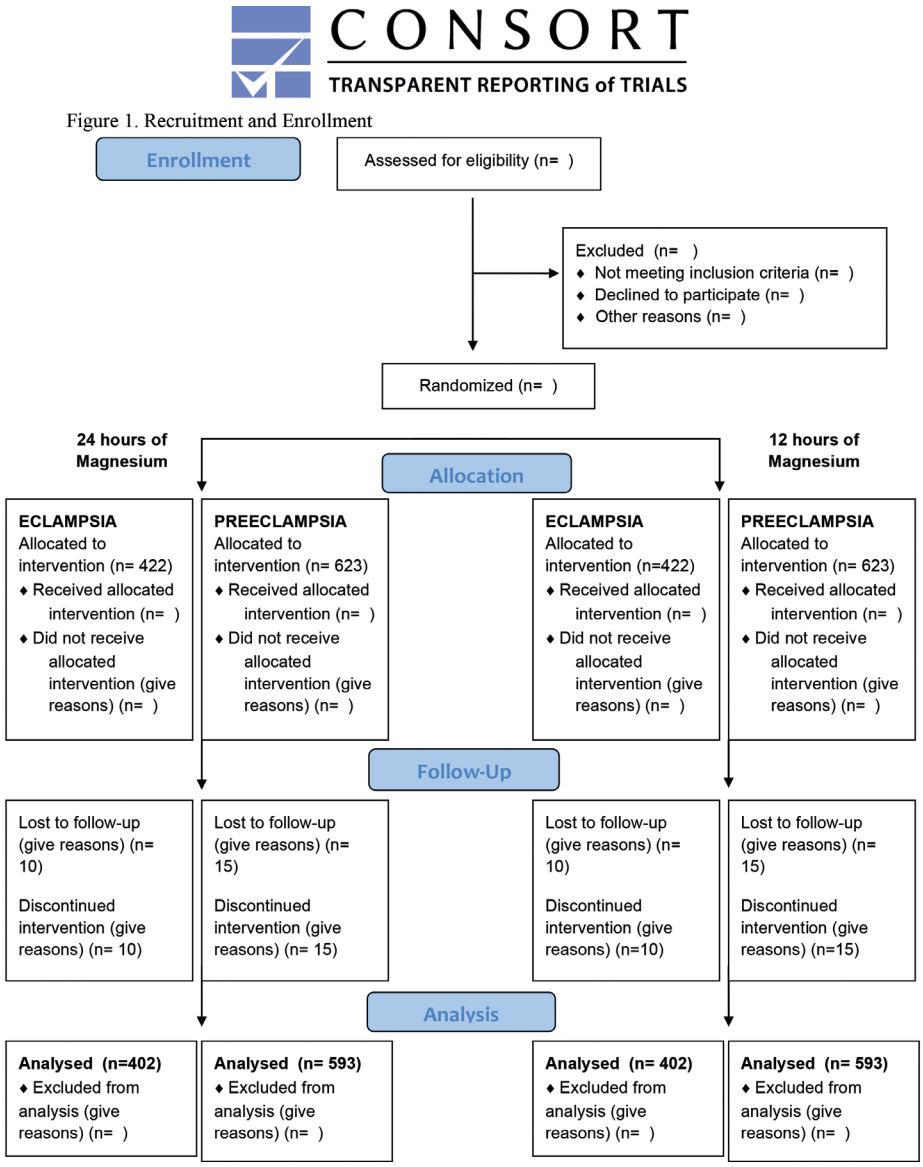

Figure 1. Recruitment and enrolment. CONSORT flow diagram outlining participant flow through each stage of the randomized controlled trial (intervention allocation, follow-up, and data analysis). CONSORT, Consolidated Standards of Reporting Trials.

Study duration

Conceptualization and securing of appropriate Institutional Review Board (IRB) approvals and funding and organization of trial materials lasted 18 months. Trial recruitment and follow-up is estimated to last 2–3 years starting October 2018.

Protocol

All women admitted to the maternity ward of KBTH as an antepartum, labouring, or postpartum patient will be assessed by the on-call obstetric resident according to the standard clinical practice. Based on initial history and physical examination, vital signs and laboratory values, clinical diagnoses will be made by the on-call obstetric team. If a patient has a clinical diagnosis of eclampsia or pre-eclampsia with severe features, she will be identified as a potential study participant. The on-call resident will review study inclusion and exclusion criteria. If a woman meets inclusion criteria, a research assistant will be notified to confirm inclusion/exclusion criteria and obtain informed consent (see consent form in supplementary file).

Participants will be enrolled into study groups by simple randomization using a computerized random number generation table (Random Number Generator V.3.0.56 for Mac). Using the table of random sequence of numbers (1 vs 2), sequentially numbered printed data collection forms will be labelled (1=control group; 2=treatment group) by researcher TB. After a participant is recruited and consented by the research assistant, the research assistant will be given the next numbered data collection form indicating the randomization group. The research assistants are not involved in the randomization process and do not have access or knowledge of the next treatment allocation. A sticker will be placed on the participants' chart to notify her clinical team of her participation and group assignment.

The research assistant will commence data collection by extracting relevant demographic and clinical data, such as medical history, past obstetric history, and history of the index pregnancy from the participant's antenatal record and supplemented by direct interview of participants. During the hospitalization, we will prospectively document events such as timing of magnesium sulfate doses, timing of any seizures, mode and timing of delivery, maternal complications, and magnesium sulfate toxicities. Neonatal information will be collected, including gestational age at delivery, birth weight, outcome of delivery (live birth vs stillbirth), neonatal intensive care unit (NICU) admission, APGAR score at 1 and 5 min and status at discharge (alive vs dead).

According to the standard protocol at KBTH, all participants will have a detailed history and physical examination done at the time of admission. Complete blood counts, clotting profile, liver and renal function tests and urine protein measurements will be performed. Strict fluid input and output monitoring will be done and recorded on the study fluids chart. All patients will have urethral catheterization retained for continuous bladder drainage

until the last dose of the magnesium sulfate. All participants will be monitored for the entire duration of $MgSO_4$ treatment by the on-call obstetrics team at least every 4 hours for blood pressure, patellar reflexes, respiratory rate, urine output and occurrence of seizures. After completion of the $MgSO_4$ injections, patients will have their blood pressure monitored every 4 hours until normalization of blood pressure, and subsequent discharge.

Apart from the duration of magnesium sulfate administration, all other clinical management of study participants will be carried out by the attending on-call obstetrician in accordance with the standard institutional care protocol at KBTH. This includes administration of antihypertensives, decision on timing and mode of delivery, induction of labour and initiation and interpretation of fetal monitoring.

Main intervention: duration of magnesium sulfate

1. Loading dose: all study participants will receive a loading dose of 4 g of intravenous $MgSO_4$ and 10 mg intramuscular $MgSO_4$ (5 g in each buttock) given at the time of antepartum, intrapartum, or postpartum diagnosis of eclampsia or pre-eclampsia with severe features.
2. Maintenance doses:
   a. Treatment group (12 hours, modified Pritchard): 5 g $MgSO_4$ intramuscular every 4 hours for a total of three doses over 12 hours starting at the time of diagnosis of eclampsia or pre-eclampsia with severe features.
   b. Control group (24 hours, modified Pritchard): 5 g $MgSO_4$ intramuscular every 4 hours for a total of six doses over 24 hours starting at the time of diagnosis of eclampsia or pre-eclampsia with severe features.
3. All doses of magnesium sulfate will be prepared and verified by the KBTH in accordance with standard hospital protocols. The loading doses will be constituted as 8 mL of 50% solution diluted with 12 mL of sterile saline to obtain 20 mL of 4 g $MgSO_4$, to be administered slowly over 15–20 min. Maintenance doses will be constituted as 10 mL of 50% $MgSO_4$ solution to obtain 5 g of $MgSO_4$, to be given as deep intramuscular injection. All doses of magnesium sulfate will be administered by clinical hospital nursing staff in accordance with standard hospital protocols.

Treatment failure

The occurrence of a seizure after completion of the third maintenance doses (MD3) and sixth maintenance doses (MD6) for the study and control groups, respectively will be regarded as a treatment failure. These patients will have the 24 hours modified Pritchard protocol restarted and completed if clinical assessment permits further magnesium sulfate therapy. After treatment failure, the management of further magnesium Sulfate is at the clinical discretion of the attending on-call obstetrician.

The occurrence of clinical evidence of toxicity (absent tendon reflexes, respiratory depression, coma) after initiation of maintenance doses that necessitate discontinuation of further maintenance doses will also be regarded as a treatment failure. In the case of $MgSO_4$ toxicities, the plan of management will be to stop further administration of $MgSO_4$ and inject 1g of calcium gluconate (10 mL of %10 solution) intravenously. The decision to reinitiate magnesium sulfate is at the clinical discretion of the attending on-call obstetrician.

Outcome measures

The primary outcome of this study will be the clinical efficacy of the magnesium sulfate regimen, defined as the absence of a seizure any time after the completion of the MD3 until discharge in the treatment (12 hours) group and after the completion of the MD6 until discharge in the control (24 hours) group.

Secondary outcome measures include:

Maternal:

1. The interval from initiation of treatment to the development of diuresis (diuresis will be defined as urine output >400 mL/4 hours).
2. Clinical evidence of toxicity (absent tendon reflexes, Respiratory rate (RR) <16 cpm, coma).
3. Side effects of magnesium (nausea/emesis, muscle weakness, absent or reduced reflexes, respiratory depression, palpitations, dizziness, drowsiness, or confusion, itching or tingling, pain and burning at the injection site, inflammation, injection abscess, bleeding, or bruising, other).
4. Acute renal failure (urine output <25 mL/hour) after initiation of treatment.
5. Pulmonary oedema.
6. Cerebrovascular accident (stroke).
7. Cardiac arrest.
8. Liver failure.
9. Coagulopathy.
10. Need for dialysis.
11. Need for ventilation.
12. Admission to ICU.
13. Length of stay (antepartum, postpartum total).
14. Time from admission to delivery.
15. Complications of delivery (placental abruption, retained placenta, postpartum haemorrhage).
16. Maternal death.

Neonatal:

1. Neonatal outcome at delivery (live birth vs stillbirth).
2. APGAR scores at 1 and 5 min.
3. Need for NICU admission.
4. Reason for NICU admission.
5. Duration of NICU admission.
6. Neonatal outcome at discharge (alive vs dead).

Statistical design

Data will be entered into REDCap and analyses will be carried out using STATA. Primary study aim is to determine whether use of the 12 hours versus 24 hours modified Pritchard regimens of magnesium sulfate impact occurrence of seizure. First, bivariate analysis will be performed to determine whether there are baseline differences between conditions (12 hours regimen, 24 hours regimen) in terms of demographics, obstetric history, medical history, and index pregnancy. Comparisons across regimens will be performed using independent samples t-tests for normally distributed continuous variables, Wilcoxon rank test for non-normally distributed continuous variables and χ^2 and Fisher's exact tests, where appropriate in the case of categorical variables. Next, the primary outcome of occurrence of a maternal seizure will be examined. Given the categorical nature of this outcome variable (yes seizure, no seizure), χ^2 test of independence will be used to determine whether the probability of experiencing a seizure across conditions. Finally, analyses will be conducted to assess secondary maternal and neonatal outcomes. In the case of continuous outcome variables independent samples t-tests will be conducted to assess whether condition predicts the continuous secondary outcome of interest. In the case of categorical outcome variables, χ^2 tests of independence will be conducted to determine whether the incidence of the categorical secondary outcome of interest differed by condition. For all analyses, Fischer's exact test will be used instead of a χ^2 test of independence should the incidence of an outcome occur in less than five individuals per condition and (Bonferroni) corrections will be applied to correct for multiple comparisons. Number needed to treat and number needed to harm will be calculated for primary and secondary outcomes. All tests will be two-tailed. Of note, outcome data will be collected for participants who discontinue or deviate from intervention protocols.

Data handling

With approval from the IRB through the KBTH, Dr Titus Beyuo (primary author) will oversee the management of data collection and data safety at KBTH in Accra, Ghana.
Patients' data collection forms will be initially identified by their 'folder number' as given at their KBTH admission, as well as their name. This will allow subsequent data collection and integration throughout their hospital course, as well as data quality control as needed. Data collection forms will only be used and accessed by authorized study co-investigators and research assistants.

Data recorded on paper data collection forms will be reviewed by Dr Titus Beyuo and then entered into a secure electronic data organization programme (REDCap) using a password protected computer. Only authorized study co-investigators and research assistants will have access to this computer. The information entered into REDCap will only include unique study numbers and will not include participants names or any other personal identifying information.

The paper data collection forms will be stored securely in a locked cabinet in a locked office in the Obstetrics and Gynecology Department at KBTH, under the direction of Dr Titus Beyuo. The records (data collection sheets) will be retained for the entire duration of the study, during which data will be accessible only by authorized investigators. After complete cleaning and quality assurance, identification numbers will be replaced by simple sequence numbers. This de-identified data will be exported from REDCap into STATA for statistical analysis. All authors will have access to the final study dataset.

Monitoring

Monitoring for quality and regulatory compliance will be overseen by the KBTH Scientific and Technical Committee in Ghana. An independent Data and Patient Safety Board was established at KBTH, consisting of Professor K. Nkyekyer (consultant obstetrician and chairman), Professor K.A. Bugyei (clinical pharmacologist and member) and Dr Ayegua Hagan (statistician and member). The Data and Patient Safety Board was created to assess the progress of the clinical study, and will review cumulative study data to evaluate safety, study conduct and scientific validity and integrity of the study. Adverse events (anaphylaxis, allergic reaction to $MgSO_4$, respiratory depression, coma) and severe adverse events (maternal morbidity or mortality secondary to anaphylaxis, allergic reaction to $MgSO_4$, respiratory depression, coma) will be collected by the principal investigator, Dr Beyuo, and reported to the Data and Patient Safety Review Board. Dr Beyuo will also be responsible for communicating any adverse event or protocol modifications on behalf of the investigators to the Data and Patient Safety Board and the IRB.

Termination of study

The study may be terminated ahead of schedule on recommendation of the Data and Patient Safety Board or by the IRB or by the investigators if interim analysis (planned for 6 months after initiation of study) shows greater than 1% difference in recurrent fits between the study and control arms.

Patient and public involvement statement

This research was done without patient involvement. Patients were not invited to comment on the study design, interpret results or contribute to the writing or editing of this document.

Ethics and dissemination

Results of the study will be shared at clinical forums at the Korle Bu Teaching Hospital and will be submitted for publication in an international peer-reviewed journal.

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3

A novel 12-hour versus 24-hour magnesium sulfate regimen in the management of eclampsia and preeclampsia in Ghana (MOPEP Study): A randomized controlled trial

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Keywords: eclampsia; preeclampsia; magnesium sulfate; seizure prophylaxis

Synopsis: Compared with 24 hours, 12 hours of intramuscular magnesium sulfate showed similar rates of seizures, with fewer side effects and shorter inpatient admission.

Authorship statement

I designed the study, performed data management, conducted the data analysis, wrote the first draft of the manuscript, and implemented the contribution of the co-authors and external reviewers up to final publication. During the whole process I asked for and implemented input and feedback from the other contributors to this study

Abstract

Objective

We compared the efficacy of a 12-hour versus 24-hour regimen of intramuscular magnesium sulfate in the management of eclampsia and preeclampsia.

Methods

This is an open-labelled parallel randomized controlled trial conducted in Accra, Ghana from November 2018 to November 2020. Participants were adult pregnant women admitted to the Korle Bu Teaching Hospital (KBTH) with a diagnosis of antepartum, intrapartum, or postpartum eclampsia or preeclampsia with severe features, having received no more than a loading dose of magnesium sulfate prior to admission at KBTH. Participants in the standard 24-hour group received a loading dose of magnesium sulfate 4g intravenous and 10g intramuscular (5g in each buttock) followed by six, 5g intramuscular maintenance doses over 24 hours. Participants in the 12-hour intervention group received the same loading dose followed by three, 5g intramuscular maintenance doses over 12 hours. The primary outcome was occurrence of seizure after completion of the assigned magnesium sulfate regimen. Secondary outcomes were magnesium sulfate toxicity, magnesium sulfate side effects, maternal outcomes (mode of delivery, duration of inpatient admission, duration of urethral catheterization), maternal complications (pulmonary edema, acute kidney injury, intensive care unit admission, death), and neonatal outcomes.

Results

Among 1176 total participants, we found no difference in occurrence of seizure after completion of the assigned regimen in the 24-hour group (n=5, 0.9%) versus the 12-hour group (n=2, 0.3%), p=0.29; RR 0.40, 95% CI 0.08, 2.04), or in occurrence of seizure any time after enrollment (n=9, 1.5% versus n=5, 0.9%, p=0.28, RR 0.55, 95% CI 0.19–1.64). Participants in the 12-hour group had a shorter duration of inpatient admission (9.4 ± 8.8 versus 7.7 ± 6.5 days, p=0.0009) and urethral catheterization (2.1 ± 1.0 versus 1.9 ± 1.3 days, p<0.0001). Rates of side effects from magnesium sulfate were lower in the 12-hour group: pain at the injection site (94.8% (n=548) versus 91.5% (n=540), p=0.03), inflammation (62.2% (n=358) versus 40.0% (n=237), p<0.0001), and bleeding or bruising at the injection site (25.1% (n=144) versus 14.4% (n=85), p<0.0001).

Conclusions

Compared with 24 hours, 12 hours of intramuscular magnesium sulfate showed similar rates of seizures, with fewer side effects and shorter inpatient admission.

Trial Registration

Prospective registration was with Pan African Clinical Trial Registry (PACTR201811515303983): https://pactr.samrc.ac.za/TrialDisplay.aspx?TrialID=4690.

Introduction

Hypertensive disorders of pregnancy (HDP), including preeclampsia and eclampsia, complicate 10% of pregnancies.[1,2] Preeclampsia and eclampsia are associated with significant maternal and neonatal morbidity and mortality.[3–7] Rates of preeclampsia and eclampsia are higher in low- and middle-income countries (LMICs), where 99% of maternal deaths secondary to HDP occur.[1–3]

Magnesium sulfate has been used for decades for seizure prophylaxis in the management of eclampsia and preeclampsia.[2,8–10] The Magpie trial demonstrated a 58% reduction in seizures among women with preeclampsia receiving magnesium sulfate.[9] A systematic review of the clinical pharmacokinetics of varying doses of intramuscular magnesium sulfate demonstrated that administration of 5g every 4 hours (the Pritchard regimen) resulted in serum concentrations within the therapeutic window between 2 and 3.5 mmol/l, while lower doses failed to achieve minimum therapeutic levels.[8] Despite evidence for clinical efficacy of the 5g maintenance dose, there is lack of consensus in the literature about optimal duration of magnesium sulfate.[9,11–14]

The two most commonly cited regimens of magnesium sulfate are the Pritchard intramuscular regimen and the Zuspan intravenous regimen, each consisting of a loading dose followed by maintenance doses continuing for 24 hours after delivery or the last seizure.[15] Notably, the Magpie trial used a 24-hour regimen that started at diagnosis and continued for 24 hours only, irrespective of delivery timing. Both intramuscular and intravenous regimens were used, with a median exposure to magnesium sulfate of 24.2 hours. The intramuscular regimen used in Magpie, which consisted of a loading dose of 4g IV and 10g intramuscular (5g in each buttock) followed by 5g intramuscular every four hours for 24 hours, is considered standard practice in Ghana.[16]

Finding the optimum duration of administration of magnesium sulfate is especially important in LMICs, where cost and monitoring of magnesium sulfate present significant challenges. Further, settings that use intramuscular injections, rather than infusion pumps, face additional challenges of multiple painful injections and potential lower compliance. To overcome these barriers, shorter regimens have been proposed. Small, underpowered studies have compared 12-hour versus 24-hour regimens of magnesium sulfate, primarily using intravenous administration.[11,14] A small study of the Sokoto (ultra-short) protocol suggests that a loading dose alone could be effective.[13] However, there are no large, adequately powered studies that compare a shorter 12-hour regimen and the 24-hour regimen of magnesium sulfate using an intramuscular injection—a common method of administration in developing countries, particularly in Africa.[15] Therefore, we aimed to compare a novel 12-hour intramuscular regimen (“Beyuo regimen”) with the standard 24-hour intramuscular regimen (“modified Pritchard regimen”) of magnesium sulfate for the management of eclampsia and preeclampsia with severe features.

Materials and Methods

This is an open-labelled parallel randomized controlled trial (RCT) comparing clinical efficacy of 12 hours versus 24 hours of intramuscular magnesium sulfate in the management of women with eclampsia and preeclampsia with severe features. The detailed study protocol is published.[17] Ethical approval was obtained from KBTH (KBTH-IRB 00096/2018) and the University of Michigan (HUM00139104).

The study was conducted at the Korle Bu Teaching Hospital (KBTH), Ghana's largest tertiary care teaching hospital.[18] KBTH is a national referral center for the southern half of Ghana and conducts approximately 9500 deliveries annually. Study participants were adult pregnant patients admitted to KBTH with a diagnosis of preeclampsia with severe features or eclampsia.

Inclusion criteria:

- Admission to KBTH maternity ward for inpatient care.
- Clinical diagnosis of antepartum, intrapartum, or postpartum preeclampsia with severe features or eclampsia. [19]
- Age 18 years or older.
- Received no more than a loading dose of magnesium sulfate prior to admission at KBTH

Exclusion criteria:

- Acute renal failure, pulmonary edema, or HELLP syndrome (hemolysis, elevated liver enzymes and low platelets)
- Comorbid diagnosis of renal disease and/or seizure disorder
- Contraindication to magnesium sulfate (drug hypersensitivity, myasthenia gravis, anuria, or oliguria).
- Received more than a loading dose of magnesium sulfate prior to admission at KBTH
- Prior intake of any other anticonvulsant in the last 72 hours.
- Age 17 or younger

Data was collected from November 2018 to November 2020. Written informed consent was obtained from all participants. Participants were assigned into study groups (1=control group; 2=intervention group) by simple randomization using a computerized random number generation table (Random Number Generator V.3.0.56 for Mac). To ensure allocation concealment, randomization was conducted by a separate member of the research team, and allocation was only revealed from a sealed envelope once a participant was recruited. Demographics, comorbid conditions, past obstetric history, and history of the index pregnancy were extracted from the participant's antenatal record and supplemented by direct interview. During the hospitalization, clinical data were prospectively collected from admission through discharge.

All study participants received a loading dose of 4g of intravenous MgSO4 and 10g of intramuscular MgSO4 (5g in each buttock). Participants in the 24-hour control group then received 5g MgSO4 intramuscular every four hours for a total of six maintenance doses over 24 hours, regardless of the timing of delivery. Participants in the 12-hour intervention group then received 5g MgSO4 intramuscular every four hours for a total of three maintenance doses over 12 hours, regardless of the timing of delivery (Figure 2). Apart from the duration of magnesium sulfate administration, all other clinical management was carried out in accordance with the standard practice at KBTH, including administration of antihypertensives, decision on timing and mode of delivery, management of induction of labour, and initiation and interpretation of fetal monitoring. Per hospital protocols, participants receiving magnesium sulfate were monitored by the on-call obstetrics team at least every four hours with measurement of blood pressure, patellar reflexes, respiratory rate, and urine output. After completion of magnesium sulfate, participants continued blood pressure monitoring every four hours until normalization. Decisions on timing of discharge was made by the on-call obstetrics team after a participant met appropriate postpartum milestones, including normal or improved blood pressures, normal or improved laboratory values, and absence of symptoms.

The primary outcome of this study was the occurrence of seizure after completion of the assigned magnesium sulfate regimen. Secondary outcome measures were the occurrence of magnesium sulfate toxicity (defined as a presence of respiratory depression with less than 16 respirations per minute or loss of deep tendon reflexes necessitating cessation of magnesium sulfate or administration of calcium gluconate)[20]; incidence of patient-reported magnesium sulfate side effects; maternal outcomes (mode of delivery, duration of inpatient admission, duration of urethral catheterization); maternal complications (pulmonary edema, acute kidney injury, intensive care unit admission, death); and neonatal outcomes.

It was estimated that a total sample size of 1186 (593 in each group) was needed to detect a difference between anticipated seizure rates of 3.55% in the 12-hour group and 1.1% in the 24-hour group, assuming a two-sided test, 5% significance level, and 80% power.[9,21]

Analyses were conducted using the intention to treat approach. Normality of continuous outcomes were assessed by inspecting skewness and kurtosis and performing the Shapiro-Wilk test, and non-normally distributed variables were expressed using median and interquartile range. Continuous laboratory values were categorized based on standard local laboratory cutoffs.[22] The primary outcome of occurrence of a maternal seizure was examined across groups using Fisher's exact test. Similarly, secondary outcomes were compared across the two groups using Wilcoxon rank test, $\chi 2$, and Fisher's exact tests where appropriate. Data management and analysis were carried out using SAS version 9.4 (SAS Institute Inc., Cary, N.C.), all tests were two-tailed, and statistical significance was defined as $p<0.05$.

Results

There were 1244 women assessed for enrollment based on a qualifying diagnosis of eclampsia or preeclampsia with severe features between October 1, 2018 and November 1, 2020 (Figure 1); of these, 1176 participants were included in the final analysis—584 in the 24-hour control group and 592 in the 12-hour intervention group. Non-adherence to the allocated protocol of magnesium sulfate was experienced by 8.2% (n=48) of the 24-hour control group versus 8.8% (n=52) of the 12-hour intervention group (p=0.72). Seven participants in the 24-hour control group declined to complete their full regimen due to side effects, compared to zero women in the 12-hour intervention group.

Participants had a median age of 31.0 years, parity of 1.0, and median body mass index (BMI) of 30.1 kg/m^2 (Table 1). Most participants received prenatal care at a government polyclinic (n=522, 47.2%) and the most common provider type was a midwife (n=704, 64.5%). One-quarter of participants received their prenatal care at KBTH, while a majority (n=844, 74.6%) were referred to KBTH from other health facilities. Seventy-nine (6.7%) participants had a history of preeclampsia in a prior pregnancy and 279 (23.7%) had pre-existing chronic hypertension.

On admission to KBTH, 116 participants (9.9%) had a diagnosis of eclampsia, and 1060 participants (90.1%) had a diagnosis of preeclampsia with severe features (Table 2). The majority of diagnoses (n=978, 84.5%) were made antepartum. Median gestational age at diagnosis was 36.3 weeks (IQR 32.7–38.7). Laboratory evaluation demonstrated 91.2% (n=951) with proteinuria, 12.3% (n=133) with AST ≥ twice the upper cutoff of normal, 8.9% (n=96) with ALT ≥ twice the upper cutoff of normal, 11.7% (n=125) with elevated creatinine >1.1 mg/dL, and 6.0% (n=67) with thrombocytopenia <100,000. Headache (n=505, 43.4%) was the most common symptom at diagnosis.

Table 3 displays the primary outcome: occurrence of seizure after completion of the assigned magnesium sulfate regimen—defined as after the third maintenance dose in the 12-hour intervention group and after the sixth maintenance dose in the 24-hour control group. There was no statistically significant difference in occurrence of seizure any time after completion of the assigned magnesium sulfate regimen between the 24-hour control group (n=5, 0.9%) and the 12-hour intervention group (n=2, 0.3%), p=0.29, RR 0.40, 95% CI 0.08–2.04). In the total population, occurrence of seizure was 1.2% (n=14) any time after enrollment and 0.6% (n=7) after completion of the assigned magnesium sulfate regimen. There were no between-group differences in occurrence of seizure any time after enrollment, after completion of the assigned magnesium sulfate regimen, or after completion of the third maintenance dose.

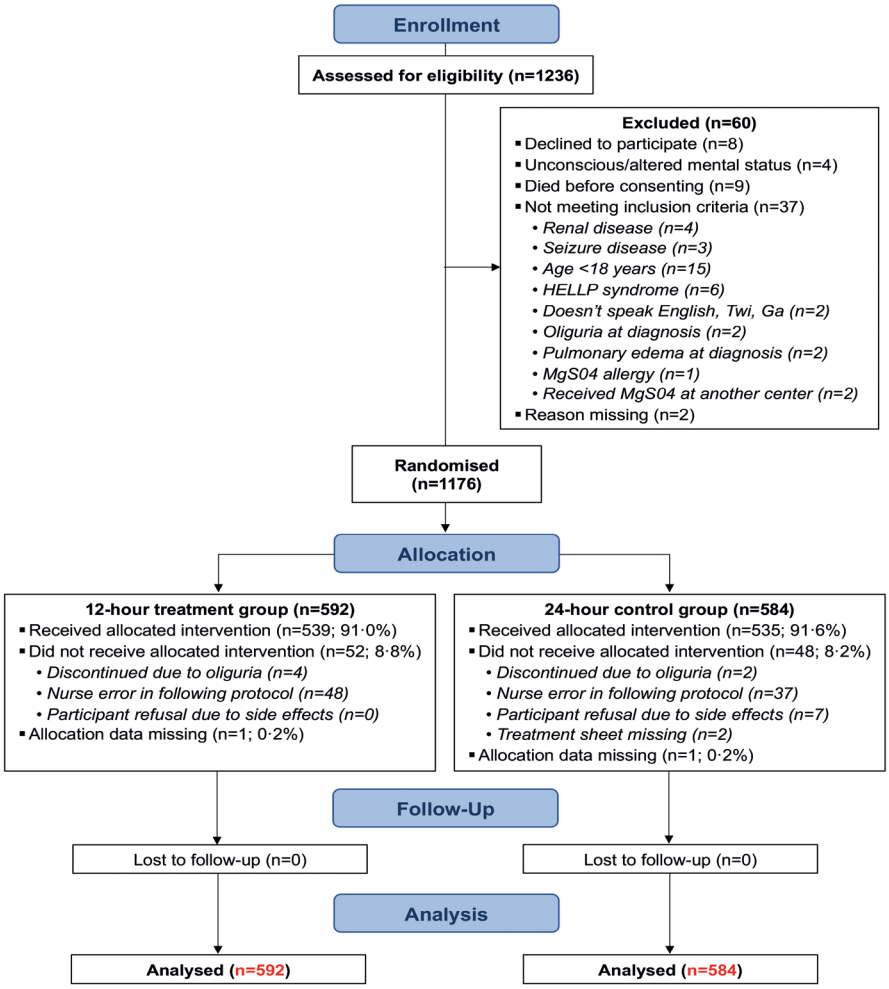

Figure 1. CONSORT Flowchart

Maximum blood pressure during hospital admission or any measured adverse maternal outcome (pulmonary edema, renal insufficiency, hemodialysis, ICU admission, or maternal death) did not differ between groups. Total length of inpatient admission (9.4 ± 8.8 versus 7.7 ± 6.5 days, p=0.0009) and duration of urethral catheterization (2.1 ± 1.0 versus 1.9 ± 1.3 days, p<0.0001) were both significantly lower in the 12-hour intervention group. Notably, rates of side effects were lower in the 12-hour group; pain at the injection site (94.8% (n=548) versus 91.5% (n=540), p=0.03), inflammation (62.2% (n=358) versus 40.0% (n=237), p<0.0001), and bleeding or bruising at the injection site (25.1% (n=144) versus 14.4% (n=85), p<0.0001) compared to the 24-hour group.

Among 1218 infants born to 1176 women, poor neonatal outcomes were driven by high rates of prematurity, with 16.7% of neonates delivered before 32 weeks of gestation and 19.0% with a birthweight less than 1500 grams. Of all neonates, 12.2% (n=147) were stillbirths and the neonatal mortality rate at time of hospital discharge was 20.4% (Table 4). In the 24-hour control group, gestational age, birth weight, and Apgar score at one and five minutes were significantly lower and NICU admission was significantly higher than the 12-hour group. There was no difference in the incidence of live birth or infant survival at discharge between the two groups.

Discussion

This study compared the 24-hour intramuscular magnesium sulfate regimen used in Magpie to a novel 12-hour "Beyuo regimen," with comparable rates of seizures. Our findings are consistent with a 2020 meta-analysis of 1124 participants across seven RCTs comparing 24-hour regimens to shorter regimens in participants with preeclampsia, which found no significant difference between groups for the primary outcome of seizure.[23] There were only two events of eclampsia reported across the trials, both occurring in the shortened regimen arm (risk difference 0.00, 95% CI -0.01–0.01, p=0.49). This meta-analysis included four RCTs conducted in Brazil,[24] Iran,[25,26] and Egypt[27] specifically comparing 12-hour to 24-hour regimens, with a total study population of 562. No individual trial demonstrated a difference in the outcome of seizure between groups; however, the number of participants in each study was small. Another small study in Nigeria[28] (n=80) also compared 12-hour versus 24-hour regimens, with no seizure events in either group. Our study adds substantially to this literature due to our large sample size, which exceeds the combined participants of the meta-analysis.

Strengths of this study include a sample size that exceeds all prior trials combined, a high rate of enrollment, and no loss to follow-up. Non-adherence to the treatment protocol was less than 9% in each group, which is low and comparable to the Magpie trial.[9] The main limitation is that the primary outcome of seizure occurred less frequently than anticipated. Thus, we are underpowered to detect a significant difference between 0.3% (n=2) seizures in the 12-hour control group and 0.9% (n=5) in the 24-hour intervention group. Based on final seizure rates, the study has 80% power to detect a significant difference of 4.1% between groups. Despite this limitation, the study demonstrates high efficacy of the 12-hour regimen among a very high-risk population, including 116 participants with eclampsia. A non-blinded approach was selected due to the ethical concern about administering three additional non-therapeutic painful intramuscular injections in the 12-hour group. Despite the limitations of a non-blinded design, the primary outcome was an immutable seizure occurrence as determined by clinical providers separate from the research team. In our study population, poor neonatal outcomes were driven by a complex referral population at the study site, neonatal risk associated with preeclampsia and

eclampsia, and high rates of prematurity. A prospective cohort study done in Accra, Ghana demonstrated that women with hypertensive disorders of pregnancy had higher rates of preterm birth, low birthweight, low Apgar scores, and 18-times higher odds of neonatal death.[29] Comparable poor neonatal outcomes among women with preeclampsia and eclampsia have also been reported in other low-resource settings. [4,5,7]

Table 1. Baseline Demographic and Clinical Characteristics of Participants

	Total (n=1176)	**24-hour control group (n=584)**	**12-hour intervention group (n=592)**
Age (years)	31.0 (27.0, 35.0)	32.0 (27.0, 35.0)	31.0 (27.0, 35.0)
Age ≥35 years	343 (29.2)	177 (30.3)	166 (28.0)
Parity category			
Nulliparous (0)	376 (32.0)	179 (30.7)	197 (33.3)
Primiparous (1)	283 (24.1)	149 (25.6)	134 (22.7)
Multiparous (2–4)	464 (39.5)	230 (39.5)	234 (39.6)
Grand Multiparity (≥5)	51 (4.3)	25 (4.3)	26 (4.4)
Gravidity	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)
Marital status			
Married	847 (73.1)	433 (74.5)	415 (71.7)
Cohabitating	35 (3.0)	21 (3.6)	14 (2.4)
Single/Divorced/Separated/ Widowed	277 (23.9)	127 (21.9)	150 (25.9)
Insurance status			
No Insurance	43 (3.8)	20 (3.5)	23 (4.0)
Public Insurance	1090 (95.4)	540 (95.4)	550 (95.3)
Private Insurance	10 (0.9)	6 (1.1)	4 (0.7)
Body mass index category (kg/m^2)			
Underweight (<18.5)	15 (1.3)	9 (1.6)	6 (1.1)
Normal weight (18.5–24.9)	253 (22.5)	134 (24.1)	119 (21.0)
Overweight (25–29.9)	287 (25.5)	146 (26.2)	141 (24.8)
Obese (≥30)	570 (50.7)	268 (48.1)	302 (53.2)
Gestational age at first antenatal visit (weeks)	16.0 (11.7, 21.0)	16.0 (11.4, 21.0)	16.0 (12.0, 21.4)

Table 1. Baseline Demographic and Clinical Characteristics of Participants *(continued)*

	Total (n=1176)	**24-hour control group (n=584)**	**12-hour intervention group (n=592)**
Facility for antenatal care			
Government tertiary hospital	230 (20.8)	105 (19.0)	125 (22.6)
Government regional/district hospital	137 (12.4)	70 (12.7)	67 (12.1)
Government polyclinic	522 (47.2)	258 (46.7)	264 (47.7)
Private hospital	157 (14.2)	85 (15.4)	72 (13.0)
Maternity home	60 (5.4)	34 (6.2)	26 (4.7)
Type of caregiver for antenatal care			
Specialist Obstetrician/ Gynecologist	259 (23.7)	118 (21.8)	141 (25.7)
Medical officer (non-obstetrician)	118 (10.8)	52 (9.6)	66 (12.0)
Midwife	704 (64.5)	368 (67.9)	336 (61.2)
Other	10 (0.9)	4 (0.7)	6 (1.1)
Referred from outside health center to KBTH	844 (74.6)	437 (77.8)	407 (71.5)
Obstetric history			
Previous preeclampsia	79 (6.7)	43 (7.4)	36 (6.1)
Previous gestational diabetes	9 (0.8)	6 (1.0)	3 (0.5)
Previous miscarriages	461 (39.2)	204 (34.9)	257 (43.4)
Previous stillbirths	69 (5.9)	26 (4.5)	43 (7.3)
Previous early neonatal deaths	26 (2.2)	15 (2.6)	11 (1.9)
Previous small for gestational age	1 (0.1)	1 (0.2)	0 (0.0)
Comorbid conditions in index pregnancy			
Chronic hypertension	279 (23.7)	146 (25.0)	133 (22.5)
Diabetes	65 (5.5)	38 (6.5)	27 (4.6)
Sickle cell disease	33 (2.8)	15 (2.6)	18 (3.0)

Data presented as n (%) or median (interquartile range)
KBTH=Korle Bu Teaching Hospital

Table 2. Characteristics of Participants at time of Diagnosis and Randomization

	Total (n=1176)	**24-hour control group (n=584)**	**12-hour intervention group (n=592)**
Inclusion diagnosis			
Eclampsia	116 (9.9)	63 (10.8)	53 (8.9)
Severe preeclampsia	1060 (90.1)	521 (89.2)	539 (91.1)
Timing of diagnosis			
Antepartum	978 (84.5)	487 (84.7)	491 (84.4)
Intrapartum	117 (10.1)	52 (9.0)	65 (11.2)
Postpartum	62 (5.4)	36 (6.3)	26 (4.5)
Gestational age at diagnosis (weeks)	36.3 (32.7, 38.7)	35.4 (32.1, 38.0)	37.1 (33.4, 39.0)
Number of gestations			
Singleton	1086 (94.3)	535 (94.4)	551 (94.2)
Twins	66 (5.7)	32 (5.6)	34 (5.8)
Systolic BP at diagnosis (mm Hg)	167.0 (155.0, 180.0)	166.0 (151.0, 180.0)	168.5 (158.0, 180.0)
Diastolic BP at diagnosis (mm Hg)	107.0 (100.0, 118.0)	108.0 (100.0, 119.0)	107.0 (100.0, 115.0)
Urine protein at diagnosis			
Negative	30 (2.9)	14 (2.7)	16 (3.0)
Trace	61 (5.9)	37 (7.2)	24 (4.6)
+1	257 (24.7)	120 (23.4)	137 (26.0)
+2	357 (34.3)	177 (34.4)	180 (34.1)
+3	237 (22.7)	118 (23.0)	119 (22.5)
+4	100 (9.6)	48 (9.3)	52 (9.9)
AST at diagnosis (units/liter) [a]			
≤33	653 (60.4)	317 (59.1)	336 (61.7)
33–66	295 (27.3)	147 (27.4)	148 (27.2)
≥66	133 (12.3)	72 (13.4)	61 (11.2)
ALT at diagnosis (units/liter) [a]			
≤33	827 (76.4)	392 (73.0)	435 (79.8)
33–66	159 (14.7)	94 (17.5)	65 (11.9)
≥66	96 (8.9)	51 (9.5)	45 (8.3)

Table 2. Characteristics of Participants at time of Diagnosis and Randomization *(continued)*

	Total (n=1176)	**24-hour control group (n=584)**	**12-hour intervention group (n=592)**
Creatinine at diagnosis (mg/dL) [a]			
≤1.1	941 (88.3)	468 (88.3)	473 (88.3)
>1.1	125 (11.7)	62 (11.7)	63 (11.8)
Platelets at diagnosis (10^3 µmol) [a]			
<100	67 (6.0)	43 (7.8)	24 (4.3)
100–149	127 (11.5)	62 (11.3)	65 (11.6)
≥150	915 (82.5)	445 (80.9)	470 (84.1)
Headache at diagnosis	505 (43.4)	275 (47.5)	230 (39.4)
Blurred vision at diagnosis	143 (12.4)	74 (12.9)	69 (11.9)
Right upper quadrant or epigastric abdominal pain at diagnosis	136 (11.8)	74 (12.9)	62 (10.7)
Nausea or vomiting at diagnosis	126 (10.9)	65 (11.3)	61 (1.05)

Data presented as n (%) or median (interquartile range)
[a]Continuous laboratory values were categorized based on standard local laboratory cutoffs: the upper end of the normal range of alanine transaminase (ALT) is 33 and aspartate transaminase (AST) is 33. Creatinine was converted from µmol/l to mg/dl using conversion factor of 0.0113. Cutoffs for abnormal values indicating severe disease were defined as transaminitis at twice the upper end of the normal range (≥66 units), creatinine >1.1 mg/dl, and thrombocytopenia <100,000.
BP=Blood Pressure; AST=Aspartate Aminotransferase; ALT=Alanine Aminotransferase

This study evaluates a new protocol for seizure prophylaxis in eclampsia and preeclampsia with severe features—the 12-hour "Beyuo regimen." In low-resource settings similar to KBTH, the cost of a longer regimen of magnesium sulfate can be significant—not simply secondary to medication costs, but also due to the personnel and monitoring required to safely administer magnesium sulfate. Further, the same low-resource settings are more likely to utilize intramuscular regimens. There is added benefit of avoiding additional injections to minimize side effects, patient discomfort, and potential non-compliance. Findings from this study, together with results of the prior smaller studies, may be considered sufficient to change clinical practice to adopt this 12-hour regimen of magnesium sulfate in settings that currently utilize intramuscular regimens and where benefits of a shorter regimen are substantial.

Importantly, in both our study and the Magpie trial, time from diagnosis to delivery was short. In our study, 66.8% (n=831) of participants delivered within 24 hours of starting magnesium sulfate, with a median time from loading dose to delivery of 14.6 hours. Similarly, in the Magpie trial, 63% of participants delivered within 24 hours of being enrolled, with a median antepartum duration of 12.5 hours. This is concordant with the World Health Organization recommendation to deliver preeclamptics with severe features

within 24 hours and eclamptics within 12 hours of diagnosis.[2] The Magpie trial concludes that their finding supporting the safety and efficacy of magnesium sulfate cannot be certain beyond 24 hours of duration. Similarly, our trial demonstrates efficacy of 12 hours of magnesium sulfate, starting at time of diagnosis and continuing for 12 hours only, irrespective of timing of delivery. In both our trial and the Magpie trial, the number of hours that a participant received magnesium sulfate after delivery was variable; this was dependent on how quickly a participant progressed from diagnosis and initiation of magnesium to delivery. Thus, high-resource centers that support close monitoring of prolonged inductions of labor for pregnancies complicated by eclampsia or preeclampsia, potentially exceeding 24-48 hours of antepartum management, must consider whether these findings can be extrapolated to their clinical setting. The extrapolation of these data from a 12-hour intramuscular regimen to an IV regimen is limited by a lack of data on the comparative efficacy and pharmacokinetics of magnesium sulfate by route of administration. Of note, the large multi-site Magpie trial included health centers using both intramuscular and IV regimens, without significant heterogeneity in efficacy. To adopt a 12-hour regimen in well-resourced health centers that use an intravenous regimen, additional research may be warranted to conclusively demonstrate equivalent efficacy to a 24-hour regimen.

Overall, we demonstrate comparable seizure rates between a 24-hour regimen of intramuscular magnesium sulfate and a shorter 12-hour regimen. Participants in the 12-hour regimen had a shorter duration of inpatient admission, shorter duration of urethral catheterization, and fewer side effects of magnesium sulfate. Especially in low-resource settings that use intramuscular magnesium sulfate, a 12-hour regimen may maintain clinical efficacy while minimizing side effects, cost, and resource-intensive monitoring.

Table 3. Maternal primary and secondary outcomes (n=1176)

	Total (n=1176)	**24-hour control group (n=584)**	**12-hour intervention group (n=592)**	**RR or Mean Difference**	**95% CI**	**p-value**
Occurrence of a seizure after completion of assigned magnesium sulfate regimen[a]	7 (0.6)	5 (0.9)	2 (0.3)	0.40	0.08–2.04	0.29[b]
Occurrence of a seizure any time after enrollment	14 (1.2)	9 (1.5)	5 (0.9)	0.55	0.19–1.64	0.28[e]

Table 3. Maternal primary and secondary outcomes (n=1176) *(continued)*

	Total (n=1176)	**24-hour control group (n=584)**	**12-hour intervention group (n=592)**	**RR or Mean Difference**	**95% CI**	**p-value**
Occurrence of a seizure any time after completion of 3rd maintenance dose	8 (0.7)	6 (1.0)	2 (0.3)	0.33	0.07–1.64	0.18[b]
Mode of delivery						**0.02**[d]
Vaginal delivery	386 (33.5)	172 (30.2)	214 (36.7)	1.21	1.03–1.43	
Cesarean section	767 (66.5)	398 (69.9)	369 (63.3)	0.82	0.70–0.97	
Maximum BP during admission						
Maximum systolic BP (mm Hg)	179.7 ± 96.3	178.0 ± 87.0	181.4 ± 104.7	3.39	-7.65–14.43	0.22[c]
Maximum diastolic BP (mm Hg)	110.7 ± 16.0	110.7 ± 16.6	110.6 ± 15.4	-0.06	-1.90–1.77	0.71[c]
Total duration of admission (days)	8.5 ± 7.7	9.4 ± 8.8	7.7 ± 6.5	-1.68	-2.57–-0.79	**0.0009**[c]
Duration of urethral catheterization (days)	2.0 ± 1.2	2.1 ± 1.0	1.9 ± 1.3	-0.16	-0.30–-0.03	**<0.0001**[c]
Maternal complications						
Pulmonary edema	13 (1.1)	7 (1.2)	6 (1.0)	0.84	0.29–2.50	0.76[d]
Diagnosed with renal insufficiency[e]	131 (11.3)	66 (11.5)	65 (11.1)	0.96	0.70–1.33	0.83[b]
Hemodialysis	3 (0.3)	1 (0.2)	2 (0.3)	1.96	0.18–21.55	0.99[b]
Intensive care unit admission	10 (0.9)	7 (1.2)	3 (0.5)	0.42	0.11–1.62	0.22[b]
Maternal death	4 (0.4)	2 (0.4)	2 (0.3)	0.99	0.14–6.97	0.99[b]
Experienced side effect of MgSo4						
Nausea or vomiting or both	118 (10.2)	56 (9.7)	62 (10.6)	1.09	0.77–1.53	0.63[d]
Muscle weakness	313 (26.8)	162 (28.0)	151 (25.6)	0.91	0.75–1.10	0.34[d]
Absent or reduced tendon reflexes	32 (2.8)	15 (2.6)	17 (2.9)	1.11	0.56–2.19	0.77[d]

Table 3. Maternal primary and secondary outcomes (n=1176) *(continued)*

	Total (n=1176)	**24-hour control group (n=584)**	**12-hour intervention group (n=592)**	**RR or Mean Difference**	**95% CI**	**p-value**
Respiratory depression	62 (5.3)	35 (6.1)	27 (4.6)	0.75	0.46–1.23	0.26[d]
Palpitations or tachycardia	122 (10.5)	69 (11.9)	53 (9.0)	0.75	0.54–1.06	0.10[d]
Dizziness	237 (20.5)	123 (21.3)	114 (19.2)	0.90	0.72–1.13	0.38[d]
Drowsiness or confusion	291 (25.0)	152 (26.3)	139 (23.6)	0.90	0.74–1.10	0.29[d]
Itching or tingling sensation	809 (69.4)	401 (69.5)	408 (69.3)	1.00	0.92–1.08	0.93[d]
Pain and burning at injection site	1088 (93.2)	548 (94.8)	540 (91.5)	0.97	0.94–0.99	**0.03**[d]
Inflammation at injection site	595 (50.9)	358 (62.2)	237 (40.0)	0.64	0.56–0.72	**<0.0001**[d]
Injection abscess	13 (1.1)	8 (1.4)	5 (0.9)	0.61	0.20–1.86	0.38[d]
Bleeding or bruising at injection site	229 (19.7)	144 (25.1)	85 (14.4)	0.57	0.45–0.73	**<0.0001**[d]

Data presented as n (%) or mean ± standard deviation

[a]Primary outcome

[c]Comparisons between 12 and 24-hour treatment groups were made using Fisher's exact test

[d]Comparisons between 12 and 24-hour treatment groups were made using Wilcoxon Rank Test

[e]Comparisons between 12 and 24-hour treatment groups made using Chi-squared

[e]Renal insufficiency is defined as a Creatinine >1.1 and/or a clinical diagnosis made based on oliguria/anuria

BP=Blood Pressure, CI=Confidence Interval, RR=Relative Risk

Table 4. Neonatal secondary outcomes (1218 neonates among 1176 women)

	Total (n=1218)	**24-hour control group (n=599)**	**12-hour intervention group (n=619)**	**RR or Mean Difference**	**95% CI**	**p-value**
Gestational age at delivery (weeks)	36.1 ± 10.3	35.5 ± 4.1	36.6 ± 13.8	1.17	0.03–2.32	**0.0009**[a]
Status of baby at delivery						0.97[b]
Livebirth	1064 (87.9)	523 (87.9)	541 (87.8)	0.99	0.96–1.04	
Stillbirth	147 (12.2)	73 (12.2)	75 (12.2)	1.06	0.74–1.36	
Birth weight (g)						**0.006**[b]
<1500	227 (19.0)	126 (21.5)	101 (16.6)	0.73	0.58–0.91	
1500–2499	425 (35.6)	221 (37.7)	204 (33.6)	0.84	0.73–0.97	
≥2500	542 (45.4)	240 (40.9)	302 (49.8)	REF	0.58–0.91	
Apgar score at five minutes[c]						**0.04**[b]
<7	159 (15.2)	90 (17.5)	69 (12.9)	0.74	0.55–0.98	
≥7	888 (84.8)	423 (84.5)	465 (87.1)	1.06	1.00–1.11	
NICU admission[c]	522 (50.2)	278 (55.1)	244 (45.6)	0.83	0.73–0.94	**0.002**[b]
Duration of NICU admission (days)[d]	11.4 ± 11.2	11.3 ± 11.0	11.5 ± 11.4	0.19	-1.91–2.28	0.90[a]
Status of baby at discharge						0.24[b]
Alive	917 (79.6)	437 (78.2)	480 (80.9)	1.04	0.98–1.10	
Dead	235 (20.4)	122 (21.8)	113 (19.1)	0.87	0.69–1.10	

Data presented as n (%) or mean ± standard deviation

[a]Comparisons between 12 and 24-hour treatment groups were made using Wilcoxon Rank Test

[b]Comparisons between 12 and 24-hour treatment groups made using Chi-squared

[c]APGAR score, NICU referral, and NICU admission are calculated among a denominator of livebirths

[d]Duration of NICU admission is calculated among a denominator of livebirths admitted to the NICU

CI=Confidence Interval; NICU=Neonatal Intensive Care Unit; RR=Relative Risk

Contribution to authorship

The study was conceptualized by TB and SAO. The study protocol was developed by TB, SOA, and ERL. Data collection was managed by TB, SOA, and ERL. Data analysis was performed by EKK. Data interpretation was performed by all authors. All authors edited, reviewed, and approved this manuscript. All authors have directly accessed and verified the underlying data reported in the manuscript.

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Conflicts of interests

The authors report no conflicts of interest.

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4

Clinical Presentation and Predictors of Eclampsia Among Women with Hypertensive Disorders of Pregnancy in Ghana

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Authorship statement

I designed the study, performed data management, conducted the data analysis with a statistician, wrote the first draft of the manuscript, and implemented the contribution of the co-authors and external reviewers up to final publication. During the whole process I asked for and implemented input and feedback from the other contributors to this study

ABSTRACT

Objectives

Eclampsia is a leading contributor to global maternal morbidity and mortality. Past studies demonstrate varying relationships between demographic and antenatal factors and subsequent development of eclampsia. This study sought to identify predictors of eclampsia in a tertiary hospital in Ghana.

Study Design

Participants were women admitted to Korle Bu Teaching Hospital in Ghana with a diagnosis of preeclampsia with severe features or eclampsia. Medical and obstetric history were extracted from medical records. Clinical information, including vital signs and maternal complications, was prospectively collected.

Main Outcome Measures

Bivariate analysis compared demographic, antenatal, obstetric history, and clinical characteristics between patients presenting with eclampsia and preeclampsia. Multivariable logistic regression identified independent predictors of eclampsia.

Results

Among 1,176 participants, 116 (9.9%) had a diagnosis of eclampsia. The majority of women with eclampsia experienced their first seizure antepartum (68.7%), in a location outside a health facility (56.5%) and witnessed by a family member (55.9%). Women with eclampsia had a median of 1.0 seizure (IQR 1.0, 2.0). Only 15 (12.9%) had a prior diagnosis of preeclampsia. There was a nearly three-fold increased odds of eclampsia in women aged <20 (aOR 2.75, 95% CI 1.10-6.89, p=0.03) and those with twin pregnancy (aOR 2.59, 95% CI 1.26-5.32, p=0.01). Decreased odds of eclampsia was observed with age ≥35 (aOR 0.32, 95% CI 0.15-0.67, p=0.002), obesity (aOR 0.44, 95% CI 0.25-0.77, p=0.004), and chronic hypertension (aOR 0.38, 95% CI 0.17-0.86, p=0.02).

Conclusions:

Understanding predictors of eclampsia is important to identify high-risk patients and make informed decisions about antenatal care.

Keywords: eclampsia; hypertensive disorders of pregnancy; seizure; maternal morbidity; maternal mortality

Introduction[1]

Hypertensive disorders of pregnancy, including preeclampsia and eclampsia, are leading contributors to global maternal morbidity and mortality. Up to 15% of direct maternal mortality is associated with hypertensive disorders of pregnancy [1]. The global priority to reduce maternal mortality, including contributions from hypertensive disorders of pregnancy, continues to be reaffirmed by the Millennium Development Goals and Sustainable Development Goals [2]. However, significant disparities in hypertensive disorders of pregnancy persist, with a disproportionate incidence and associated morbidity and mortality in low- and middle-income countries (LMICs). In Sub-Saharan African countries such as Ghana, hypertensive disorders of pregnancy have overtaken hemorrhage as the leading cause of maternal mortality in many tertiary hospitals [1,3].

The most serious manifestation of hypertensive disorders of pregnancy is eclampsia, which is clinically defined as the occurrence of seizure in women who meet diagnostic criteria for preeclampsia, without other etiologies of seizures [4]. Global incidence of eclampsia has significantly declined over the past two decades [5] due to management of preeclamptic patients with magnesium sulfate, guided by the Collaborative Eclampsia trial [6] and Magpie trial [7]. However, incidence of eclampsia remains disproportionally high in LMICs [1,8,9]. The incidence of eclampsia ranges from 1.6-10 cases per 10,000 deliveries in high-income countries to 6-157 cases per 10,000 deliveries in LMICs [5,10,11]. In pregnancies complicated by eclampsia, maternal complications are significant and include placental abruption with coagulopathy, intensive care unit admission, and maternal mortality [1,5,12]. Neonatal outcomes are also poor, with high rates of preterm gestational age at delivery, stillbirth, and perinatal mortality [5,9,12].

Past studies have shown varying relationships between demographic factors, physical symptoms, and development of eclampsia. Risk factors for development of hypertensive disorders of pregnancy in general include history of preeclampsia, extremes of reproductive age, cigarette smoking, nulliparity, and multiple gestations [11,13]. However, compared to women with less-severe forms of hypertensive disorders of pregnancy, risk factors for development of eclampsia are less well-defined. Identifying patients at high risk for developing eclampsia is an important tool for health systems to focus monitoring and resources, particularly in low-resource settings. This study uses a large group of women with preeclampsia and eclampsia to explore antenatal predictors of eclampsia in an urban tertiary hospital in Ghana.

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1 Abbreviations:
LMICs=low- and middle-income countries
KBTH=Korle Bu Teaching Hospital
ALT=Alanine transaminase
AST=Aspartate transaminase

Methods

Study participants were adult pregnant women admitted to Korle Bu Teaching Hospital (KBTH) in Accra, Ghana. KBTH is Ghana's largest tertiary care teaching hospital, with a large academic Obstetrics and Gynecology department and a high-risk obstetric population. KBTH conducts approximately 9,500 deliveries yearly. Inclusion criteria were age ≥18 years, admission to KBTH for peripartum management, and a clinical diagnosis of preeclampsia with severe features or eclampsia.

Data was collected between October 2018 and November 2020 as part of the overarching MOPEP study [14]. Data collection consisted of direct participant interviews and extraction of clinical information from participants' medical records. On admission, data including demographics, medical and obstetric history, and characteristics of the index pregnancy were extracted from the medical record and blood pressure values were recorded. Laboratory values were also recorded on admission if clinically obtained, including creatinine, platelets, Alanine transaminase (ALT), Aspartate transaminase (AST), and proteinuria. Participants were interviewed on admission to obtain relationships status, insurance status, and any demographics and medical history missing from their medical record. In addition, participants were asked if the following four symptoms were present on admission to KBTH: headache, vision changes, right upper quadrant or epigastric pain, and nausea or vomiting.

Data was captured in REDCap and transferred to SAS 9.4 (SAS Institute Inc., Cary, N.C) for data management and analysis. The clinical characteristics of seizure episodes such as the timing, number, place of occurrence, and identification of any witnesses, were described using a frequency distribution for all participants with a diagnosis of eclampsia. The normality for all continuous variables was assessed using skewness and kurtosis, and the Shapiro-Wilk test. As all continuous variables were non-normally distributed, results were presented using median and interquartile range. Bivariate analysis was performed to compare demographic and clinical history characteristics and clinical and laboratory factors on presentation by diagnosis of eclampsia or preeclampsia with severe features. Comparisons between diagnosis groups were performed using Wilcoxon Rank test for continuous variables and Chi-square or Fisher's exact test for categorical variables where appropriate. Missing data were not included in statistical comparisons. Demographic and clinical factors independently associated with eclampsia from bivariate analyses and other clinically relevant variables were considered candidates for inclusion in a multivariable logistic regression model. All calculated p-values were two-sided and statistical significance interpreted using 95% confidence intervals.

Ethical approval was obtained from the KBTH Institutional Review Board (KBTH-IRB 00096/2018) and the University of Michigan Institutional Review Board (HUM00139104). Study participants provided written informed consent.

Results

Of 1,176 total participants, 116 (9.9%) had a clinical diagnosis of eclampsia and 1,060 (90.1%) had a diagnosis of preeclampsia with severe features. Among the 116 women diagnosed with eclampsia, the median number of seizures experienced was 1.0 (Table 1). The majority (68.7%, n=79) had their first seizure in the antepartum period, at a median gestational age of 34.7 weeks. Of the 27 (23.5%) participants who were diagnosed with postpartum eclampsia, the first seizure occurred at a median of 1.0 day postpartum. The majority of participants (56.5%, n=65) experienced their first seizure at a location outside a health facility that was witnessed by a family member or a non-health professional (55.9%, n=62). Only 15 (12.9%) were diagnosed with preeclampsia prior to the occurrence of a seizure.

Regarding key demographics and clinical history, women with eclampsia were most frequently aged 20-34 years (77.6%, n=90), nulliparous (41.2%, n=47), and normal weight (36.3%, n=37) (Table 2). Chronic hypertension, diabetes, and sickle cell disease were comorbid conditions in 6.0%, 3.5%, and 5.2% of pregnancies complicated by eclampsia respectively. Eleven percent (n=12) had a twin pregnancy and 0.9% (n=1) had a prior pregnancy complicated by preeclampsia. Compared to women with preeclampsia, those with eclampsia were more likely to be younger than age 20 (9.5% v 1.8%) and less likely to be age 35 or older (12.9% vs 30.9%). Women with eclampsia were more likely to be nulliparous (41.2% vs 31.0%), less likely to have BMI ≥30 at the first antenatal visit (29.4% v 52.8%), less likely to have chronic hypertension (6.0% vs 25.7%), and more likely to have a twin pregnancy (11.0% v 5.2%).

On admission to the hospital, women with eclampsia had a median systolic blood pressure of 170.0 and median diastolic blood pressure of 110.0 (Table 3). During the entire intrapartum admission, minimum-to-maximum ranges of recorded blood pressures for women with eclampsia were 125.0-280.0 systolic and 75.0-194.0 diastolic. Laboratory assessment performed on admission demonstrated 97.3% (n=112) with proteinuria, 25.5% (n=26) with AST elevated above twice the normal value, 15.7% (n=16) with ALT elevated above twice the normal value, 17.8% (n=18) with creatinine >1.1 mg/dL, and 8.6% (n=9) with severe thrombocytopenia (platelets <100 x 10^3 µmol). Headache was the most common symptom on admission, experienced by 54.6% (n=60) women with eclampsia. Degree of blood pressure elevation was similar between women with eclampsia versus preeclampsia. Compared to preeclampsia, a higher proportion of women with eclampsia had severe abnormalities in AST (25.5% vs 10.9%), ALT (15.7% vs 8.2%), and creatinine (17.8% vs 11.1%). Women with eclampsia were also more likely to have a headache (54.6% vs 42.3%) and vision changes (29.6% vs 10.6%).

As shown in Table 4, demographic and clinical factors significant in bivariate analysis were included in a final adjusted logistic regression model. After adjusting for parity, marital status, and preeclampsia in a prior pregnancy, women with increased odds of an

eclampsia diagnosis were younger than 20 (aOR 2.75, 95% CI 1.10-6.89, p=0.03) and had a twin pregnancy (aOR 2.59, 95% CI 1.26-5.32, p=0.01). Decreased odds of eclampsia diagnosis was associated with age ≥35 (aOR 0.32, 95% CI 0.15-0.67, p=0.002), obesity (aOR 0.44, 95% CI 0.20-0.54, p=0.004), and chronic hypertension (aOR 0.38, 95% CI 0.17-0.86, p=0.02).

Table 1. Characteristics of women with eclampsia (n=116)

Characteristic	n (%) or median (interquartile range)
Timing of first seizure[a]	
Antepartum	79 (68.7)
Intrapartum	9 (7.8)
Postpartum	27 (23.5)
Gestational age at diagnosis, weeks[b]	34.7 (30.4, 39.0)
Number of days postpartum at diagnosis[c]	1.0 (0.0, 8.0)
Number of seizures[d]	1.0 (1.0, 2.0)
Location of first seizure[e]	
Not in a health facility (e.g. home or vehicle)	65 (56.5)
Referring health facility	27 (23.5)
Korle Bu Teaching Hospital	23 (20.0)
Identification of seizure witness[f]	
Family member/non-health professional	62 (55.9)
Health professional	49 (44.1)
Preeclampsia diagnosed prior to seizure	
Yes	15 (12.9)
No	65 (56.0)
Unknown	36 (31.0)

[a]Missing data: n=1
[b]If diagnosed antepartum or intrapartum; missing data: n=67
[c]If diagnosed postpartum; missing data: n=8
[d]Missing data: n=4
[e]Missing data: n=1
[f]Missing data: n=5

Table 2. Demographics and clinical history, by diagnosis

Characteristic	Total (n=1,176)	Eclampsia (n=116)	Preeclampsia (n=1,060)	p-value
Age group, years				**<0.001[a]**
<20	30 (2.6)	11 (9.5)	19 (1.8)	
20-34	803 (68.3)	90 (77.6)	713 (67.3)	
≥35	343 (29.2)	15 (12.9)	328 (30.9)	
Parity category[b]				**0.02[a]**
Nulliparous	376 (32.0)	47 (41.2)	47 (41.2)	
Primiparous	283 (24.1)	32 (28.1)	32 (28.1)	
Multiparous (2-4)	464 (39.5)	30 (26.3)	30 (26.3)	
Grand Multiparity (≥5)	51 (4.3)	5 (4.4)	5 (4.4)	
BMI category[c], kg/m^2				**<0.001[a]**
Underweight (<18.5)	15 (1.3)	4 (3.9)	11 (1.1)	
Normal weight (18.5-24.9)	253 (22.5)	37 (36.3)	216 (21.1)	
Overweight (25-29.9)	287 (25.5)	31 (30.4)	256 (25.0)	
Obese (≥30)	570 (50.7)	30 (29.4)	540 (52.8)	
Marital status[d]				**0.003[a]**
Married	847 (73.1)	68 (59.7)	779 (74.6)	
Cohabitating	35 (3.0)	4 (3.5)	31 (3.0)	
Single/Separated/Widowed/ Divorced	277 (23.9)	42 (36.8)	235 (22.5)	
Insurance status[e]				0.29[a]
No insurance	43 (3.8)	7 (6.2)	36 (3.5)	
Public	1,090 (95.4)	105 (92.9)	985 (95.6)	
Private	10 (0.9)	1 (0.9)	9 (0.9)	
Number of prenatal visits[f]	5.0 (3.0, 7.0)	4.0 (2.0, 7.0)	5.0 (3.0, 7.0)	**0.01[g]**
Comorbid conditions in index pregnancy				
Chronic hypertension	279 (23.7)	7 (6.0)	272 (25.7)	**<0.001[a]**
Diabetes	65 (5.5)	4 (3.5)	61 (5.8)	0.39[a]
Sickle cell disease	33 (2.8)	6 (5.2)	27 (2.6)	0.10[a]
Number of gestations[h]				**0.01[a]**
Singleton	1,086 (94.3)	97 (89.0)	989 (94.8)	
Twins	66 (5.7)	12 (11.0)	54 (5.2)	
Preeclampsia in a prior pregnancy	79 (6.7)	1 (0.9)	78 (7.4)	**0.005[a]**

Data presented as n (%) or median (interquartile range)
[a]Comparisons between eclampsia and preeclampsia groups tested with Chi-Squared or Fisher's Exact Test
[b]Missing data: n=2
[c]Missing data: n=51
[d]Missing data: n=17
[e]Missing data: n=33
[f]Missing data: n=91
[g]Comparisons between eclampsia and preeclampsia groups tested with Wilcoxon Rank Test
[h]Missing data: n=24

Table 3. Clinical factors on presentation and hospital admission, by diagnosis

Characteristic	Total (n=1,176)	Eclampsia (n=116)	Preeclampsia (n=1,060)	p-value
Gestational age at diagnosis, weeks[a]	36.0 (32.6, 38.7)	34.7 (30.4, 39.0)	36.3 (32.7, 38.7)	**0.04**[b]
Systolic BP at diagnosis, mm Hg[b]	168.0 (155.0, 180.0)	170.0 (154.0, 186.0)	167.0 (155.0, 180.0)	0.35[b]
Diastolic BP at diagnosis, mm Hg[c]	108.0 (100.0, 118.0)	110.0 (100.0, 120.0)	107.0 (100.0, 117.0)	0.12[b]
Urine protein at diagnosis[d]				**0.01**[e]
Negative	33 (2.9)	3 (2.7)	30 (2.9)	
Trace	69 (6.0)	8 (7.1)	61 (5.9)	
+1	269 (23.3)	12 (10.7)	257 (24.7)	
+2	398 (34.5)	41 (36.6)	357 (34.3)	
+3	268 (23.2)	31 (27.7)	237 (22.7)	
+4	117 (10.1)	17 (15.2)	100 (9.6)	
AST at diagnosis, units/liter[f]				**<0.001**[e]
≤33	653 (60.4)	41 (40.2)	612 (62.5)	
33-66	295 (27.3)	35 (34.3)	260 (26.6)	
≥66	133 (12.3)	26 (25.5)	107 (10.9)	
ALT at diagnosis, units/liter[g]				**0.002**[e]
≤33	827 (76.4)	64 (62.8)	763 (77.9)	
33-66	159 (14.7)	22 (21.6)	137 (14.0)	
≥66	96 (8.9)	16 (15.7)	80 (8.2)	
Creatinine at diagnosis, mg/dL[h]				**0.05**[e]
≤1.1	941 (88.3)	83 (82.2)	858 (88.9)	
>1.1	125 (11.7)	18 (17.8)	107 (11.1)	
Platelets at diagnosis, x 10^3 µmo[i]i				0.07[e]
<100	67 (6.0)	9 (8.6)	58 (5.8)	
100-149	127 (11.5)	18 (17.1)	109 (10.9)	
≥150	915 (82.5)	78 (74.3)	837 (83.4)	
Presence of symptoms at diagnosis				
Headache[j]	505 (43.4)	60 (54.6)	445 (42.3)	**0.01**[e]
Blurred vision[k]	143 (12.4)	32 (29.6)	111 (10.6)	**<0.001**[e]

Table 3. Clinical factors on presentation and hospital admission, by diagnosis *(continued)*

Characteristic	Total (n=1,176)	Eclampsia (n=116)	Preeclampsia (n=1,060)	p-value
Right upper quadrant or epigastric abdominal pain[l]	136 (11.8)	14 (13.1)	122 (11.7)	0.66[e]
Nausea or vomiting[m]	126 (10.9)	19 (17.4)	107 (10.2)	**0.02**[e]

Data presented as n (%) or median (interquartile range)
[a]Missing data: n=67
[b]Comparisons between eclampsia and preeclampsia groups tested with Wilcoxon Rank Test
[c]Missing data: n=4
[d]Missing data: n=4
[e]Comparisons between eclampsia and preeclampsia groups tested with Chi-Squared or Fisher's Exact Test
[f]Missing data: n=95
[g]Missing data: n=94
[h]Missing data: n=110
[i]Missing data: n=67
[j]Missing data: n=13
[k]Missing data: n=20
[l]Missing data: n=22
[m]Missing data: n=20
Abbreviations: BP, blood pressure; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase

Table 4. Antenatal factors associated with diagnosis of eclampsia versus preeclampsia

Characteristic	Unadjusted Odds Ratio	95% CI	P-value	Adjusted Odds Ratio	95% CI	P-value
Age group, years						
<20	4.59	2.12-9.95	<0.001	2.75	1.10-6.89	**0.03**
20-34	REF	REF	REF	REF	REF	REF
≥35	0.36	0.21-0.64	<0.001	0.32	0.15-0.67	**0.002**
Parous (ref: nulliparous)	0.64	0.43-0.95	0.03	1.29	0.79-2.10	0.32
Married (ref: non-married[a])	0.51	0.34-0.75	0.0008	0.72	0.45-1.17	0.19
BMI category, kg/m^2						
Underweight (<18.5)	2.12	0.64-7.02	0.04	1.85	0.53-6.47	0.33
Normal weight (18.5-24.9)	REF	REF	REF	REF	REF	REF
Overweight (25-29.9)	0.71	0.42-1.18	0.44	0.90	0.52-1.57	0.71
Obese (≥30)	0.32	0.20-0.54	<0.001	0.44	0.25-0.77	**0.004**
Chronic hypertension	0.19	0.09-0.40	<0.001	0.38	0.17-0.86	**0.02**
Twin gestation (ref: singleton)	2.27	1.17-4.38	0.02	2.59	1.26-5.32	**0.01**
Preeclampsia in a prior pregnancy	0.11	0.02-0.79	0.03	0.21	0.03-1.55	0.13

[a]Non-married is defined as single or separated or widowed or divorced or cohabitating

Discussion

Our study provides important epidemiologic data on the timing of eclampsia occurrence. We demonstrate that the majority of eclamptic patients experienced their first seizure antepartum, in a location outside a health facility, and witnessed by a family member. This is consistent with the literature in contemporary low-resource settings and high-income settings in the past, which demonstrates high rates of antepartum diagnosis of eclampsia, with a substantial proportion of seizures occurring outside of healthcare settings. A 2005 UK study demonstrated that 21% of women had their first seizure at home [5], and a 2000

U.S. study found that 82% of first seizures occurred at home [12]. In a prospective study of women with eclampsia in Tanzania, 71% of seizures occurred at home [15]. In these studies, rates of seizures occurring antepartum ranged from 45-53% [5,12,15]. Mean gestational age at diagnosis was 34.2 weeks in the UK [5] and 35 weeks in Tanzania [15]. Of seizures occurring postpartum, most occurred within 48 hours of delivery, but ranged from 0 to 13 days postpartum [12,15]. In our study, only 12.9% of women were diagnosed with preeclampsia prior to the development of a seizure. This is comparable to a case control study in Tanzania [9], in which less than half of eclamptics were identified as high-risk; a prospective study in Tanzania [15], in which only 9% were diagnosed with preeclampsia prior to seizure; and a nationwide study in the UK [5], in which 38% of eclamptics had known hypertension and proteinuria in the week prior to their seizure. In a U.S. study of 53 eclamptics over 12 years, only nine cases were felt to be potentially preventable, and in 60% of women, their seizure was the first sign of a hypertensive disorder of pregnancy. Especially in LMICs, high rates of seizures outside of healthcare settings and low rates of preeclampsia diagnosed prior to onset of seizures suggest a need for improved models of antenatal screening, risk stratification, and monitoring. Additional research is needed to understand if women who developed seizure at home could benefit from counseling on symptoms of hypertensive disorders of pregnancy, more frequent antenatal care in the third trimester, or utilization of home blood pressure monitoring.

We describe the clinical presentation of women who are admitted with eclampsia and compare it to women with preeclampsia. The maximum blood pressures experienced by women with eclampsia in our study are consistent with a retrospective case series of patients with eclampsia in U.S. hospitals (1987-1999), demonstrating a maximum blood pressure of 228/136 mm Hg [12]. Our population of women with eclampsia had a higher frequency of proteinuria and a lower frequency of severe thrombocytopenia compared to the U.S. study, in which 49% of women with eclampsia had proteinuria, 19% had ALT or AST elevated to twice the normal value, and 27% had platelets <100 x 10^3 µmol [12]. Women with preeclampsia in Canada, New Zealand, Australia, and the UK demonstrate that predictors of adverse maternal outcomes include lower platelet count, higher AST levels, and higher blood pressure [16]. However, when examining predictors of a diagnosis of eclampsia, a prospective observational study in Tanzania demonstrates that elevated blood pressure and proteinuria are poor predictors of eclampsia [15]. Our findings demonstrate that a diagnosis of eclampsia is associated with a higher proportion of severe elevations in ALT, AST, and creatinine, but no significant difference in severe thrombocytopenia. Importantly, in our study, laboratory values were drawn on hospital admission and the vast majority of women with eclampsia experienced a seizure prior to admission; thus, we cannot determine if laboratory abnormalities are a precursor of more severe disease or a consequence of the seizure itself.

Compared to women with preeclampsia, we demonstrate that risk factors for the development of eclampsia include age <20 years and twin pregnancy.

Conversely, advanced maternal age, obesity, and chronic hypertension were associated with lower odds of eclampsia. Most existing literature on eclampsia compares risk factors between pregnancies complicated by eclampsia and uncomplicated pregnancies, with risk factors for eclampsia including multiple gestation, primiparity, younger age, and elevated BMI [8]. Few studies have tried to understand risk factors for more severe disease among women with hypertensive disorders of pregnancy. The study of women with preeclampsia in Canada, New Zealand, Australia, and the UK demonstrated that predictors of adverse maternal outcomes among women with hypertensive disorders of pregnancy include earlier gestational age at diagnosis, nulliparity, and cigarette smoking [16]. In our study, by comparing women with eclampsia to those with preeclampsia with severe features, two interesting, phenotypically distinct risk profiles emerged—even though the blood pressures were not different between the two groups. A diagnosis of preeclampsia with severe features was associated with advanced maternal age, obesity, and chronic hypertension—suggestive of preexisting maternal endothelial dysfunction with an abnormal metabolic profile as the etiology of hypertensive disorders in this population. Conversely, a diagnosis of eclampsia was associated with younger age and twin gestation. Our observation that the blood pressure profiles were similar between groups may suggest that blood pressure level, per se, may not be a direct correlate of eclampsia in this cohort, but rather that primary placental dysfunction may underly the etiology of hypertensive disorders in the women who developed eclampsia. This dichotomy in risk factor profiles between preeclampsia with severe features and eclampsia counters the theory that hypertensive disorders of pregnancy exist on a single continuum.

Strengths of our study include prospective data collection in a large sample of women with hypertensive disorders of pregnancy, including 116 women with eclampsia. We add to the existing literature by exploring the predictiveness of risk factors among women with the most complicated hypertensive disorders of pregnancy in our comparison of women with preeclampsia with severe features and those with eclampsia. Limitations include the timing of data collection; laboratory evaluation and assessment of symptoms were done on hospital admission, but the vast majority of women with eclampsia experienced a seizure prior to admission. Thus, we are unable to determine if the greater degree of neurologic symptoms and laboratory abnormalities experienced by women with eclampsia is predictive of eclampsia or a consequence of the seizures. Despite this limitation, our results provide important insight into the typical clinical presentation of patients with eclampsia, including expected blood pressure ranges, laboratory values, and symptoms. Additional limitations include data collection at a single study site at a tertiary care center, which may limit generalizability of findings. Finally, data in this paper was collected as part of a randomized control trial comparing two durations of magnesium sulfate in seizure prophylaxis. However, since the data presented here was collected prior to randomization and administration of magnesium sulfate, it is unlikely that results were affected.

Conclusion

Among 116 women with eclampsia, we demonstrate that the majority experienced their first seizure antepartum and in a location outside a health facility. An evaluation of antenatal factors demonstrated that younger age and twin pregnancy were associated with increased odds of eclampsia, while older age, obesity, and chronic hypertension were associated with lower odds of eclampsia. Future studies should explore the epigenetics of eclampsia and preeclampsia with severe features to help unravel the unique etiologies of these apparently distinct disease entities. Understanding the predictiveness of antenatal factors in the development of preeclampsia versus eclampsia is important to guide monitoring and management decisions, make informed decisions about antenatal monitoring, enhance patient counseling, focus limited resources, and ultimately improve patient outcomes.

Contributors:

Titus Beyuo: I declare that I participated in the conceptualization, study protocol development, data collection and management, data interpretation, and manuscript editing and review for this study and that I have seen and approved the final version of the manuscript. I have no conflicts of interest.

Emma R. Lawrence: I declare that I participated in the study protocol development, data collection and management, data interpretation, and manuscript editing and review for this study and that I have seen and approved the final version of the manuscript. I have no conflicts of interest.

Emily K. Kobernik: I declare that I participated in the data analysis, data interpretation, and manuscript editing and review for this study and that I have seen and approved the final version of the manuscript. I have no conflicts of interest.

Samuel Oppong: I declare that I participated in the conceptualization, study protocol development, data collection and management, data interpretation, and manuscript editing and review for this study and that I have seen and approved the final version of the manuscript. I have no conflicts of interest.

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A Comparative Analysis of Neonatal Outcomes in Pregnancies Complicated by Preeclampsia and Eclampsia in Ghana

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Keywords: Eclampsia, preeclampsia, neonatal outcome, LMIC, Ghana

Synopsis: Pregnancies complicated by eclampsia were twice as likely to have poor neonatal outcomes compared with preeclampsia, even after controlling for gestational age.

Authorship statement

I designed the study, performed data management, conducted the data analysis, wrote the first draft of the manuscript, and implemented the contribution of the co-authors and external reviewers up to final publication. During the whole process I asked for and implemented input and feedback from the other contributors to this study

ABSTRACT

Objective

To describe and compare neonatal outcomes in pregnancies complicated by preeclampsia with severe features and eclampsia.

Methods

This is a secondary analysis of data collected as part of a randomized controlled trial at the Korle Bu Teaching Hospital in Ghana. Participants were adult pregnant women with preeclampsia with severe features or eclampsia. Data includes prospectively collected medical and obstetric history, intrapartum events, and neonatal outcomes.

Results

Median gestational age at delivery was 36.6 weeks (IQR 33.3-38.9). Median birthweight was 2.3kg (IQR 1.6, 3.0), with 227 (19.0%) birthweights <1500g. One hundred sixty-one neonates (15.4%) had an APGAR score <7 at 5 minutes and 147 (12.1%) were stillbirths. Of livebirths, half (n=522, 50.2%) were admitted to the NICU and 7.3% (n=89) died prior to discharge. A composite of poor neonatal outcomes was experienced by 57.9% (n=704) of babies and was twice as likely with a maternal diagnosis of eclampsia (OR 1.91, p=0.04). For each increasing week of gestational age, the probability of a poor neonatal outcome was reduced by 39% (OR 0.61, p<0.0001).

Conclusion

Preeclampsia with severe features and eclampsia are associated with poor neonatal outcomes. Pregnancies complicated by eclampsia were twice as likely to have poor neonatal outcomes.

Introduction

Worldwide, hypertensive disorders of pregnancy are a serious complication of pregnancy that contribute to poor maternal and neonatal outcomes [1-4]. The incidence of preeclampsia and eclampsia is higher in low- and middle-income countries (LMIC) [3], where associated morbidities are also more significant [3,5]. Global estimates of rates of eclampsia range from 0.1% in Europe to up to 4% in sub-Saharan Africa [2,6]. Fatality rates of eclampsia similarly varies widely, from 0-2% in high-income countries to 18% in low-income countries [7]. In Ghana, where this study was conducted, incidence of hypertensive disorders of pregnancy is estimated at 7.6% [8,9], and institutional reports from two major tertiary-level hospitals suggest hypertensive disorders have overtaken hemorrhage as the leading cause of maternal mortality [8].

Pregnancies complicated by preeclampsia and eclampsia are prone to poor neonatal outcomes due to preterm delivery, impaired uteroplacental perfusion, and maternal-fetal hypoxia during seizures. In LMIC, capacity for neonatal support is limited, increasing morbidity and mortality for vulnerable neonates [6]. Previous studies have reported high rates of stillbirth, neonatal death, low birthweight, and Neonatal Intensive Care Unit (NICU) admission in pregnancies complicated by preeclampsia and eclampsia [6,10-12]. Some studies suggest that these poor neonatal outcomes can be explained by preterm gestational age alone [1], while others find persistent differences compared to uncomplicated pregnancies even when controlling for gestational age and birthweight [12,13].

Few studies have explored differences in neonatal outcomes between pregnancies complicated by preeclampsia and eclampsia [1,10,12]. The most significant consequences of hypertensive disorders of pregnancy are seen in sub-Saharan Africa, where neonatal outcomes have not been fully described. Understanding relationships between maternal disease severity and neonatal outcomes will guide patient counseling and allow targeting of limited resources to the most at-risk neonates. Therefore, our study aims to describe and compare neonatal outcomes in pregnancies complicated by preeclampsia with severe features and eclampsia at the Korle Bu Teaching Hospital in Ghana.

Materials and Methods

This is a secondary analysis of data collected as part of a randomized controlled trial evaluating the impact of magnesium sulfate regimens on maternal seizure rate among women with preeclampsia with severe features and eclampsia [14]. Ethical approval was granted by the Scientific and Technical Committee of the Korle Bu Teaching Hospital (KBTH-IRB 00096/2018) and the University of Michigan Institutional Review Board (HUM00139104).

The study site was the Korle Bu Teaching Hospital (KBTH), Ghana's largest tertiary care hospital located in the capital city of Accra. Study participants were adult pregnant women admitted to KBTH with a diagnosis of preeclampsia with severe features or eclampsia [15]. Written informed consent was obtained for all participants.

Data collection was carried out between October 2018 and November 2020. Data, including past medical and obstetric history, was extracted from participants' medical records. During their intrapartum hospitalization, clinical information was prospectively collected, including mode and timing of delivery, gestational age at delivery, birthweight, delivery outcome, NICU admission, APGAR score, and status at discharge. All babies were followed through discharge from the hospital.

Our primary outcome was a composite of poor neonatal outcomes, defined as one or more of the following: stillbirth, very low birthweight <1500g, 5-minute APGAR score <7, NICU admission, or a livebirth with a subsequent death before discharge. Secondary outcomes included the individual components of the primary outcome composite.

Analysis was done using SAS 9.4 (SAS Institute Inc., Cary, N.C). A composite of poor neonatal outcomes was created, as defined above. Normality of all continuous variables was determined by assessing skewness and kurtosis, and the Shapiro-Wilk test. Demographic and obstetric characteristics were described for the total population, using median (interquartile range) and proportions. Bivariate analysis was performed to compare demographic and obstetric history characteristics between women with a diagnosis of preeclampsia with severe features and eclampsia, using Wilcoxon Rank test, Chi-square, and Fisher's exact test where appropriate. Next, neonatal outcomes were described for the total population and compared across maternal diagnosis of preeclampsia with severe features versus eclampsia. To account for multiple gestations, the denominator for neonatal variables was all births.

Bivariate analysis was performed to identify potential predictors of the composite of poor neonatal outcomes. Factors significant in bivariate analysis and other clinically relevant factors were considered candidates for inclusion in a multivariable logistic regression model. Separate models were run for the composite poor neonatal outcome, and then for each of the four elements of the composite. Models were adjusted for age and parity. To examine the relationship between poor neonatal outcomes across gestational age, we reported the results of the logistic regression models as predicted probabilities. All calculated p-values were two-sided and a p-value <0.05 was considered statistically significant.

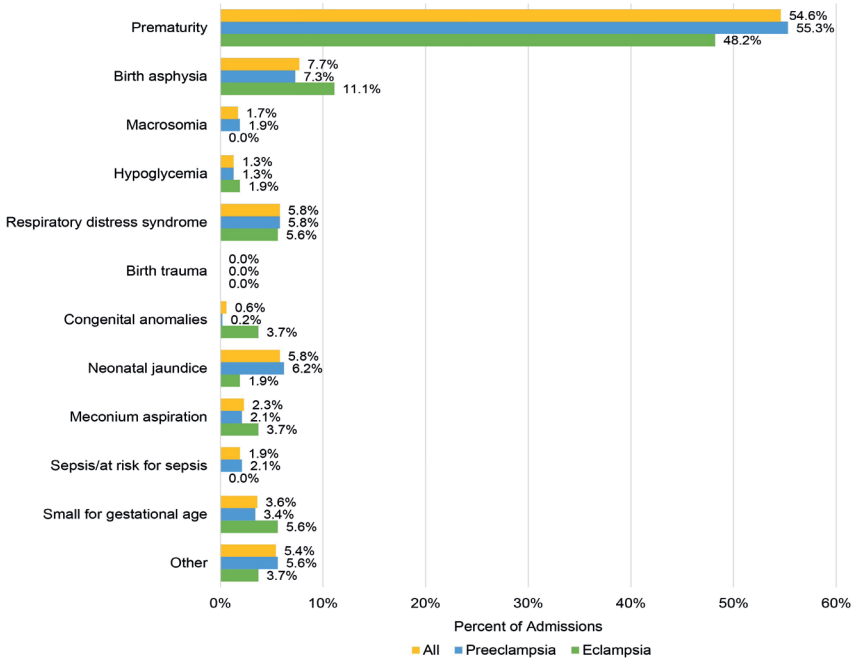

Figure 1. Reasons for Neonatal Intensive Care Unit Admission

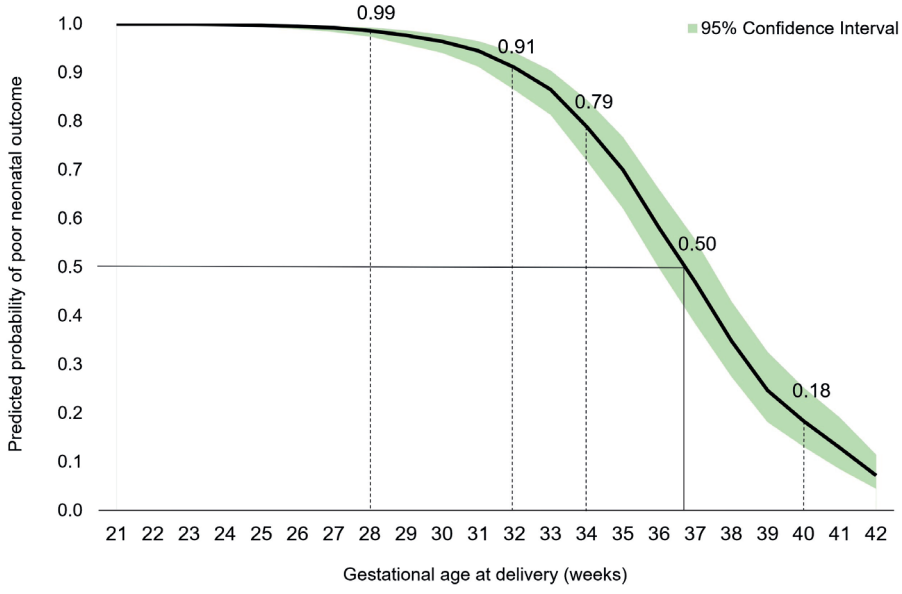

Figure 2. Probability of Poor Neonatal Outcome by Gestational Age

Table 1. Patient Characteristics by Maternal Diagnosis of Preeclampsia and Eclampsia

Characteristic	Total (n=1176)	Preeclampsia (n=1060)	Eclampsia (n=116)	p-value
Age, year[a]	31.0 (27.0, 35.0)	31.0 (27.0, 36.0)	27.0 (23.0, 33.0)	**<0.001**[b]
Age, group				**<0.001**
<20	30 (2.6)	19 (1.8)	11 (9.5)	
21-34	803 (68.3)	713 (67.3)	90 (77.6)	
≥35	343 (29.2)	328 (30.9)	15 (12.9)	
Parity, number[a]	1.0 (0.0, 2.0)	1.0 (0.0, 3.0)	1.0 (0.0, 2.0)	**0.006**[b]
Parity, group				**0.02**
Nulliparous	376 (32.0)	329 (31.0)	47 (41.2)	
Primiparous	283 (24.1)	251 (23.7)	32 (28.1)	
Multiparous (2-4)	464 (39.5)	434 (40.9)	30 (26.3)	
Grand Multiparity (5+)	51 (4.3)	46 (4.3)	5 (4.4)	
Pre-pregnancy BMI, kg/m^2 [a]	30.1 (25.3, 35.6)	30.6 (25.7, 35.9)	26.5 (23.3, 31.6)	**<0.001**[b]
Chronic hypertension	279 (32.7)	272 (25.7)	7 (6.0)	**<0.001**
Mode of delivery				0.75
Vaginal delivery	386 (33.5)	350 (33.6)	36 (32.1)	
Cesarean section	767 (66.5)	691 (66.4)	76 (67.9)	
Number of gestation				**0.01**
Singleton	1,086 (94.3)	989 (94.8)	97 (89.0)	
Twins	66 (5.7)	54 (5.2)	12 (11.0)	

Denominator is all pregnancies, n=1176
Data presented as n (%) and compared with chi-squared test unless otherwise specified
[a]Data presented as median (interquartile range)
[b]Comparisons between preeclampsia with severe features and eclampsia tested using Wilcoxon Rank test
[c]Comparisons between preeclampsia with severe features and eclampsia tested using Fisher's exact test

Results

Among 1176 total participants, median age was 31.0 years and 29.2% (n=343) were of advanced maternal age, defined as age 35 or older (Table 1). Median parity was 1.0, with 376 (32.0%) nulliparous and 46 (4.3%) grand multiparous women. Regarding relevant medical history, median pre-pregnancy BMI was 30.1 and 32.7% (n=279) had a diagnosis of chronic hypertension. The majority of pregnancies were singletons (n=1086, 94.3%) and two-thirds were delivered by cesarean section (n=767, 66.4%). Of total participants, 1060 (90.1%) had a diagnosis of preeclampsia with severe features and 116 (9.9%) had eclampsia. Participants with eclampsia were younger, more likely to be nulliparous, had lower BMI, were less likely to have chronic hypertension, and were more likely to have twins compared to participants with preeclampsia.

There were 1218 babies born to the 1176 women in our study (Table 2). Median gestational age at delivery was 36.6 weeks and 12.1% (n=147) were stillbirths. Median birthweight was 2.3kg, with 19.0% (n=227) of babies having a birthweight <1500g. Among livebirths, median APGAR score at 1 and 5 minutes were 7.0 and 8.0 respectively, and half (n=522, 50.2%) were admitted to the NICU. The most common reasons for NICU admission were prematurity (n=285, 54.6%) and birth asphyxia (n=40, 7.7%) (Figure 1). Of babies admitted to the NICU, median length of stay was 8.0 days. Of all babies born alive, 7.3% (n=89) died prior to discharge, with a median survival of 2.0 days (Table 2). Overall, 79.6% (n=917) babies were alive at time of discharge and 20.4% (n=235) were either a stillbirth or died between delivery and discharge. The composite of poor neonatal outcomes was experienced by 57.9% (n=704) of all babies. Of total participants, 1097 babies were born to mothers with preeclampsia with severe features and 121 babies were born to mothers with eclampsia. Babies born to women with eclampsia more often experienced stillbirth, lower APGAR score at 1 and 5 minutes, and higher rate of NICU admission, and a higher proportion experienced the poor neonatal outcome composite.

Table 3 demonstrates unadjusted and adjusted odds ratios for the impact of a diagnosis of eclampsia on the composite poor neonatal outcome and each element of the composite. Compared to preeclampsia, babies born from a pregnancy complicated by eclampsia had approximately twice the odds of a poor neonatal outcome (aOR: 1.91, 95% CI 1.03-3.54, p=0.04). For each increasing week of gestational age, the chance of a poor neonatal outcome was reduced by 39% (OR 0.61, p<0.001). Figure 2 demonstrates probabilities of the poor neonatal outcome composite by gestational age, with progressively improved outcomes with increasing gestational age. The probability of a poor neonatal outcome was 99% at 28 weeks, 79% at 34 weeks, and 18% at 40 weeks, with a 50% chance of a poor neonatal outcome at 36.7 weeks. BMI and mode of delivery were not significant predictors of the composite poor neonatal outcome in this population of women.

Table 4 demonstrates adjusted odds ratios for all variables significantly associated with the composite poor neonatal outcome and each element of the composite, including maternal diagnosis (preeclampsia versus eclampsia), BMI, mode of delivery, and gestational age. Variables significantly associated with at least one secondary outcome are described below.

Maternal diagnosis: Of the four individual elements of the composite, eclampsia was associated only with 5-minute Apgar <7 (OR 1.81, p=0.03).

Gestational age at delivery: Among all pregnancies, for every 1-week increase in gestational age, there was a significant decrease in chance of stillbirth (OR 0.77, p<0.001); birthweight <1500g (OR 0.43, p<0.001); 5-minute APGAR <7 (OR 0.77, p<0.001); NICU admission (OR 0.82, p<0.001); and livebirth with a subsequent death before discharge (OR 0.76, p<0.001).

Table 2. Neonatal Outcomes by Maternal Diagnosis of Preeclampsia and Eclampsia

Characteristic	Total (n=1218)	Preeclampsia (n=1097)	Eclampsia (n=121)	p-value
Gestational age at delivery, weeks[a]	36.6 (33.3-38.9)	36.6 (33.4-38.9)	35.3 (32.0-39.1)	0.25[b]
Gestational age at delivery, group				0.18
<32.0 weeks	197 (16.7)	172 (16.0)	25 (22.9)	
32.0-37.0 weeks	431 (36.4)	394 (36.7)	37 (33.9)	
≥37.0 weeks	555 (46.9)	508 (47.3)	47 (43.1)	
Outcome of delivery				**0.05**
Livebirth	1,964 (87.9)	966 (88.5)	98 (82.4)	
Stillbirth	147 (12.1)	126 (11.5)	21 (17.7)	
Birthweight, grams[a]	2.3 (1.6-3.0)	2.3 (1.6-3.0)	2.1 (1.5-2.9)	0.19[b]
Birthweight, group				0.38
<1500g	227 (19.0)	200 (18.5)	27 (23.9)	
1500–2499g	425 (35.6)	388 (35.9)	37 (32.7)	
≥ 2500g	542 (45.4)	493 (45.6)	49 (43.4)	
1-minute APGAR, score[a,d]	7.0 (6.0-8.0)	7.0 (6.0-8.0)	7.0 (5.0-7.0)	**0.002[b]**
5-minute APGAR, score[a,d]	8.0 (7.0-9.0)	8.0 (7.0-9.0)	8.0 (7.0-8.0)	**0.01[b]**
5-minute APGAR, group[d]				0.13[c]
≤3	21 (2.0)	20 (2.1)	1 (1.1)	
4-6	140 (13.4)	122 (12.7)	18 (20.2)	
≥7	886 (84.6)	816 (85.2)	70 (78.7)	
NICU admission[d]				
Yes	522 (50.2)	468 (49.3)	54 (60.0)	**0.05**
No	518 (49.8)	482 (50.7)	36 (40.0)	
Duration of NICU admission, days[a,e]	8.0 (3.0-15.0)	8.0 (3.0-15.0)	9.0 (4.0-15.0)	0.31[b]
Livebirth with a subsequent death before discharge[d]	89 (7.3)	79 (7.2)	10 (8.3)	0.67
Length of inpatient survival, days[a,f]	2.0 (1.0-5.0)	2.0 (1.5-5.0)	3.0 (1.0-6.5)	0.92[b]
Status of baby at discharge				0.06
Alive	917 (79.6)	837 (80.3)	80 (72.7)	
Dead	235 (20.4)	205 (19.7)	30 (27.3)	
Composite of poor neonatal outcomes				**0.002**
Yes	704 (57.9)	618 (56.4)	86 (71.1)	

Table 2. Neonatal Outcomes by Maternal Diagnosis of Preeclampsia and Eclampsia *(continued)*

Characteristic	Total (n=1218)	Preeclampsia (n=1097)	Eclampsia (n=121)	p-value
No	512 (42.1)	477 (43.6)	35 (28.9)	

Denominator is all babies to account for multiple gestations, n=1218
Data presented as n (%) and compared with chi-squared test unless otherwise specified
[a]Data presented as median (interquartile range)
[b]Comparisons between preeclampsia with severe features and eclampsia tested using Wilcoxon Rank test.
[c]Comparisons between preeclampsia with severe features and eclampsia tested using Fisher's exact test
[d]Among liveborn infants
[e]Among liveborn infants admitted to the NICU
[f]Among liveborn infants who die prior to discharge
NICU: Neonatal intensive care unit

Table 3. Impact of Maternal Diagnosis of Eclampsia (Versus Preeclampsia) on Neonatal Outcomes

Neonatal Outcome	Unadjusted Odds Ratio	Adjusted Odds Ratio	95% Confidence Interval	p-value
Composite poor neonatal outcome	1.91	1.91	1.03-3.54	**0.04**
Stillbirth	1.56	1.57	0.78-3.17	0.21
Birthweight <1500g	1.51	0.85	0.33-2.18	0.74
5-minute APGAR <7	1.88	1.81	1.05-3.14	**0.03**
NICU admission	1.47	1.13	0.67-1.90	0.66
Livebirth with a subsequent death before discharge	1.15	0.61	0.23-1.63	0.32

All models adjusted for age, parity, body mass index, mode of delivery, and gestational age at delivery
NICU: Neonatal intensive care unit

Table 4. Clinical Predictors of Poor Neonatal Outcomes

Predictor	Adjusted Odds Ratio	95% Confidence Interval	p-value
Composite of poor neonatal outcomes			
Eclampsia (compared with preeclampsia)	1.91	1.03-3.54	0.04
Gestational age at delivery, weeks	0.61	0.57-0.65	**<0.001**

Table 4. Clinical Predictors of Poor Neonatal Outcomes *(continued)*

Predictor	Adjusted Odds Ratio	95% Confidence Interval	p-value
Cesarean section (compared with vaginal)	1.13	0.81-1.57	0.48
Pre-pregnancy BMI, kg/m^2	0.99	0.97-1.01	0.26
Stillbirth			
Eclampsia (compared with preeclampsia)	1.57	0.78-3.17	0.21
Gestational age at delivery, weeks	0.77	0.73-0.81	**<0.001**
Cesarean section (compared with vaginal)	0.18	0.11-0.27	<0.001
Pre-pregnancy BMI, kg/m^2	0.99	0.96-1.02	0.49
Birthweight <1500g			
Eclampsia (compared with preeclampsia)	0.85	0.33-2.18	0.74
Gestational age at delivery, weeks	0.43	0.38-0.48	**<0.001**
Cesarean section (compared with vaginal)	0.75	0.39-1.43	0.38
Pre-pregnancy BMI, kg/m^2	0.96	0.92-0.99	**0.02**
5-Minute APGAR <7			
Eclampsia (compared with preeclampsia)	1.81	1.05-3.14	**0.03**
Gestational age at delivery, weeks	0.77	0.74-0.80	**<0.001**
Cesarean section (compared with vaginal)	0.47	0.33-0.66	**<0.001**
Pre-pregnancy BMI, kg/m^2	0.98	0.96-1.01	0.11
NICU admission			
Eclampsia (compared with preeclampsia)	1.13	0.67-1.90	0.66
Gestational age at delivery, weeks	0.82	0.79-0.85	**<0.001**
Cesarean section (compared with vaginal)	3.81	2.76-5.26	**<0.001**
Pre-pregnancy BMI, kg/m^2	0.99	0.97-1.01	0.24
Livebirth with a subsequent death before discharge			
Eclampsia (compared with preeclampsia)	0.61	0.23-1.63	0.32

Table 4. Clinical Predictors of Poor Neonatal Outcomes *(continued)*

Predictor	Adjusted Odds Ratio	95% Confidence Interval	p-value
Gestational age at delivery, weeks	0.76	0.71-0.81	**<0.001**
Cesarean section (compared with vaginal)	4.15	1.96-8.77	**<0.001**
Pre-pregnancy BMI, kg/m^2	1.00	0.97-1.03	0.95

All models adjusted for age and parity
NICU: Neonatal intensive care unit

Mode of delivery: Compared to vaginal delivery, cesarean section was associated with decreased stillbirth (OR 0.18, p<0.001) and a decreased 5-minute APGAR <7 (OR 0.47, p<0.001), but was associated with a 4-fold increase in NICU admission (OR 3.81, p<0.001) and a 4-fold increased odds of livebirth with a subsequent death before discharge (OR 4.15, p<0.001). Mode of delivery was not significantly associated with birthweight <1500g.

Pre-pregnancy BMI: Higher BMI was associated with a decreased risk of birthweight <1500g (OR 0.96, p=0.02). This is likely driven by a higher proportion of very low BMI <18.5 in the poor outcome group. BMI was not a significant predictor of stillbirth, 5-minute APGAR <7, NICU admission, or livebirth with a subsequent death before discharge.

Discussion

This study of women delivering at a tertiary hospital in Ghana highlights the fact that poor neonatal outcomes are common in pregnancies complicated by preeclampsia and eclampsia. In our population of 1218 babies born to women with preeclampsia with severe features or eclampsia, poor neonatal outcomes were experienced by more than half of all babies, and poor outcomes were twice as likely in women with a diagnosis of eclampsia compared with preeclampsia. For every 1-week increase in gestational age at delivery after 24 weeks, there was a significant decrease in chance of stillbirth, birthweight <1500g, 5-minute APGAR <7, NICU admission, and livebirth with a subsequent death before discharge, as well as in the composite of poor neonatal outcomes. These findings are consistent with prior studies that demonstrate an association between hypertensive disorders of pregnancy and preterm delivery, stillbirth, low birthweight, and neonatal death [3,6,12,13].

In our study, even after controlling for gestational age, pregnancies complicated by eclampsia were 1.9 times more likely to experience a poor neonatal outcome. A small study in Ecuador compared mild preeclampsia cases to severe cases and found lower

APGAR scores and more preterm births, low birthweight infants, and NICU admissions in severe cases [10]. These findings were consistent with two American studies in 2000 and 2002 [16,17] and a 2005 Turkish study comparing severe preeclampsia to both mild preeclampsia and chronic hypertension [18]. However, a 1999 comparison of severe preeclampsia and hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome concluded that increased neonatal morbidity and mortality associated with HELLP syndrome were likely fully explained by differences in gestational age alone [1].

High rates of prematurity and low APGAR scores—and subsequent need for neonatal resuscitation and support—highlight the importance of facility delivery attended by trained providers. In our study, 47% of babies were born preterm (<37 weeks) and 17% before 32 weeks gestation. Of all livebirths, 50% were admitted to the NICU for a higher level of care, suggesting that delivery at a tertiary care facility with NICU capabilities may be lifesaving. In babies born to eclamptic mothers, despite lower 5-minute APGAR scores, rates of livebirth with a subsequent death before discharge were equivalent to their preeclamptic counterparts. This suggests that poor neonatal outcomes seen in LMICs may be partially mitigated by tertiary-level NICU care as is provided by KBTH in our study. This is supported by the findings of the multi-country analysis of Demographic and Health Survey data, which suggests that eclampsia is associated with increased risk of early neonatal mortality, but neonatal mortality decreased with facility delivery [11]. In a series of eclamptic patients in Egypt, prematurity and poor neonatal services were cited as the most common etiology of perinatal death [6].

Regarding mode of delivery, we demonstrate an interesting, complicated relationship with neonatal outcomes. Compared to vaginal delivery, cesarean section is associated with 82% lower risk of stillbirth and 53% lower risk of 5-minute APGAR <7. However, cesarean section is conversely associated with a 4-fold increase in both NICU admission and livebirth with a subsequent death before discharge. This suggests that cesarean section may prevent intrapartum demise, but contribute to NICU admission of clinically tenuous neonates who often die in the NICU. Additional research is needed to further explore this relationship.

This study has a number of strengths. First, our study involved a large population of babies born to pregnancies complicated by preeclampsia with severe features and eclampsia in an LMIC setting. We include key detailed clinical data from antenatal care, throughout intrapartum admission, and until discharge of babies. We also calculate a composite of poor neonatal outcomes, which may be a more clinically beneficial indicator of health status than a single component of the composite. Additionally, the study was conducted at a very busy tertiary obstetric care center that is supported by a level three neonatal intensive care facility and has high rates of hypertensive disorders of pregnancy and maternal complications. This allowed us a unique opportunity to study a substantial group of pregnancies complicated by eclampsia and varied neonatal outcomes. Despite these strengths, we recognize that generalization of our results may be limited due to

our data collection at a single tertiary site in Ghana. In addition, neonatal outcomes were only collected through hospital discharge, with a median of eight days of follow-up post-delivery. Finally, this paper is a secondary analysis of data collected as part of a randomized controlled trial comparing rates of seizures between two durations of magnesium sulfate. There is a potential that different durations of exposure to magnesium sulfate may impact the results presented in this study; however, this is unlikely given universal exposure to magnesium sulfate. An analysis of neonatal outcomes stratified by exposure to magnesium sulfate regimens, which demonstrated no clinically significant differences, will be described elsewhere. The interpretation of our results must be made within the context of these limitations.

Our study explores neonatal outcomes in pregnancies complicated by preeclampsia with severe features and eclampsia in sub-Saharan Africa, where pregnancy complications are high. We demonstrate very high rates of poor neonatal outcomes. Worse neonatal outcomes among eclamptic patients are driven by low APGAR scores, with similar rates of survival at time of hospital discharge, suggesting that capacity for neonatal resuscitation at the study site was lifesaving. Our calculation of predicted probabilities of poor neonatal outcomes based on gestational age can be used to guide selection of personnel and equipment needed at high-risk deliveries and referral of antepartum patients to higher-level facilities. Recognizing that hypertensive disorders of pregnancy are common, maternal status can rapidly worsen, and transfer from rural locations may not be timely, our high demonstrated rate of poor neonatal outcomes highlights the need for capacity building for neonatal resuscitation at district hospitals and health centers. Understanding predictors of poor neonatal outcomes allows LMIC health systems and health centers to allocate limited resources and personnel to care for the highest-risk neonates. Additional studies are needed to assess long-term survival, growth, and development outcomes among babies born to pregnancies complicated by preeclampsia and eclampsia.

Author contributions: The study was conceptualized by TB and SAO. The study protocol was developed by TB, SOA, ERL, and CAM. Data collection was managed by TB, SOA, and ERL. Data analysis was performed by EKK. Data interpretation was performed by all authors. All authors edited, reviewed, and approved this manuscript. All authors have directly accessed and verified the underlying data reported in the manuscript.

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6

Impact of Antenatal Care on Maternal and Neonatal Outcomes in Pregnancies Complicated by Preeclampsia and Eclampsia in Ghana

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Authorship statement

I designed the study, performed data management, conducted the data analysis, wrote the first draft of the manuscript, and implemented the contribution of the co-authors and external reviewers up to final publication. During the whole process I asked for and implemented input and feedback from the other contributors to this study

Abstract

Background

Poor outcomes associated with hypertensive disorders of pregnancy can be reduced with early identification. Our study explores how aspects of antenatal care, including timing, frequency, and type of facility and provider, is associated with clinical outcomes in pregnancies complicated by preeclampsia and eclampsia.

Methods

This secondary analysis was nested in a randomized control trial. Participants were adult pregnant women with preeclampsia or eclampsia at a tertiary hospital in Ghana. Measures of antenatal care utilization included timing of first visit, number of total visits, facility type, provider type, and referral status. Based on World Health Organization recommendations, pregnancies were categorized by ≥ four visits, ≥ eight visits, and adequate visits for gestational age at delivery. Outcomes were a composite of maternal complications and a composite of poor neonatal outcomes. Multivariate logistic regressions identified associations with antenatal care factors.

Results

Among 1176 participants, antenatal care was initiated at a median of 16.0 weeks gestation (IQR 11.7-21.0). The median number of antenatal visits was 5.0 (IQR 3.0-7.0), with 72.9% attending ≥ four visits, 19.4% attending ≥ eight visits, and 54.9% attending World Health Organization-defined adequate visits. Care was most frequently provided in a government polyclinic (n=522, 47.2%) and by a midwife (n=704, 65.1%). The odds of the composite maternal complications were lower in women who received antenatal care at a tertiary level hospital (aOR 0.47, $p = 0.01$). The odds of poor neonatal outcome were lower in women who received antenatal care at a tertiary level hospital (aOR 0.56, $p < 0.001$), by a specialist Obstetrician/Gynecologist (aOR 0.58, $p < 0.001$), and who attended ≥ eight visits (aOR 0.67, $p = 0.04$). Compared to attendants, referrals had twice the odds of a maternal complication (aOR 2.12, $p = 0.007$) and poor neonatal outcome (aOR 1.68, $p = 0.002$).

Conclusions

Fewer complications are seen in Ghanaian women with preeclampsia and eclampsia who receive antenatal care at tertiary facilities. Attending eight or more antenatal visits reduced the odds of poor neonatal outcomes, however, did not impact serious maternal complications. Quality of antenatal care is essential, not just quantity.

Keywords

Antenatal care; prenatal care; hypertensive disorders of pregnancy; pregnancy induced hypertension; preeclampsia; eclampsia; Africa; LMIC

Background

Hypertensive disorders of pregnancy (HDP) include gestational hypertension, preeclampsia, and eclampsia, and complicate 10% of pregnancies worldwide.(1–3) Failure to timely identify and manage HDP can lead to significant maternal morbidity, including seizure, stroke, acute kidney injury, and death.(4) In low- and middle income countries (LMIC), HDP account for 10-15% of maternal deaths.(1,2) Due to an increasing burden of comorbid medical conditions in reproductive age women and the greater complexity of managing HDP, hypertensive disorders have overtaken postpartum hemorrhage as the leading cause of maternal mortality in many LMICs.(3)

While HDP may not be entirely preventable, associated morbidity and progression to severe preeclampsia and eclampsia may be reduced with quality and timely antenatal care and obstetric management.(5) Early initiation of antenatal care (ANC) is important to establish accurate dating and identify risk factors for HDP, including chronic hypertension, history of HDP in a prior pregnancy, and obesity.(6) The risk of developing HDP can be reduced with the initiation of oral aspirin in women with risk factors,(7) and calcium supplementation in regions with low calcium consumption.(8) Continued, frequent engagement in ANC throughout the second and third trimester allows regular monitoring of blood pressures, which may facilitate earlier detection of HDP.(6) In instances of severe HDP which necessitates prompt delivery, ANC allows for identification, referral, and management of these cases. In instances of less severe HDP prior to term, regular ANC allows for continued close monitoring of blood pressure, laboratory values, and symptoms.(6)

In 2016, the World Health Organization (WHO) increased their 2002 recommendations from four antenatal visits in a pregnancy to eight antenatal visits, with first contact in the first 12 weeks' gestation and subsequent contacts at 20, 26, 30, 34, 36, 38 and 40 weeks' gestation. The overarching goal of this change was to reduce stillbirths, reduce pregnancy complications, and support a positive pregnancy experience.(9) A 2018 systematic review demonstrated a reduction in the occurrence of HDP in women who received more ANC.(10) Among women who do develop HDP, there is very limited research on the impact of antenatal care on maternal and neonatal health outcomes. To fill this gap, our study describes the timing and quantity of antenatal care attended by a group of women who developed preeclampsia and eclampsia, and explores how aspects of antenatal care, including timing, frequency, and type of provider, is associated with clinical outcomes in pregnancies complicated by preeclampsia and eclampsia.

Methods

Study design

This is a secondary analysis of data collected as part of a randomized control trial (RCT) that evaluated the impact of magnesium sulfate duration on efficacy of seizure prophylaxis among women with preeclampsia with severe features and eclampsia.(11,12) The published study protocol provides details of this RCT.(11) Apart from duration randomization to 12 versus 24 hours of magnesium sulfate, women received the standard of care at Korle Bu Teaching Hospital (KBTH), with all clinical care decisions made by the on-call obstetrics team. Ethical approval was granted by the Scientific and Technical Committee of the KBTH (KBTH-IRB 00096/2018) and the University of Michigan (HUM00139104). Written informed consent was obtained from all participants.

Setting

This study was conducted at the Korle Bu Teaching Hospital in Ghana's capital city of Accra. KBTH is a large tertiary care teaching hospital that provides antenatal care and labor and delivery services for women living in Accra as well as referral cases across southern Ghana. KBTH conducts approximately 9,500 deliveries each year. HDP are currently the leading cause of maternal mortality at KBTH.(3) The government of Ghana provides free antenatal care services in all public health facilities for all pregnant women, implemented through the National Health Insurance Scheme. Pregnant women only need to show evidence of pregnancy to register for this free service.

Participants

Participants were adult pregnant patients admitted to KBTH with a diagnosis of preeclampsia with severe features or eclampsia. Exclusion criteria were the presence on admission of acute renal failure, Hemolysis Elevated Liver enzymes and Low Platelet (HELLP) Syndrome, pulmonary edema, a co-morbid maternal diagnosis of renal disease or seizure disorder, and age 17 or younger.

Variables

Outcome variables were two composites of maternal and neonatal outcomes. A composite of severe maternal complications was defined as any one of the following: development of pulmonary edema, development of acute kidney injury (AKI), intensive care unit (ICU) admission or maternal death. A composite of poor neonatal outcomes was defined as any one of the following: stillbirth, birthweight less than 1500 grams, five-minute APGAR less than 7, NICU admission, or livebirth with death before discharge.

Predictor variables were all available measures of antenatal care utilization, which included gestational age at first antenatal visit, number of total antenatal visits, facility type of primary antenatal care, provider type for primary antenatal care, and referral to KBTH (versus received antenatal care at KBTH). See Supplemental Table 1 for definitions of

facility and provider types in Ghana. Gestational age at first antenatal visit was categorized based on whether the first visit occurred in the first trimester, defined as prior to fourteen weeks and zero days gestation. The total number of antenatal visits was categorized both as equal to or greater than four visits and as equal to or greater than eight visits, based on the prior and current WHO recommendations. Using WHO's schedule of recommended visits,(9) an "adequate ANC visits" variable was created, defined as achieving a minimum number of recommended ANC visits based on gestational age at delivery.

Potential confounder variables included in the adjusted models were age, parity (parous vs not parous), marital status (married vs not married), and health insurance status (insured vs not insured). These variables were selected by the authors based on their clinical and sociodemographic relevance.(13) Gestational age at delivery was included as a confounder for models evaluating total number of ANC visits, having 4 or more visits, having 8 or more visits, and referral status.(14)

Data sources

Data was extracted from participants' medical records and supplemented by direct interview of participants, including past medical history, past obstetric history, and history of the index pregnancy. Data on antenatal care factors included level of facility where antenatal care, and type of primary antenatal care provider. During the admission for labor and delivery, extracted data including mode and timing of delivery and occurrence of maternal complications. Neonatal information was collected from delivery through discharge, including gestational age at delivery, birthweight, outcome of delivery, NICU admission, APGAR score, and status at discharge.

Statistical analysis

Data was collected using paper forms, entered into REDCap for data storage and organization, and downloaded into SAS 9.4 (SAS Institute Inc., Cary, N.C) for analysis. First, sociodemographic, and antenatal care factors were described for the total population. The normality of continuous variables was determined using Shapiro-Wilk test and assessing skewness and kurtosis. Non-normally distributed numerical variables (age, body mass index, gestational age at delivery, gestational age at first antenatal care visit, and number of antenatal visits) were presented using medians and interquartile range. Unadjusted bivariate analyses were performed to compare sociodemographic and antenatal care factors across composite outcomes, using Wilcoxon Rank test, Chi-squared, and Fisher's exact test where appropriate. For each antenatal care variable, separate multivariable logistic regression models were performed to identify associations between the antenatal care factor and each of two outcomes: composite of severe maternal complications (yes vs no) and composite of poor neonatal outcomes (yes vs no). Possible confounders were identified based on epidemiological and clinical knowledge. Each model was adjusted for age, parity, marital status, and insurance status. Models evaluating total number of ANC visits, having four or more visits, having eight or more visits, and referral status were

also adjusted for gestational age at delivery. Missing data were assumed to be missing completely at random and were not included in statistical comparisons. All statistical tests were two-sided and a p-value < 0.05 was considered statistically significant.

Results

Between October 2018 and October 2020, 1,176 total pregnant participants were enrolled. Of these, 1,060 women (90.1%) had a diagnosis of preeclampsia with severe features, and 116 women (9.9%) had eclampsia. Participants had a median age of 31.0 years (interquartile range (IQR): 27.0, 35.0), and most were married (n=847, 73.1%) and had public insurance through Ghana's National Health Insurance Scheme (n=1090, 95.4%). Median gestational age at delivery was 36.6 weeks (IQR: 33.3, 38.9) with 36.4 % (n=431) delivering between 32.0 and 37.0 weeks and 16.7% (n=197) delivering prior to 32.0 weeks (see Table 1).

Antenatal care use

Antenatal care was initiated at a median of 16.0 weeks (IQR 11.7 – 21.0), and 40.4% (n=444) had an antenatal visit in the first trimester. The median number of antenatal visits was 5.0 (IQR 3.0 – 7.0), with 72.9% (n=791) attending four or more visits and 19.4% (n=210) attending eight or more visits. Half of participants (n=645, 54.9%) had an adequate number of ANC visits based on their gestational age at delivery and the WHO recommended schedule of visits (Table 1, Figure 1). All antenatal care visits had both a corresponding blood pressure recorded, and a urine protein level recorded. The most common type of facility for prenatal care was a government polyclinic (n=522, 47.2%), and the most frequent type of provider a midwife (n=704, 65.1%). The majority (n=844, 74.6%) were referred from another institution to KBTH for hospital admission.

Maternal complications

Overall, the composite of severe maternal complications was experienced by 148 participants (12.7%) (Table 2, Supplemental Table 2). Although the number of ANC visits (uOR 0.85, p <0.01), ≥ four ANC visits (uOR 0.48, p <0.001) and ≥ 8 ANC visits (uOR 0.48, p = 0.01) were all associated with decreased odds of the composite of severe maternal complications in the unadjusted analysis (Table 2), these relationships were no longer significant in the final adjusted model (Table 3). Patients achieving WHO-defined adequate ANC visits, the gestational age at first antenatal care visit, and type of healthcare provider for antenatal care were also not significantly associated with the composite of severe maternal complications. Receiving antenatal care at a government tertiary hospital was associated with a 53% decreased odds of experiencing the severe maternal complication composite (aOR 0.47, 95% CI 0.26-0.85, p = 0.01). Compared to patients who received their antenatal care at KBTH, those who were referred to KBTH for labor and delivery or postpartum care had 2.0 higher odds of experiencing a severe maternal complication (aOR 2.00, 95% CI 1.16 – 3.45, p = 0.01).

Table 1. Demographic characteristics and antenatal care information

Characteristic	**All Participants** n = 1176
Age, years [a]	31.0 (27.0, 35.0)
Parity group, n (%) Nulliparous Multiparous	376 (32.0) 798 (68.0)
Marital status, n (%) Married Not Married	847 (73.1) 312 (26.9)
Insurance status, n (%) Insurance No Insurance	1100 (96.2) 43 (3.8)
Gestational age at delivery, weeks [a]	36.6 (33.3, 38.9)
Gestational age at first antenatal visit, weeks [a]	16.0 (11.7, 21.0)
First antenatal visit in first trimester, n (%)	444 (40.4)
Antenatal visits, total number [a]	5.0 (3.0, 7.0)
≥ four antenatal visits, n (%)	791 (72.9)
≥ eight antenatal visits, n (%)	210 (19.4)
Adequate ANC visits based on WHO recommendations, n (%) [b] Adequate Inadequate	645 (54.9) 531 (45.2)
Level of facility for primary antenatal care, n (%) Government tertiary hospital Gov regional/district hospital Government polyclinic Private hospital Maternity home	230 (20.8) 137 (12.4) 522 (47.2) 157 (12.4) 60 (5.4)
Type of primary caregiver for antenatal care, n (%) Specialist OBGYN Medical officer Midwife	259 (24.0) 118 (10.9) 704 (65.1)
Referred, n (%)	844 (74.6)

[a] Data presented as median (interquartile range)

[b] Defined as achieving a minimum number of recommended ANC visits based on the World Health Organization (WHO) schedule of recommended visits and the woman's gestational age at delivery NOTE: Data missing for parity (n = 2), marital status (n=17), body mass index (n=51), insurance status (n=33), gestational age at delivery (n = 37), gestational age at first trimester visit (n = 98), first trimester visit (n = 78), number of antenatal visits (n = 91), level of facility for primary antenatal care (n = 70), primary caregiver (n = 95), referral (n = 45).

Table 2: Unadjusted bivariate analysis of sociodemographic and antenatal characteristics across composite of severe maternal complications and composite of poor neonatal outcomes

Characteristic	Maternal Complication Composite [a]			Poor Neonatal Outcome Composite [b]		
	Yes (n = 148)	No (n = 1018)	*P*	Yes (n = 707)	No (n = 508)	*P*
Age, years [c]	32.0 (28.0, 35.0)	31.0 (27.0, 35.0)	0.35	31.0 (27.0, 36.0)	31.0 (27.0, 35.0)	0.48
Parity group, n (%)[d] Nulliparous Multiparous	40 (27.2) 107 (72.8)	332 (32.7) 685 (67.4)	0.19	228 (32.3) 477 (67.7)	168 (33.1) 340 (66.9)	0.79
Marital status, n (%)[d] Married Not Married	111 (76.0) 35 (24.0)	727 (72.5) 276 (27.5)	0.37	503 (72.0) 196 (28.0)	366 (73.4) 133 (26.7)	0.60
Insurance status, n (%)[d] Insurance No Insurance	131 (92.9) 10 (7.1)	961 (96.8) 32 (3.2)	0.02	663 (96.4) 25 (3.6)	478 (96.2) 19 (3.8)	0.87
Gestational age at delivery, weeks [c]	37.0 (33.9, 39.0)	33.9 (30.6, 36.0)	<.001	34.0 (31.4, 36.6)	38.4 (37.1, 39.9)	<.001
Gestational age at 1st antenatal visit, weeks [c]	16.0 (11.0, 20.1)	16.0 (12.0, 21.3)	0.29	16.0 (11.7, 21.0)	15.9 (11.3, 21.0)	0.48
First antenatal visit in first trimester, n (%)[d]	52 (40.0)	387 (40.4)	0.93	258 (39.8)	203 (41.8)	0.49
Antenatal visits, number [c]	4.0 (3.0, 6.0)	5.0 (3.0, 7.0)	<.001	4.0 (3.0, 6.0)	6.0 (4.0, 8.0)	<.001
≥ four antenatal visits, n (%)[d]	75 (58.6)	707 (74.7)	<.001	425 (65.7)	399 (83.5)	<.001
≥ eight antenatal visits, n (%)[d]	14 (10.9)	194 (20.5)	0.01	76 (11.8)	146 (30.5)	<.001
WHO-defined adequate ANC visits, n (%)[d]	79 (53.4)	559 (54.9)	0.73	401 (56.7)	271 (53.4)	0.24

Table 2: Unadjusted bivariate analysis of sociodemographic and antenatal characteristics across composite of severe maternal complications and composite of poor neonatal outcomes *(continued)*

Characteristic	**Maternal Complication Composite** [a]			**Poor Neonatal Outcome Composite** [b]		
	Yes (n = 148)	No (n = 1018)	*P*	Yes (n = 707)	No (n = 508)	*P*
Facility for primary antenatal care, n (%)[d] Government tertiary hospital Gov regional/ district hospital Government polyclinic Private hospital Maternity home	18 (13.7) 18 (13.7) 69 (52.7) 19 (14.5) 7 (5.3)	209 (21.7) 118 (12.2) 450 (46.6) 136 (14.1) 52 (5.4)	0.30	106 (16.3) 99 (15.2) 299 (45.9) 105 (16.1) 42 (6.5)	138 (28.2) 43 (8.8) 237 (48.4) 55 (11.2) 17 (3.5)	<.001
Type of primary caregiver for antenatal care, n (%)[d] Specialist OBGYN Medical officer Midwife	23 (18.3) 18 (14.3) 85 (67.5)	232 (24.6) 97 (10.3) 616 (65.2)	0.16	132 (20.8) 70 (11.0) 434 (68.2)	144 (29.8) 49 (10.1) 290 (60.0)	0.002
Referred, n (%)[d]	128 (87.1)	708 (72.7)	<.001	541 (79.1)	320 (65.7)	<.001

[a] Composite of severe maternal complication is defined as **"**Yes" to Pulmonary Edema or AKI or Hemodialysis or ICU admission or maternal death**.**

[b] Composite of poor neonatal outcome is defined as "Yes' ' to Stillbirth or birth weight <1500g or APGAR at 5 minute <7 or Yes to NICU admission or born alive but died before discharge. Calculated among 1218 births.

[c] Data presented as median interquartile range and comparisons tested using Wilcoxon Rank test.

[d] Comparisons between outcome groups tested using Chi-squared or Fisher's exact test.

Table 3. Antenatal care factors associated with composite of maternal complications and composite of poor neonatal outcomes

	Maternal Complication [a]			**Poor Neonatal Outcome** [b]		
Characteristic	uOR (95% CI)	aOR (95% CI)	*P*	uOR (95% CI)	aOR (95% CI)	*P*
Gestational age at 1st antenatal visit	0.99 (0.96, 1.01)	0.98 (0.95, 1.01) [c]	0.12	0.99 (0.98, 1.01)	0.99 (0.97, 1.01) [c]	0.29
First antenatal visit in first trimester	0.98 (0.68, 1.43)	1.09 (0.74, 1.61) [c]	0.65	0.92 (0.72, 1.17)	0.96 (0.75, 1.23) [c]	0.74
Number of antenatal visits	0.85 (0.79, 0.92)	0.95 (0.87, 1.04) [d]	0.27	0.79 (0.75, 0.84)	0.94 (0.88, 1.00) [d]	0.06
≥ four visits	0.48 (0.33, 0.70)	0.78 (0.50, 1.22) [d]	0.27	0.38 (0.28, 0.51)	0.83 (0.56, 1.22) [d]	0.34
≥ eight visits	0.48 (0.27, 0.85)	0.79 (0.42, 1.49) [d]	0.47	0.30 (0.22, 0.41)	0.67 (0.46, 0.97) [d]	0.04
WHO-defined adequate ANC visits	0.94 (0.67, 1.33)	1.03 (0.71, 1.49) [c]	0.87	1.15 (0.91, 1.44)	1.20 (0.95, 1.53) [c]	0.13
Facility for primary antenatal care	0.56 (0.33, 0.97)	**0.47 (0.26, 0.85)** [c]	**0.01** 0.85	0.61 (0.45, 0.83)	**0.56 (0.41, 0.77)** [c]	**<.001** **0.002**
Government tertiary hospital	1.00 (0.57, 1.74)	0.95 (0.53, 1.71) [c]	REF 0.83	1.83 (1.23, 2.71)	**1.96 (1.29, 2.97)** [c]	REF **0.045**
Gov regional/ district hospital	REF 0.91 (0.53, 1.57)	REF 0.94 (0.54, 1.64) [c]	0.72	REF 1.51 (1.05, 2.19)	REF **1.47 (1.01, 2.15)** [c]	**0.04**
Government polyclinic	0.88 (0.38, 2.01)	0.86 (0.37, 1.98) [c]		1.96 (1.09, 3.53)	**1.88 (1.04, 3.40)** [c]	
Private hospital						
Maternity home						
Type of primary caregiver for antenatal care	0.72 (0.44, 1.17)	0.61 (0.36, 1.03) [c]	0.06 0.30	0.61 (0.46, 0.81)	**0.58 (0.43, 0.77)** [c]	**<.001** 0.77
Specialist OBGYN	1.35 (0.78, 2.34)	1.35 (0.76, 2.38) [c]	REF	0.96 (0.64, 1.42)	0.94 (0.63, 1.41) [c]	REF
Medical officer	REF	REF		REF	REF	
Midwife						

Table 3. Antenatal care factors associated with composite of maternal complications and composite of poor neonatal outcomes *(continued)*

	Maternal Complication [a]			**Poor Neonatal Outcome** [b]		
Characteristic	uOR (95% CI)	aOR (95% CI)	*P*	uOR (95% CI)	aOR (95% CI)	*P*
Referred	2.53 (1.53, 4.18)	**2.12 (1.23, 3.66)** [d]	**0.007**	1.97 (1.52, 2.57)	**1.68 (1.20, 2.35)** [d]	**0.002**

[a] Composite of maternal complication is defined as **"**Yes" to Pulmonary Edema or AKI or Hemodialysis or ICU admission or maternal death.
[b] Composite of poor neonatal outcome is defined as "Yes' ' to Stillbirth or birth weight <1500g or APGAR at 5 minute <7 or Yes to NICU admission or born alive but died before discharge.
[c] Multivariable logistic regression models are adjusted for age, parity, marital status, health insurance
[d] Multivariable logistic regression models are adjusted for age, parity, marital status, health insurance and gestational age at delivery
uOR: unadjusted odds ratio
aOR: adjusted odds ratio

Neonatal outcomes

Among 1218 babies born to the participants, poor neonatal outcomes were experienced by 58.2% (n=707) (Table 2, Supplemental Table 2). In the final adjusted model, patients achieving WHO-defined adequate ANC visits and attending four or more ANC visits were not significantly associated with the composite of poor neonatal outcomes. However, attending eight or more ANC visits was associated with 33% lower odds of experiencing a poor neonatal outcome (aOR 0.67, 95% CI 0.46 – 0.97, p = 0.04). In addition, receiving antenatal care at a tertiary level hospital is associated with 44% reduced odds of experiencing poor neonatal outcome (aOR 0.56, 95% CI 0.41 - 0.77, p < 0.001), and receiving care from an obstetrician/gynecologist specialist results in a 42% reduced odds of poor neonatal outcome (aOR 0.58, 95% CI 0.43 - 0.77, p < 0.001). Compared to attendants, women who were referred had 68% increased odds of a poor neonatal outcome (aOR 1.68, 95% CI 1.20 – 2.35, p = 0.002).

Discussion

Main findings

In a population of Ghanaian women with preeclampsia and eclampsia, we found that only half of participants had an adequate number of ANC visits based on their gestational age at delivery and the WHO recommended schedule of visits. Achieving adequate ANC visits was not associated with improved health outcomes. Meeting the current WHO recommendations to attend eight or more antenatal visits was associated with lower odds of a poor neonatal outcome, however, was not associated with a lower rate of the maternal complication composite. The odds of experiencing a severe maternal complication was lower in women who received their antenatal care at a tertiary level hospital, and the odds of experiencing a poor neonatal outcome was lower in women who received their

antenatal care at a tertiary level hospital and by a specialist obstetrician/gynecologist. Compared to attendants, women who were referred to KBTH had twice the odds of having a severe maternal complication and a poor neonatal outcome.

Findings in context of literature

This study demonstrates the importance of frequent antenatal care in reducing poor neonatal outcomes, however, the frequency of antenatal alone is not sufficient to reduce serious maternal complications. Having an adequate number of ANC visits was not associated with maternal or neonatal health outcomes. Although antenatal care is universally recommended and valued, results from evidence-based evaluation of antenatal care has been varied. Many studies have shown a relationship between fewer antenatal visits and worse pregnancy outcomes, including low birthweight, preterm birth, and neonatal death(15–17), however others have failed to demonstrate improved outcomes associated with number of antenatal visits(18), particularly in low risk populations.(19) A 2010 Cochrane Review evaluated the impact of reduced antenatal visits and found no adverse perinatal outcomes in high income countries, but significantly higher rates of perinatal mortality in LMIC. (20)

Our findings demonstrate the protective benefits of receiving antenatal care at a tertiary facility and by an OBGYN specialist. Provider and facility type may be proxy for quality of care, and reflect settings of improved monitoring, earlier detection of hypertensive disorders, and thus improved outcomes. Alternatively, this finding could be explained by unmeasured factors that predispose certain groups of pregnant women to receive care at tertiary level facilities. These findings reinforce the importance of risk stratification early in antenatal care to identify higher-risk patients who may benefit from early referral to tertiary-level, specialist care. This must be carefully balanced with the potential for overcrowding at tertiary level facilities, and the need to build capacity for quality care at primary and secondary care levels.

Most studies of antenatal care have focused on quantitative differences in the number of prenatal visits.(10,15) However, our results suggest that in pregnant women at risk of developing preeclampsia and eclampsia, quality of antenatal care is essential, not just quantity. While of critical importance, evaluating quality of antenatal care is more difficult.(21) No single metric exists to evaluate quality of antenatal care; proposed metrics include early initiation of prenatal care, monitoring of specific physical and laboratory parameters, providing prenatal and intrapartum education, promotion of breastfeeding and family planning education, and a positive patient experience with a perception of respectful maternity care.(22,23,24) Despite all women in our study developing a serious complication of pregnancy, either preeclampsia or eclampsia, many began their antenatal care as low-risk pregnancies. This highlights the importance of every pregnant woman receiving early, quality antenatal care. Comprehensive history-taking and risk-stratification provide the opportunity to initiate daily aspirin and calcium supplementation, which reduces the risk of developing preeclampsia in select women.(7) Further, if complications

develop, accurate confirmation of dating, known trends in blood pressures, and serial assessment of fetal well-being are all essential to informed management of complications. Finally, benefits of quality care extend to women being well counseled, trusting their healthcare providers, and having a positive pregnancy experience even in the face of complications. In women with preeclampsia and eclampsia, who have elevated risks of recurrence in future pregnancies(4), this counseling and trust is critical for future reproductive outcomes.

Strengths and limitations

Strengths of this study include a large population of high-risk participants, including a large number of pregnancies complicated by eclampsia. Extensive clinical information was collected, including occurrence and timing of each antenatal visit, and this data was linked to outcomes during labor and delivery and in the immediate postpartum period. Limitations of the study include data collection at a single urban tertiary care hospital, which may limit generalizability to other facilities in dissimilar locations. Since a large proportion of participants were referred from other facilities, this may represent an especially complicated population. Although data was collected on whether blood pressure and urine protein were checked at each antenatal visit, additional information on quality of antenatal care is not available for analysis. Finally, given the observation nature of data collection on antenatal care utilization, we are unable to determine if antenatal care variables caused the observed differences in clinical outcomes. Additional research is needed to untangle the complex impact that unmeasured and unmeasurable factors, including socioeconomic status and patient agency, have on both antenatal care utilization and clinical outcomes.

Conclusion

Overall, severe maternal morbidity and mortality resulting from HDP remain high in many LMICs despite known interventions and management protocols. This may in part be due to limited access to and utilization of quality ANC. In a population of high-risk Ghanaian women with preeclampsia and eclampsia, we demonstrate that the frequency of antenatal care alone may not be sufficient to reduce severe maternal and neonatal complications. In pregnant women at risk of developing preeclampsia and eclampsia, quality of antenatal care is essential, not just quantity. Our findings highlight the importance of risk stratification of pregnancies early in antenatal care and referral to tertiary-level, specialist care for the highest risk patients. Importantly, preeclampsia and eclampsia often develop in previously low-risk patients. Thus, every pregnant woman should have access to quality evidence-based antenatal care to optimize detection and management if complications develop.

List of abbreviations

Hypertensive disorders of pregnancy (HDP)
Low- and middle-income countries (LMIC)
Antenatal care (ANC)
World Health Organization (WHO)
Randomized control trial (RCT)
Korle Bu Teaching Hospital (KBTH)
Hemolysis Elevated Liver enzymes and Low Platelet (HELLP)
Acute kidney injury (AKI)
Intensive care unit (ICU)

Declarations:

Ethics approval and consent to participate: Ethical approval was granted by the Scientific and Technical Committee of the KBTH (KBTH-IRB 00096/2018) and the University of Michigan IRB (HUM00139104). Written informed consent was completed by all participants. All methods were carried out in accordance with relevant guidelines and regulations.

Competing interests: The authors declare that they have no competing interests

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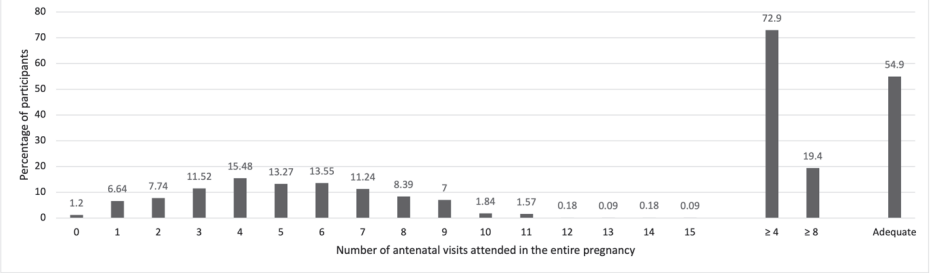

Figure 1: Number of antenatal visits attended, grouped by WHO recommendations

Supplemental Table 1: Definitions of facility types and caregiver types

Facility types for antenatal care	
Government tertiary hospital	Government-owned teaching hospital that provides tertiary level healthcare services and are involved in teaching and research. Provides highest-level referral services. Care provided by OBGYN specialists, general practitioner doctors, and midwives.
Government regional/district hospital	Government-owned hospital that provides secondary level care at the district or regional level. Serves as a referral center for polyclinics and health centers. Care provided by general practitioner doctors and midwives, and sometimes by OBGYN specialists.
Government polyclinic	Government-owned hospital that provides primary level care. Care provided by midwives, and often by general practitioner doctors.
Private hospital	Private, for-profit hospitals owned by individuals and companies. Care provided by midwives, and often by general practitioner doctors.
Maternity home	Primary level facilities that provide only obstetric care. Care is provided by midwifes.
Caregiver types for antenatal care	
Specialist OBGYN	Doctor who has specialized in obstetrics and gynecology, including a 2-year "house officer" training and a 3-5 year residency training in obstetrics and gynecology.
Medical officer	General practitioner doctors who have completed a 2-year "house officer" training, which includes 6-months of focused OBGYN training.
Midwife	Nurse who has completed advanced training in obstetric care.

Supplemental Table 2: Composite of maternal complications and composite of poor neonatal outcomes, by component

Variable	n	%
Maternal composite	148	12.7
Pulmonary edema	13	1.1
Acute kidney injury	131	11.3
Hemodialyzed	3	0.3
ICU admission	10	0.9
Maternal death	4	0.4
Poor neonatal outcome	707	58.2
Stillbirth	145	12.0
Birthweight < 1.5kg	231	19.4
5 minute APGAR < 7	304	25.5
NICU admission	527	45.4
Neonatal death	91	7.5

NOTE: values in column will not equal total due to multiple responses
ICU: Intensive care unit
NICU: Neonatal intensive care unit

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7

Preeclampsia Knowledge Among Postpartum Women Treated for Preeclampsia and Eclampsia at Korle Bu Teaching Hospital in Accra, Ghana

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Authorship statement

I contributed to defining the research question, proposed the methodology and the experimental design, carried out the experiments together with a medical student whom I supervised, and did the data analysis together with the student and a statistician. The student wrote the first draft (therefore, I am second author) and revised it after the comments of myself (which were quite many) and the other co-authors

ABSTRACT

Background

Preeclampsia/eclampsia is a major cause of maternal morbidity and mortality worldwide, yet patients' knowledge about their diagnosis of preeclampsia/eclampsia is not well understood. Our study examines patient knowledge among women with preeclampsia/eclampsia in a large urban hospital in Ghana.

Methods

Postpartum women with a diagnosis of preeclampsia or eclampsia were asked to complete a survey 2-5 days after delivery that assessed demographic information, key obstetric factors, and questions regarding provider counseling. Provider counseling on diagnosis, causes, complications, and future health effects of preeclampsia/eclampsia was quantified on a 4-point scale ('Counseling Composite Score'). Participants completed an objective knowledge assessment regarding preeclampsia/eclampsia, scored from 0 to 22 points ('Preeclampsia/Eclampsia Knowledge Score' (PEKS)). Linear regression was used to identify predictors of knowledge score.

Results

A total of 150 participants were recruited, 88.7% (133) with preeclampsia and 11.3% (17) with eclampsia. Participants had a median age of 32 years, median parity of 2, and mean number of antenatal visits of 5.4. Approximately half of participants reported primary education as their highest level of education. While 74% of women reported having a complication during pregnancy, only 32% of participants with preeclampsia were able to correctly identify their diagnosis, and no patients diagnosed with eclampsia could correctly identify their diagnosis. Thirty-one percent of participants reported receiving no counseling from providers, and only 11% received counseling in all four categories. Even when counseled, 40-50% of participants reported incomplete understanding. Out of 22 possible points on a cumulative knowledge assessment scale, participants had a mean score of 12.9±0.38. Adjusting for age, parity, and the number of antenatal visits, higher scores on the knowledge assessment are associated with more provider counseling (β 1.4, SE 0.3, $p<0.001$) and higher level of education (β 1.3, SE 0.48, $p=0.008$).

Conclusions

Counseling by healthcare providers is associated with higher performance on a knowledge assessment about preeclampsia/eclampsia. Patient knowledge about preeclampsia/eclampsia is important for efforts to encourage informed healthcare decisions, promote early antenatal care, and improve self-recognition of warning signs—ultimately improving morbidity and reducing mortality.

Key Words: maternal health, pregnancy, preeclampsia, eclampsia, patient knowledge, patient education, provider counseling, sub-Saharan Africa

Background

Preeclampsia and eclampsia are leading causes of maternal morbidity and mortality [1]. The burden of preeclampsia and eclampsia are most significant in low- and middle-income countries (LMICs), where hypertensive disorders of pregnancy account for 10-15% of maternal deaths [1, 2]. In many LMICs, including the West African country of Ghana, hypertensive disorders of pregnancy have overtaken hemorrhage as the leading cause of maternal mortality [3, 4].

In pregnancies complicated by preeclampsia and eclampsia, improved outcomes are seen with early identification of symptoms, prompt presentation to healthcare facilities, and subsequent management with antihypertensive medications, magnesium sulfate, and delivery of the fetus and placenta [2, 5-8]. Development of preeclampsia or eclampsia is a significant risk factor for recurrence in subsequent pregnancies [7]. Since preeclampsia and eclampsia are exclusively complications of pregnancy, antenatal care (ANC) visits and intrapartum admission are important opportunities for patient counseling [9, 10]. Prenatal education on symptoms of preeclampsia and eclampsia may result in improved outcomes [11-14], with studies linking understanding of counseling to higher rates of women taking action and reporting symptoms [15].

Despite the important connections between women's knowledge and agency in identifying warning signs and seeking appropriate care, little research has addressed the patient perspective. Studies conducted in high-income countries demonstrate that only half of patients were counseled on signs and symptoms of preeclampsia [16], even though counseling by healthcare providers is associated with increased patient knowledge [16-18].

In LMICs, healthcare providers and patients face unique challenges, including lower general education levels and health literacy, and limited access to and utilization of antenatal care services [19,20]. Previous research in Ghana [17], Tanzania [21, 22], and Malaysia [23] all demonstrate low levels of knowledge about preeclampsia among pregnant women. However, none of these studies focused on women with a clinical diagnosis of preeclampsia or eclampsia.

A better understanding of a patient's knowledge about her diagnosis and implications for future pregnancies is important in caring for high-risk women. However, the experience and knowledge of women with preeclampsia and eclampsia in LMICs is largely unknown. The current study fills this gap—evaluating counseling, understanding, and knowledge of postpartum women diagnosed with preeclampsia and eclampsia in a large urban tertiary hospital in Ghana.

Methods

This study took place at the Korle Bu Teaching Hospital (KBTH), Ghana's largest tertiary care hospital located in the capital city of Accra. The maternity unit serves both patients receiving antenatal care and referral cases from the southern half of the country, with approximately 9,500 deliveries per year.

Study participants were identified through the ongoing MOPEP Trial, a randomized controlled trial of comparative dosing regimens of magnesium sulfate for management of preeclampsia and eclampsia [24]. Inclusion criteria were admission to KBTH with a diagnosis of eclampsia or preeclampsia with severe features, age 18 years or older, and fluency in English or Twi/Akan.

Data collection was completed between November 2019 and March 2020 by two research assistants, one of whom was fluent in Twi/Akan. Eligible participants were recruited in the postpartum inpatient ward at least two days after delivery, and a written informed consent process was completed. A standardized survey was verbally administered by a research assistant. Surveys were completed at the bedside in the language choice of the participant.

Demographic information and obstetric history were collected from the participants' clinical charts. The survey consisted of two parts. Part I (24 questions) focused on patient perceptions of provider counseling about their clinical diagnosis. This section assessed the recollection and comprehension of information provided by the healthcare provider on four counseling categories: diagnosis, causes, possible complications, and future health effects, including likelihood of recurrence in future pregnancies. A counseling composite score was created ranging from 0-4 possible points, where one point was awarded for a participant responding 'Yes' to being counseled on any of the four categories. Participants who responded 'Yes' to being counseled on any of these four categories were then asked a follow-up question regarding their perceived level of understanding of the counseling. Understanding was graded on a 4-point scale: None, Some, Most, or All. The interviewer explained that 'Some' meant understanding less than half of the information provided, while 'Most' meant understanding more than half. During data analysis, 'Less than 50% Understanding' was defined as a response of 'None' or 'Some' and 'More than 50% Understanding' was defined as a response of 'Most' or 'All.'

Part II (10 questions) was an objective knowledge assessment, adapted to the local Ghanaian context from a survey developed by the Preeclampsia Foundation [16]. Participants were asked multiple choice and true/false questions about risk factors, symptoms, and management of preeclampsia. Responses were summed to generate a cumulative Preeclampsia/Eclampsia Knowledge Score (PEKS), with a total of 22 possible points. This cumulative knowledge score was used as the primary outcome variable.

Surveys were completed via pen and paper, entered into REDCap, and downloaded into STATA (Version 16.0 StataCorp. 2019) for cleaning and analysis. Descriptive statistics were calculated for all key variables using means and proportions. Bivariate linear regression analysis was used to evaluate the relationship between the PEKS, demographic and clinical factors, and counseling indicators. Significant variables in our bivariate model were included in a multivariate linear regression analysis, which was also adjusted by age, parity, and number of antenatal visits, as these are often linked to knowledge of pregnancy-related factors. All tests were two-tailed and a p value of <0.05 was accepted as significant.

Table 1: Demographic Factors

Characteristic	Participants (n=150)
Age, years[a]	32 (18-47)
Participant Reported Language Used for Healthcare	
English	33 (22.0)
Twi	117 (78.0)
Highest Level of Completed Education	
None	1 (0.7)
Primary	70 (47.0)
Secondary	39 (26.2)
Tertiary	39 (26.2)
Clinical Diagnosis	
Preeclampsia	133 (88.7)
Eclampsia	17 (11.3)
Parity[a]	2 (1-10)
Primiparous	55 (36.7)
Multiparous	95 (63.3)
Primary Caregiver During Pregnancy	
Specialist obstetrician/gynecologist	42 (29.2)
Medical officer (non-obstetrician)	9 (6.0)
Midwife	90 (60.4)
Other	1 (0.7)
None	7 (4.7)
Number of Antenatal Appointments Attended[a]	5.3 (0-14)
0-3	42 (28.0)
≥4	108 (72.0)
Diagnosis of Chronic Hypertension (index pregnancy)	
Yes	33 (22.0)
No	117 (78.0)
Previous Hypertensive Disorder of Pregnancy (previous pregnancies)	
Preeclampsia/Eclampsia	10 (6.7)
Gestational hypertension	11 (7.3)

Data presented as n (%) unless otherwise noted
[a]Median (range)

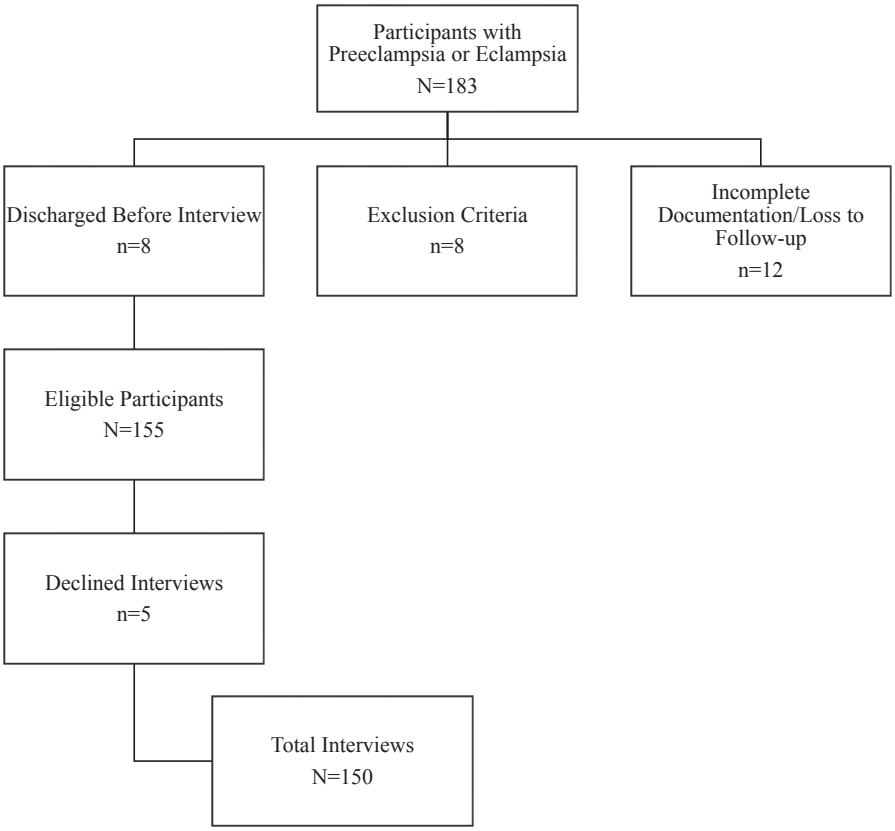

Figure 1: Participant Recruitment Flow Chart

Results

From November 2019-March 2020, a total of 150 participants completed the study (Figure 1). Table 1 illustrates participant demographics. Participants had a median age of 32 years (range 18-47) and 63.3% (95) were multiparous. Approximately half (70) of participants reported their highest completed level of education as 'Primary.' A majority (133, 88.7%) of participants were diagnosed with preeclampsia, while 17 (11.3%) of participants were diagnosed with eclampsia. Regarding history of hypertensive disorders of pregnancy, 33 (22.0%) participants had a comorbid diagnosis of chronic hypertension, 10 (6.7%) had preeclampsia/eclampsia in a prior pregnancy, and 11 (7.3%) had gestational hypertension in a prior pregnancy. Most women received care from a midwife (90, 60.4%), attended four or more antenatal visits (108, 72%), and conducted their healthcare communication primarily in Twi/Akan (117, 78%).

Figure 2 illustrates participant responses regarding their understanding of their diagnosis. Only 24% of participants with preeclampsia correctly identified their diagnosis, and none of the participants with eclampsia were able to correctly identify their diagnosis. Additionally, 86 (61.4%) participants reported never hearing about preeclampsia/eclampsia during their pregnancy. While 74% of participants correctly identified that preeclampsia/eclampsia is very serious, almost two-thirds of participants (92, 62%) said they do not understand it well enough to explain it to another person and 73% (108) said they do not know what to do in future pregnancies to prevent the condition or improve its outcome (Table 2).

Figure 3 demonstrates participant perceptions of provider counseling. Eighty-eight (58.7%) women said they received an explanation from a healthcare provider about their diagnosis, 40 (26.7%) about causes of the condition, 74 (49.3%) about complications, and 35 (23.3%) about future health effects. Of those who reported receiving counseling on these topics, 44.0% of women who received information about their diagnosis, 50% who received information about the causes, 39.2% who received information about potential complications, and 42.9% who received information about future health effects said they understood less than half of information provided. Figure 4 illustrates the 'Counseling Composite' Score for participants. The largest proportion of participants (47, 31.3%) did not receive counseling on any of the four categories.

Out of 22 possible points on the PEKS, participants scored a mean of 13 (SD 4.5) with a range of 2-21. Table 3 demonstrates bivariate linear regression, evaluating the relationship between the PEKS and demographics, obstetric factors, and perceived level of counseling. Variables significantly associated with PEKS included language used for healthcare, level of education, comorbid chronic hypertension, and history of preeclampsia/eclampsia in a previous pregnancy. Patient-reported provider counseling in each of the four categories, as well as the composite counseling score, were also significant. After adjusting for age, parity, and number of attended antenatal visits, higher level of education and a higher counseling composite score were significant contributors to a participant's PEKS (Table 4). Each level of increasing education— no education, primary, secondary, and tertiary—was associated with 1.3 points increase on the PEKS (β 1.3, SE 0.48, p=0.008). Each increase of one point on the counseling composite score was associated with 1.4 points increase on the PEKS (β 1.4, SE 0.3, p<0.001). Compared to participants who did not receive any counseling, participants counseled on all four domains scored on average 5.2 points higher on the knowledge score (50% increase). Figure 5 demonstrates the knowledge score for participants at each level of the counseling composite score, adjusted by the other variables in our final model.

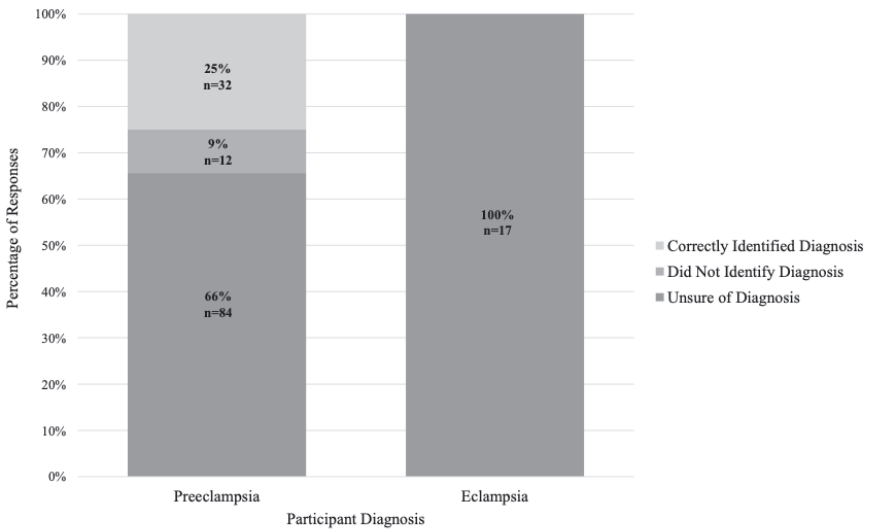

Figure 2: Participants' Ability to Correctly Identify Diagnosis

Discussion

Our study explores the patient perspective of knowledge and counseling on preeclampsia/eclampsia in an urban LMIC setting. Although 74% of women recognized having a complication during their pregnancy, one-third of women reported receiving no counseling from a provider regarding their condition. The biggest gap in counseling appears to be counseling on causes of the condition, with more than two-thirds of participants reporting no counseling on causes. Even when women reported being counseled, a large proportion reported understanding less than half of the information provided. Seventy-three percent of participants reported not knowing what to do to prevent or improve their condition in future pregnancies. Out of 22 possible points on the knowledge assessment, the average knowledge score was 13. Our multivariate analysis demonstrated that after controlling for age, parity, and number of antenatal visits, a higher knowledge score was predicted by a higher level of education and an increased amount of direct provider counseling.

Consistent with findings from studies of pregnant women in the United States [16], elsewhere in Ghana [17], and in other LMICs [21-23], our study demonstrates a low level of knowledge about preeclampsia/eclampsia. In the United States, 57% of participants reported being counseled on signs and symptoms of preeclampsia/eclampsia [16], compared to only 49% in our Ghanaian population. Importantly, our study population consisted of women with a recent clinical diagnosis of preeclampsia or eclampsia undergoing inpatient management

of this complication of pregnancy. It is especially imperative for this particular population to have an adequate level of knowledge and understanding, as the condition has directly impacted their just completed pregnancies, may continue to impact their health in the postpartum period, and is more likely to recur in their future pregnancies. Our study demonstrated a significant relationship between provider counseling on preeclampsia and participants' knowledge score. This key relationship has not been extensively explored but agrees with findings from the United States [16, 18]. Education level was also a significant predictor of knowledge score, which is concordant with other studies performed in Ghana [17] and the United States [18]. Other studies demonstrated that higher literacy, multiparity, and history of preeclampsia in a prior pregnancy were predictive of knowledge scores [18]. These relationships were significant in our bivariate analysis but were no longer significant in our adjusted final model.

In 2016, updated World Health Organization (WHO) guidelines increased the number of recommended antenatal visits from four to eight, with the goal of better preventing and managing pregnancy-related or concurrent disease and providing health education [25]. Of note, our study demonstrated that the number of attended antenatal visits did not correlate with a higher PEKS score. While direct provider counseling increased a participant's PEKS score, more frequent antenatal visits did not. This finding suggests that while increasing the frequency of antenatal visits may be important for many reasons, addressing systemic barriers to effective patient-provider communication, education, and counseling is important to see meaningful change in patient knowledge. Regarding ANC attendance and patient knowledge, our study fills a gap in the literature, as there are few studies that examine women's knowledge of preeclampsia and its correlation to the number of antenatal care visits, especially when examined as a continuous variable in linear regression. Within sub-Saharan Africa, studies show that patient education level is linked to increased knowledge regarding preeclampsia [17] and birth preparedness and complication readiness [26]. One study concluded that ANC attendance increased participant knowledge of obstetric danger signs during pregnancy and childbirth by approximately 2.5 times; however, this study treated ANC attendance as a binary yes/no variable, preventing the examination of a dose-response relationship between the number of ANC visits and knowledge. Additionally, this study demonstrated that most participants were only able to identify vaginal bleeding as a warning sign, while less than half were able to identify any of the symptoms of preeclampsia as an obstetric warning sign [27]. This finding is consistent with another study that demonstrated less than one-third of participants could identify preeclampsia-specific warning signs [26]. This suggests that current ANC practices may not provide education and counseling that is comprehensive of all dangerous pregnancy-related complications. Addressing this problem requires a multidisciplinary approach and patients may benefit from other WHO-recommended methods of antenatal education such as group antenatal visits and community-based education [25].

Table 2. Knowledge Assessment

Assessment	Participants (n=150)
Do you feel like you understand your condition well enough to explain it to someone else?	
Yes	57 (38.3)
No	75 (50.3)
I don't know	17 (11.4)
Do you know what to do in future pregnancies to prevent this condition or improve upon its outcome?	
Yes	40 (27.0)
No	84 (56.8)
I don't know	24 (16.2)
Who helped you the most with understanding your condition?	
Doctor	54 (36.7)
Midwife	32 (21.8)
Nurse	3 (2.0)
Family member	8 (5.4)
Other	5 (3.4)
None of the above	45 (30.6)
When did you first hear about preeclampsia?	
During pregnancy	54 (38.6)
Month of pregnancy[a]	6.65±-1.74 (2-9)
I never heard about it	86 (61.4)
How serious of a health issue do you think preeclampsia is?	
Not at all serious	5 (3.5)
Somewhat serious	26 (17.9)
Very serious	49 (33.8)
Extremely serious, even life-threatening	62 (42.8)
I don't know	3 (2.1)
Preeclampsia/Eclampsia Knowledge Score[a]	13.1±-4.5 (2-21)

Data presented as n (%) unless otherwise noted
Mean±SD (range)

Our study fills an important gap in the literature by exploring multiple predictors of patient knowledge, evaluating patient comprehension of provider counseling, and assessing the role of counseling in patient knowledge of preeclampsia in a LMIC setting. Strengths of the study include being embedded within a larger randomized controlled trial, which allowed our study population to consist entirely of women whose recent pregnancies were complicated by preeclampsia or eclampsia. To our knowledge, this is the first study of its kind to assess knowledge in this key targeted population. Participant knowledge of preeclampsia was assessed using a previously validated objective assessment created by the Preeclampsia Foundation [16], modified to the local context after extensive pilot testing. Although performed at a single site, the Korle Bu Teaching Hospital provides care for a wide range of attendants and referral patients from Ghana's capital city of Accra, as well as surrounding peri-urban and rural areas—supporting generalizability across Ghana. Diversity of participants is reflected in the range of age, language, education level, and number of ANC visits represented by our sample.

Limitations include challenges with language and translation, particularly because there is no direct Twi/Akan translation of "preeclampsia" or "eclampsia." A pilot period, with feedback from patients and healthcare providers, was utilized to standardize translation of English questions into Twi/Akan. However, nuanced differences in translation may persist, causing bias between participants who completed the survey in English versus in Twi/Akan. Survey questions were verbally presented by a research assistant in the participant's language of choice to minimize limitations with literacy. Interviews were completed in an inpatient hospital setting, with potential for participants to be hesitant to respond negatively about counseling from their healthcare providers. However, research assistants had no role in patient care and the informed consent process outlined standards of confidentiality and anonymity. Additional limitations include recall bias, where participants with higher health literacy and more knowledge about preeclampsia may recall that more provider counseling was performed. Recall bias was minimized by not disclosing correct responses to the knowledge questions until the entire survey was complete. Additionally, recall bias could have unequally affected patients diagnosed with eclampsia, especially regarding provider counseling during antenatal and pre-delivery care. Lastly, additional studies are required to assess retention of knowledge over time and changes in knowledge after a patient's outpatient postpartum visit.

Table 3: Preeclampsia/Eclampsia Knowledge Score Bivariate Analysis

Factor	Preeclampsia/Eclampsia Knowledge Score			
	Mean±SD	β	95% CI	p-value
Demographic Characteristics				
Age, years				
<20	5.60±-3.65	-8.95	-12.95 – -4.95	<0.001
20-24	12.01±-3.37	-2.49	-4.88 – -0.11	0.041
25-29	12.83±-3.98	-1.69	-3.65 – -0.26	0.088
30-34	14.54±-4.35	REF	REF	REF
35-39	12.63±-4.77	-1.91	-3.77 – -0.06	0.044
≥40	14.9±-4.51	0.35	-2.62 – 3.33	0.815
Main Language Used for Healthcare				
English	15.21±-3.11	2.75	1.03 – 4.47	0.002
Twi	12.46±4.70	REF	REF	REF
Highest Level of Completed Education				
None	7.00±0.00	-4.61	-13.12 – 3.88	0.285
Primary	11.61±-4.75	REF	REF	REF
Secondary	13.49±-4.23	1.87	0.19 – 3.56	0.030
Tertiary	15.49±-3.27	3.87	2.18 – 5.56	<0.001
Clinical Diagnosis				
Preeclampsia	13.18±-4.39	REF	REF	REF
Eclampsia	12.18±-5.64	-1.00	-3.32 – 1.31	0.392
Parity[a]				
Primiparous	12.31±-4.39	REF	REF	REF
Multiparous	13.5±-4.36	1.20	-0.32 – 2.71	0.120
Primary Caregiver During Pregnancy				
Specialist obstetrician/ gynecologist	14.14±-4.15	1.54	-0.04 – 3.12	0.056
Medical officer (non-obstetrician)	17.33±-2.24	4.73	1.78 – 7.69	0.002
Midwife	12.60±-4.37	REF	REF	REF
Other	10.0±0.00	-2.60	-11.11 – 5.91	0.547
None	8.00±5.63	-4.60	-7.92 – -1.28	0.007
Number of Antenatal Appointments Attended[a]				
0-3	12.69±-5.29	REF	REF	REF
≥4	13.21±-4.23	0.52	-1.11 – 2.16	0.529
Diagnosis of Chronic Hypertension				
Yes	14.88±-3.71	2.32	0.59 – 4.06	0.009

Table 3: Preeclampsia/Eclampsia Knowledge Score Bivariate Analysis *(continued)*

Factor	Preeclampsia/Eclampsia Knowledge Score			
	Mean±SD	β	95% CI	p-value
No	12.56±-4.63	REF	REF	REF
Previous Preeclampsia/Eclampsia				
Yes	16.10±-4.04	3.25	0.35 – 6.15	0.028
No	12.85±-4.51	REF	REF	REF
Previous Gestational Hypertension				
Yes	12.91±-4.50	-0.17	-2.99 – 2.65	0.905
No	13.08±-4.56	REF	REF	REF
Previous Hypertensive Disorder of Pregnancy				
Yes	14.43±-4.49	1.58	-0.52 – 3.69	0.139
No	12.84±-4.53	REF	REF	REF
Provider Counseling				
Did your health caregiver provide information about your diagnosis?				
Yes	14.65±-3.56	3.83	2.47 – 5.18	<0.001
No	10.82±-4.85	REF	REF	REF
Did your health caregiver provide information about your causes?				
Yes	15.38±-3.34	3.15	1.57 – 4.73	<0.001
No	12.23±-4.64	REF	REF	REF
Did your health caregiver provide information about your complications?				
Yes	14.92±-2.99	3.66	2.31 – 5.00	<0.001
No	11.26±-5.05	REF	REF	REF
Did your health caregiver provide information about your future health effects?				
Yes	15.54±-2.98	3.23	1.57 – 4.89	<0.001
No	12.31±-4.67	REF	REF	REF
Provider Counseling Composite Score				
Counseled on 0 of 4 components	9.78±-4.93	REF	REF	REF
Counseled on 1 of 4 components	13.52±-4.04	3.73	1.76 – 5.71	REF
Counseled on 2 of 4 components	14.00±-3.45	4.21	2.57 – 5.86	REF
Counseled on 3 of 4 components	15.41±-2.44	5.62	3.62 –7.62	REF
Counseled on 4 of 4 components	16.38±-3.01	6.59	4.35 – 8.83	REF

Table 4. Preeclampsia/Eclampsia Knowledge Score Multivariate Analysis

Model[a]	β	95% CI	p-value
Age	0.05	-0.08 – 0.17	0.453
Language of Healthcare	-0.25	-2.12 – 1.62	0.790
Education Level	1.29	0.34 – 2.23	0.008
Parity	0.24	-0.22 – 0.71	0.306
Antenatal Care (category)	0.36	-1.03 – 1.75	0.609
Diagnosis of Chronic Hypertension	1.29	-0.25 – 2.83	0.101
Previous Preeclampsia/Eclampsia	0.77	-1.77 – 3.31	0.550
Counseling Composite Score	1.35	0.87 – 1.84	<0.001

[a]R squared=0.36

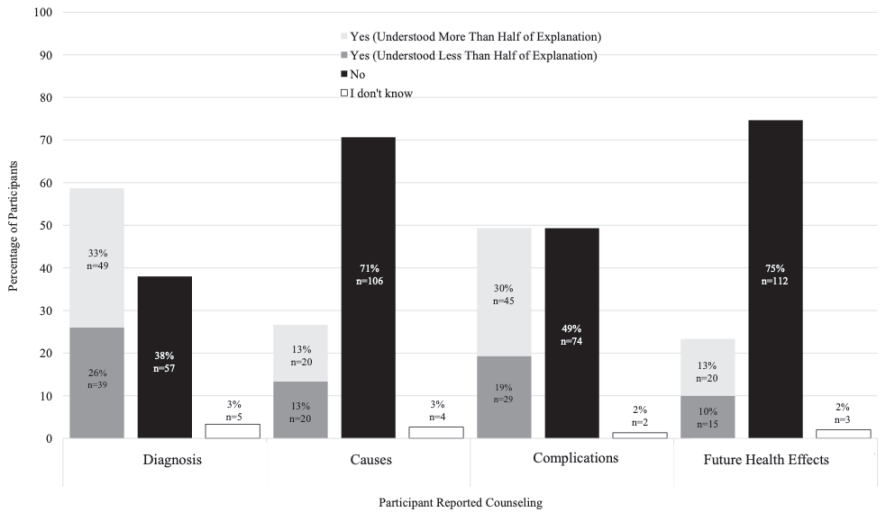

Figure 3: Reported Counseling on Diagnosis, Causes, Complications, and Future Health Effects

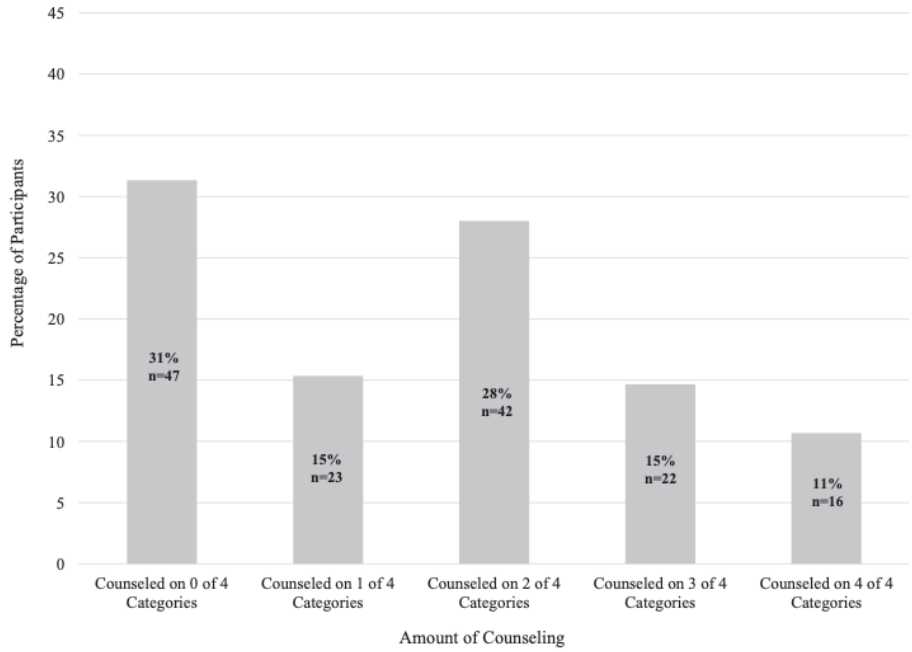

Figure 4: Reported Amount of Provider Counseling on Diagnosis, Causes, Complications and Future Health Effects (Counseling Composite Score)

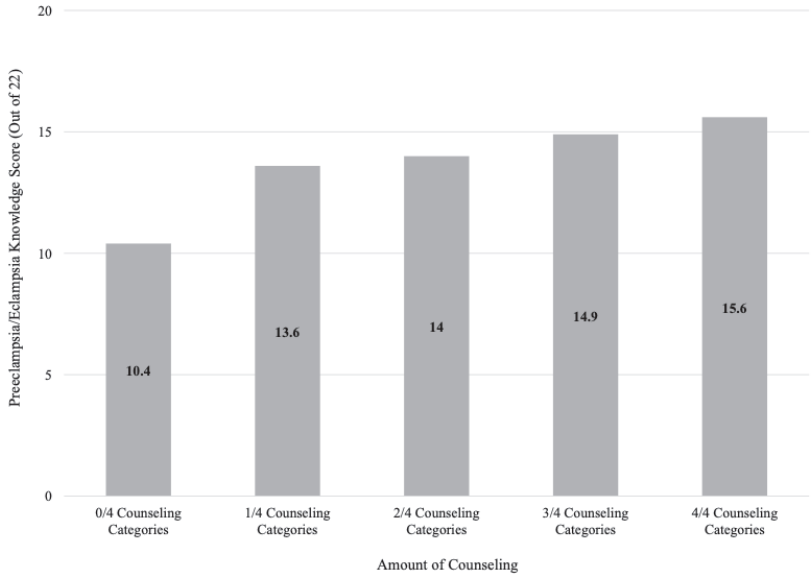

Figure 5: Impact of Provider Counseling on Preeclampsia/Eclampsia Knowledge Assessment Score

Conclusions

Our study highlights the importance of provider-based counseling in improving knowledge about preeclampsia. We demonstrate that average knowledge about preeclampsia is low, and increased counseling by healthcare providers is associated with higher knowledge scores. Knowledge about preeclampsia is important so patients may identify warning symptoms of new or worsening disease, improve healthcare-seeking behavior, and make informed healthcare decisions [15]. Given significant risk of recurrence in subsequent pregnancies, patient knowledge about causes, prevention, and recurrence of preeclampsia can promote early prenatal visits and hospital deliveries for these high-risk women. While we acknowledge there are many systemic barriers that can make counseling difficult for providers, improving counseling and ensuring that patients understand their diagnosis of preeclampsia/eclampsia is likely to improve outcomes. Findings from this research have significant implications for developing educational interventions to address knowledge gaps and improve patient counseling. Additional research is needed to evaluate the impact of educational interventions on patient knowledge, and to explore the relationship between patient knowledge and maternal and neonatal outcomes.

Abbreviations:

PEKS: Preeclampsia/Eclampsia Knowledge Score
LMIC: low- and middle-income country
ANC: antenatal care
KBTH: Korle Bu Teaching Hospital
WHO: World Health Organization

Declarations:

Ethics approval and consent to participate:
Ethical approval was granted by the Scientific and Technical Committee of the Korle Bu Teaching Hospital (KBTH-IRB 00096/2018) and the University of Michigan Institutional Review Board (HUM00139104). Participants completed written consent at the time of enrollment.

Consent for publication:
Not applicable.

Availability of data and materials:
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests:
The authors declare that they have no competing interests

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Authors' contributions:
All listed authors meet criteria for authorship. ERL, CAM, TB, and SAO made substantial contributions to conception and design of the work. AJ, ERL, and CAM were significantly involved with data acquisition and analysis. All authors drafted and revised the work, approved the submitted version, and agreed to be personally accountable for their own contributions to the work.

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Exploring self-blame and the perceived causes of preeclampsia in urban Ghana

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Authorship statement

I contributed to defining the research question, proposed the methodology and the survey design, carried out the survey together with a medical student whom I supervised, and did the data analysis together with the student. The student wrote the first draft (therefore, I am second author) and revised it after the comments of myself and the other co-authors

SYNOPSIS

Many women blame themselves for the development of preeclampsia, and patients may benefit from an explicit discussion about the causes of preeclampsia with their healthcare provider.

Preeclampsia/eclampsia is a major complication of pregnancy in developing countries. [1, 2] Whilst the existing literature focuses on the epidemiological and clinical aspects, the present study explores patient experience with preeclampsia/eclampsia among women in Ghana.

Participants were adult postpartum women diagnosed with preeclampsia with severe features or eclampsia, admitted to Korle Bu Teaching Hospital (KBTH), Accra, Ghana. Ethical approval for this study was granted by KBTH (KBTH-IRB/00096/2018) and the University of Michigan (HUM00139104). Participants were identified using maternity ward admission logs and provided written consent for inclusion in this study. The participants completed a postpartum survey, administered by a research team member, including questions about self-blame and perceived provider counseling. Participant understanding was assessed using a fact-based knowledge assessment. Multiple logistic regression analysis was used to evaluate predictors of self-blame.

From November 2019 to March 2020, 150 participants were recruited, 133 (88.7%) with preeclampsia and 17 (11.3%) with eclampsia. Participants had a mean age of 31.4 years, 54 (36%) were primiparous, and 71 (47%) had only undergone primary education.

Regarding perceptions of self-blame, 10 (6.8%) participants were told that development of preeclampsia/eclampsia was their fault, 26 (17.5%) believed it was their fault, and 58 (38.7%) believed they could have done something differently to prevent it. Of these women, the most common response regarding prevention was decreasing emotional stress during pregnancy, and 32 (55%) prevention responses were based on misperceptions (**Table 1**).

Table 1 Participant responses on perceived self-blame and prevention of preeclampsia

Survey question	All participants (n=150)
Did your condition cause you emotional distress?[a]	
Yes	84 (56.4%)
No	54 (36.2%)
I don't know	11 (7.4%)
Did your condition cause you financial burden?[a]	
Yes	99 (66.9%)
No	35 (23.6%)
I don't know	14 (9.5%)
Do you plan to get pregnant again?[a]	
Yes	52 (34.7%)
No, because of my experience with preeclampsia	16 (10.7%)
No, for other reasons	44 (29.3%)
I don't know	28 (25.3%)
Were you told by anyone that development of this condition during pregnancy was your fault?[a]	
Yes	10 (6.8%)
No	134 (90.5%)
I don't know	4 (2.7%)
Do you believe that development of this condition during your pregnancy was your fault?[a]	
Yes	26 (17.5%)
No	94 (63.1%)
I don't know	29 (19.5%)
Do you believe there is something you could have done to prevent the development of this condition during your pregnancy?	
Yes	58 (38.7%)
No	64 (42.7%)
I don't know	28 (18.7%)
If you believe you could have done something differently, what could you have done to prevent preeclampsia?	**Participants who believe they could have prevented preeclampsia (n=58)**[b]
Decreasing emotional stress ("Thinking too much," "Shouting," Feeling depressed")	16 (27.5%)
Decreasing physical stress/working less ("Working too much," "Should have relaxed more")	8 (13.7%)
Medication compliance	8 (13.7%)
Changing diet/weight	7 (12.1%)
Earlier ANC/medical care	7 (12.1%)
"If I had known earlier"	6 (10.3%)
"If I had received more information"	5 (8.6%)
"I should not have gotten pregnant"	1 (1.7%)
"I should not have been afraid to come to the hospital"	1 (1.7%)
"If I had not gotten family planning, this wouldn't have happened"	1 (1.7%)

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[a]Total number of responses <150 due to missing data

[b]Total number of responses >58 due to participants reporting multiple prevention responses.

In an adjusted logistic regression analysis, predictors of self-blame (believing it was their fault) included a woman being told preeclampsia was her fault (OR 7.6, 95% CI 1.3–45.5, *P*<0.05), and a woman believing there was something she could have done to prevent preeclampsia (OR 10.0, 95% CI 2.6–38.9, *P*<0.05). Self-blame was independent of diagnosis (preeclampsia versus eclampsia), delivery outcome (live birth versus stillbirth), and education level. Self-blame was also independent of perceived provider counseling and the participant's score on the knowledge assessment.

Future reproductive plans were affected, with 16 (10.7%) women not planning on future pregnancies due to their experience with preeclampsia/eclampsia. Eighty-four (56.4%) participants experienced emotional distress and 99 (66.9%) reported experiencing a financial burden.

Regardless of perceived quality of intrapartum care, self-blame may be an important aspect of the patient experience of preeclampsia/eclampsia and is dependent on whether a patient is told that development of the condition is her fault. This suggests that women may benefit from an explicit statement that development of preeclampsia/eclampsia is not their fault. Understanding the patient experience can help develop counseling tools and policies that support women affected by preeclampsia/eclampsia.

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Footnotes
CONFLICTS OF INTEREST
The authors have no conflicts of interest.

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‘I don’t really understand this BP’: Women’s knowledge, attitudes, and experiences with preeclampsia in Ghana

Short title: Women’s knowledge, attitudes, and experiences with preeclampsia in Ghana

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Authorship statement

I contributed to defining the research question, proposed the methodology and the study design, conducted the study together with a medical student whom I supervised, and did the data analysis together with the student. The student wrote the first draft (therefore, I am second author) and revised it after the comments of myself and the other co-authors

ABSTRACT

Preeclampsia and eclampsia are common, serious complications of pregnancies, often presenting as obstetric emergencies. In low- and middle-income countries, limited numbers of healthcare providers and a high volume of critically ill patients can negatively impact provider communication and counseling. Lack of knowledge and awareness of preeclampsia and eclampsia among pregnant women can lead to delays in health seeking behavior. Our study uses grounded theory to explore patients' experience of preeclampsia and eclampsia in a low-resource setting. Participants were postpartum women diagnosed with preeclampsia or eclampsia at Korle Bu Teaching Hospital in Ghana. Interviews consisted of semi-structured, open-ended questions regarding participant understanding of their diagnosis of preeclampsia and eclampsia; counseling from their healthcare providers; and experiences with their delivery, monitoring, and treatment. Qualitative thematic analysis was performed according to the Attride-Sterling analytical framework, using NVivo 12. A total of 45 women were interviewed, 88.9% with preeclampsia and 11.1% with eclampsia. Major themes identified include participants' low general knowledge of their diagnosis, inadequate counseling from healthcare providers, and resulting emotional distress. Women desire more information regarding their diagnosis and associate their health-seeking behaviors with counseling they receive from healthcare providers. Women also acknowledge the systemic barriers that make patient care and counseling challenging for providers, especially in low- and middle-income countries. These findings highlight the global need for improved models of counseling and health education for women with pregnancies complicated by preeclampsia and eclampsia.

Introduction

Preeclampsia and eclampsia are common and serious complications of pregnancies across the world (1-2), affecting 2-10% of pregnancies (3) and contributing to maternal morbidity and mortality, as well as poor neonatal outcomes (4-6). The incidence and burden of preeclampsia and eclampsia are higher in low- and middle-income countries (LMICs) like Ghana (1,7). In some hospitals in Ghana, preeclampsia and eclampsia have overtaken postpartum hemorrhage as the leading cause of maternal mortality (8-9).

Preeclampsia and eclampsia often present as obstetric emergencies (7), which require prompt action (10), repeated administration of medications (11), and preterm delivery of neonates with Neonatal Intensive Care Unit (NICU) admission (4-5). Prolonged postpartum hospital admission is often needed for both mothers and their neonates (12). In LMICs, the experience of labor and delivery can be stressful, overwhelming, and painful (13-15) due to obstetric environments being limited by the number of providers and a high volume of critically ill patients. This creates challenges for communication and counseling (16-17).

While a significant amount of research has been conducted on the clinical care and healthcare outcomes of pregnancies complicated by preeclampsia and eclampsia, limited prior research has been done on the patient perspective. Using in-depth semi-structured interviews, our study aims to explore the experience of postpartum women in Ghana whose pregnancies were complicated by preeclampsia or eclampsia. Gaining a better understanding of attitudes, knowledge, and experiences of these patients may inform improved counseling and care of this high-risk obstetric population.

Methods

Study setting

Our study was conducted at the Korle Bu Teaching Hospital, which is a large tertiary referral hospital located in Accra, Ghana. The maternity unit conducts approximately 10,000 deliveries per year. Patients receiving care at Korle Bu include those who reside in Accra, as well as referral cases from Accra and throughout southern Ghana. In Ghana, the majority of women receive antenatal care through the government healthcare system, which consists of a hierarchical system of district hospitals, regional hospitals, and tertiary care hospitals. In 2016, the World Health Organization began recommending at least eight antenatal visits (18), an increase over the previous recommendation of visits, which 89% of pregnant women in Ghana routinely received as of 2017 (19). Data from the 2019 Ghana Malaria Indicator Study suggest that only 40.7% of women received 8 or more ANC visits during their last pregnancy (20), and while recommended, it is not clear what percentage were screened for blood pressure and urine protein at each visit. Preeclampsia with severe features and

eclampsia are managed with inpatient admission, administration of magnesium sulfate for seizure prophylaxis, antihypertensive medication, and prompt delivery (21-23).

Ethical approval for the study was granted by the Scientific and Technical Committee of the Korle Bu Teaching Hospital (KBTH-IRB 00096/2018) and the University of Michigan Institutional Review Board (HUM00139104).

Participants

Study participants were patients admitted to the Korle Bu Teaching Hospital with a clinical diagnosis of preeclampsia with severe features or eclampsia. Inclusion criteria were age 18 years or older and fluency in either English or Twi/Akan.

Recruitment

Participants were identified using admission logbooks on the maternity wards, which listed the name and basic demographic information for every admission to the maternity ward for labor or scheduled cesarean section. The logbooks were reviewed every morning and evening by the research assistant, and clinical charts of new admissions were reviewed to assess for a qualifying clinical diagnosis of preeclampsia or eclampsia. All participants with a qualifying diagnosis were purposefully recruited based upon their diagnosis, and recruitment continued until thematic saturation was achieved.

Grounded theory

Grounded theory is a qualitative approach for collecting and analyzing data without imposing previously constructed theoretical frameworks (24-25). This approach was used to capture participants' perspectives without assuming they would conform to the researchers' ideas about preeclampsia and eclampsia in Ghana.

Data collection

Data collection was completed between November 2019 and January 2020 by two trained research assistants, one of whom was an American female medical student and the other was a Ghanaian male research assistant fluent in Twi/Akan. Research assistant training focused heavily on qualitative interviewing techniques, using mock interviews, immediate feedback, and ongoing review and discussion of transcripts to ensure consistent and appropriate application of the principles of qualitative interviewing (26). In addition, research assistant training included orientation to the sensitive nature of interview topics and culturally appropriate approaches to asking about poor pregnancy outcomes. Written informed consent was obtained from all participants. Participants had the option to pause or stop the interviews at any time, and to skip any questions that caused significant distress. Participants first met the research assistants during the informed consent process and were oriented to the job title and credentials of the research assistants. Research activities were conducted in either English or Twi/Akan, based on the participants' choice. Interviews were conducted face-to-face during the participants' admission on

the postpartum inpatient ward, at least two full days following delivery. The only people present for the interview were the participant and one research assistant. Each interview consisted of a series of semi-structured, open-ended questions regarding the patient's perspective and experience of preeclampsia/eclampsia (see supplementary file 1). The interview lasted approximately 30 to 60 minutes included probes focused on participants' understanding of their diagnosis, experiences with counseling and treatment, challenges faced, and reflections on emotional and financial impact. The list of probes was written in English and translated to Twi/Akan by an external consultant with fluency in English and Twi/Akan and expertise in linguistics. Probes were then back-translated into English to ensure accuracy. Prior to data collection, the questions were pilot tested in a comparable population of pregnant women. Demographic information was collected from each participant's clinical record and entered into a REDCap database. Data included age, education level, clinical diagnosis (preeclampsia vs eclampsia), gestational age at delivery, mode of delivery, need for NICU admission, primary language used for healthcare, and length of hospital admission. Interviews were conducted until thematic saturation was reached, reflecting no new information being gained from subsequent interviews. No repeat interviews were performed.

Analysis

Demographic data were transferred from REDCap to STATA (Version 16.0 StataCorp. 2) for statistical analysis. Interviews were audio recorded, those done in Twi/Akan were translated from Twi/Akan to English by a research assistant fluent in both languages, and then transcribed verbatim. The accuracy of translation was validated by review of five randomly selected transcripts by an external individual fluent in both English and Twi/Akan. No field notes were taken. Transcriptions were not returned to participants to review, and participants did not give feedback on the findings. Interview transcripts were entered into NVivo 12, which was used to organize the qualitative coding process. All transcripts were read by two of the researchers, who conducted independent in vivo coding (27), and then worked together to generate a preliminary list of thematic codes in keeping with the Attride-Sterling thematic analysis construct of 'basic themes' that preclude the identification of organizing and global themes (28). A third researcher reviewed the list of codes against selected interviews. The research team then discussed each code and developed a coding dictionary. Each interview was coded according to the coding dictionary, with weekly discussions regarding any questions, concerns, or inconsistencies. Group discussions were used to resolve coding issues. Once the first round of basic themes were identified, group discussion anchored in the Attride-Sterling framework (28) guided further development of organizing and global themes, resulting in the final themes presented here. Reporting for this study was completed based on the COREQ checklist for qualitative research (see supplementary file 2) (29).

Results

Table 1 demonstrates the demographics of interviewed women. Forty-seven sequential women meeting inclusion criteria were recruited and all agreed to participate, however two women were discharged prior to the planned interview. A total of 45 women were interviewed—88.9% (n=40) with preeclampsia and 11.1% (n=5) with eclampsia. Approximately half of the interviews (n=24, 53.3%) were conducted in English and the remainder were conducted in Twi/Akan. Participants had a median age of 31 years and median parity of two. Forty-four percent (n=20) of participants were primiparous. The median gestational age at delivery was 37.6 weeks, two-thirds of deliveries were via cesarean section (n=30, 66.7%), and the median length of maternal hospital admission was seven days. Seven women (15.6%) experienced a stillbirth. Of women with a live birth, half of their babies required a NICU admission, with a median NICU admission of eight days.

Table 1: Demographic Factors of Participants (N=45)

Characteristic	n (%) or median (range)
Language Used for Interview	
English	24 (53.3)
Not English	21 (46.7)
Age, years	31 (18-42)
Highest Level of Completed Education[a]	
None	1 (2.3)
Primary	16 (37.2)
Secondary	12 (27.9)
Tertiary	14 (32.6)
Clinical Diagnosis	
Preeclampsia	40 (88.9)
Eclampsia	5 (11.1)
Length of Hospital Admission, days	7 (3-30)
Parity	2 (1-6)
Primiparous	20 (44.4)
Multiparous	25 (55.6)
Gestational Age at Delivery, weeks	37.6 (21.3-42.3)
Mode of Delivery	
Vaginal	15 (33.3)
C-section	30 (66.7)
Outcome of Delivery	
Livebirth	38 (84.4)
Stillbirth	7 (15.6)

Table 1: Demographic Factors of Participants (N=45) *(continued)*

Characteristic	n (%) or median (range)
NICU Admission[b]	19 (50.0)
Length of NICU Admission, days	8 (1-60)
Status of Baby at Discharge[c]	
Alive	35 (92.1)
Dead	3 (7.9)

[a]Out of 44 participants due to missing data
[b]Out of 38 live births
[c]Out of 38 live births

The global themes identified include: 1) women do not feel confident in their understanding of their diagnosis; 2) women perceive inadequate counseling and education from healthcare providers; 3) both of these ideas contribute to significant emotional distress of women diagnosed with preeclampsia/eclampsia; and 4) the resulting negative emotions and lack of information can lead to problems with medical compliance among this population. The following sections provide illustrative quotes demonstrating each of these themes. Each quote is followed by the participant's age and number of obstetric deliveries preceded by the term 'para.' If a participant's diagnosis progressed from preeclampsia to eclampsia, it is noted below following her age and number of deliveries. We have also noted participants who experienced a stillbirth. If not directly specified, participants were diagnosed with preeclampsia and had a live birth. Additional quotes per theme can be found in Figure 1.

Figure 1. Representative quotations illustrating global themes

Women do not understand their diagnosis

When asked about their knowledge of their diagnosis of preeclampsia or eclampsia, many women responded that they did not know anything about the condition in general.

So far, I don't know anything about it [preeclampsia]. I've never heard anything about this thing before… So… I don't know about it. I don't know what to say. (*Age 26, Para 1, experienced eclampsia*)

In fact, many women did not even know the actual name of their diagnosis, and simply referred to it as 'BP.' This was consistent throughout many interviews.

I don't actually understand this BP. (*Age 24, Para 2, experienced eclampsia*)

Referring to preeclampsia/eclampsia simply as 'BP' led to significant diagnostic confusion, as demonstrated by Figure 2. Women were not able to distinguish their diagnosis from chronic hypertension, leading to confusion about both the diagnosis and the causes of the condition. Many women incorrectly believed that emotional stress contributed to the development of their condition.

Figure 2. Interview Excerpt Demonstrating Diagnostic Confusion

While many women acknowledged they did not understand their own diagnosis, they expressed a desire to learn more about their condition.

I want more information so I can take good care of myself again in my next pregnancy. (*Age 39, Para 1, experienced eclampsia, and stillbirth*)

Many women specifically expressed a desire to know more information so that they could be more informed and take action in subsequent pregnancies.

[Providers] should explain to us what we did on our part to cause this so we can do something to prevent this from happening. *(Age 24, Para 2, experienced eclampsia)*

Inadequate counseling and communication from healthcare providers

The majority of participants discussed at length the inadequacy of the counseling they received about their diagnosis from healthcare providers. Women describe a healthcare setting that does not include the patient in discussion of her diagnosis.

They haven't really explained anything to me. All they come and ask how I'm doing, go and do labs, get this medicine and [tell me to] take it. They never explained what is wrong with me. (*Age 30, Para 1 – this participant is a nurse)*

Inadequate explanations from providers led to dissatisfaction with medical care. Additionally, many participants described a general sense of dismissal regarding the patient's input in their own healthcare.

I actually blame the place I was going for antenatal care because the nurses don't let you explain, they don't let you tell your side of it. They don't actually ask you what is wrong with you for you to explain… Then they tell you "oh I guess you are fine because you have strength" [you look healthy]. (*Age 28, Para 1, experienced stillbirth*)

If participants wanted information, instead of relying on counseling from providers at antenatal visits, they had to have some baseline level of working knowledge of the condition—especially in knowing which questions to ask.

When I was going for antenatal, it seems that all the information that you need, you will have to ask. They don't really give you much information... So, you have to ask virtually everything. (*Age 21, Para 1*)

In addition to the lack of disease-specific counseling, participants described a lack of explanations of procedures involved with preeclampsia treatment. Participants also spoke about being overwhelmed by the number of providers working on them at the same time.

One person should come one at a time. Because if I'm taking an [intravenous access] and they're setting a line for me, I don't expect you to be pricking my hand as well or injecting me, on the other side. Another person injected my buttocks here, no, it's too much for me. I can't take it. (*Age 30, Para 3*)

Participants expressed frustration about inadequate explanations, or explanations that were difficult to understand due to use of medical jargon. This led to significant negative feelings toward providers and how they treat admitted patients.

They treat us like we don't know what's going on.... [providers] just come and do whatever they like... and they will respond to you if they see fit... you can go to [a provider] and question them and nobody explains. (*Age 27, Para 1*)

I don't think [providers give explanations to patients]. They just give you the term and then they just leave you to try and understand it on your own. And it's not fair. (*Age 27, Para 1*)

Inadequate counseling and communication from healthcare providers led to women seeking information via alternate sources (see Figure 1 for more examples).

That [A negative interaction where the physician failed to provide an explanation] was the reason I decided not to go to the hospital anymore. I decided to see an herbalist and she started to give me the BP drugs. (*Age 28, Para 2, experienced eclampsia*)

In some cases, a lack of counseling led to decreased compliance with medical advice.

Yes, I did not get a good explanation. So, the [healthcare providers] started to tell me to go and do something and I didn't do it.... Will you blame me for that? (*Age 35, Para 4)*

Emotional distress

Interviewed participants described many reasons why their experience with preeclampsia was challenging. These reasons included needing to undergo a caesarean section for delivery, the experience of medication administration, worrying about the well-being of their babies—especially those who were admitted to the NICU, and the financial burden caused by the condition. Additionally, it appeared the emotional distress that was experienced by many patients was related directly to their lack of understanding about the condition, to which their experience with providers was a major contributor.

No one told me anything and then just yesterday they told me I have this condition. I feel terrified and it's painful. (*Age 28, Para 1, experienced stillbirth)*

Many women described a sense of shock and feeling unprepared for preeclampsia/eclampsia and its consequences during their pregnancy. One respondent even commented directly that more information earlier in her pregnancy would have helped her cope with the condition.

All I can say is that if I had information earlier, then psychologically, I would have felt better. (*Age 30, Para 3)*

The negative emotions and lack of understanding of their condition also led to women feeling responsible for development of the condition, resulting in feelings of self-blame.

It was quite stressful… I kept asking myself lots of questions. I wanted to know where I went wrong because I thought everything had been quite OK. (*Age 30, Para 3)*

The lack of information from providers contributed significantly to negative emotions and fear experienced by women when they were diagnosed with preeclampsia. However, when women did receive counseling about their diagnosis, they described some of their emotional burden being alleviated.

It was not easy because I was afraid [of the diagnosis of preeclampsia]… but they told me and they educated me about [preeclampsia]. They explained things to me and then I accepted it. (*Age 32, Para 4)*

Provider barriers

While there is overwhelming evidence regarding inadequate communication, many patients explicitly recognized barriers that make it more challenging for providers to provide sufficient counseling (See Figure 3). Many participants acknowledged that providers have a very large number of patients to simultaneously care for.

Figure 3. Barriers Faced by Health Care Providers

[The providers] are doing their best. But ... they have limitations. They don't have enough time. They have so many people to attend to and I think their duties are quite huge. (*Age 30, Para 3*)

In addition, participants recognized provider limitations due to general attitudes and misperceptions toward the necessity of healthcare.

I thought [going to antenatal care] was not needed at all. *(Age 38, Para 3)*

These barriers, along with others acknowledged by participants, demonstrate just a few of the systemic barriers providers face when providing care and counseling to patients.

Discussion

This qualitative study of 45 women with preeclampsia/eclampsia in Ghana illustrated that across age, education, and language spoken, there was a general lack of knowledge regarding the diagnosis, inadequate counseling by healthcare providers, and resulting significant emotional distress. Many women reported not knowing the name of their diagnosis or understanding what it was, and in some cases, those misunderstandings or diagnostic confusion directly contributed towards feelings of self-blame. Women also reported that providers did not include them in discussions about their own healthcare. Many reported that their questions were either not invited or were dismissed. This led to feelings of dissatisfaction with the medical system and frustration with medical care.

Many women expressed a desire to learn more about their condition and felt that being more knowledgeable would have allowed them to take action in their current pregnancy, or to make informed decisions in subsequent pregnancies. Some women even sought information from alternative sources; during antenatal care, they did this by talking with family and friends and getting advice from religious sources and traditional healers. During their inpatient admission, some participants reported reading their own medical chart and searching on the internet. It is worthy to note that participants attributed inadequate counseling from medical providers to their own non-compliance with medical recommendations. These themes were consistent across participants, including those who were fluent in English and those with high levels of education.

Limited prior research has been conducted on the patient perspective on preeclampsia, with the majority of exiting literature focused on preeclampsia knowledge. The findings of this study are consistent with studies completed in both high-income countries, such as the U.S. and Australia (30-32), as well as LMICs, like Ghana, Nigeria, Tanzania, and Malaysia (33-38), which demonstrate overall low levels of knowledge regarding preeclampsia. This lack of knowledge is not only shown with objective knowledge assessments but is also directly acknowledged by study participants themselves. While many of our participants expressed low levels of knowledge about preeclampsia, they also demonstrated a desire to have more information regarding their condition—whether through reading their own charts or seeking information on the internet or from friends. This is consistent with other studies that have demonstrated patient desire for more knowledge regarding preeclampsia (30). This presents an opportunity for patient education, especially within the healthcare setting. In fact, several studies show patients have more objective knowledge regarding preeclampsia/eclampsia if they have had a discussion about their condition with a healthcare provider (32, 35, 39). The lack of patient knowledge is tied to the nature of interactions with healthcare providers, as demonstrated by our participants who expressed frustration regarding the amount of initiative patients must take in order to ask, ‘the right questions.’ This was also seen in a Nigerian study, which directly correlated the educational value of antenatal care visits

with patient knowledge and directed questioning (37). Without preexisting knowledge, patients are unable to gain more information from their providers. This has significant implications, as it is known that when women receive prenatal education on symptoms of preeclampsia, it may result in improved outcomes (40-44).

Overall, our participants expressed a general dissatisfaction with their interactions with healthcare providers. This is consistent with a wide body of literature worldwide regarding healthcare provider communication and the lack thereof, as well as maltreatment of women during maternity care (15, 37, 45-46). This maltreatment and lack of communication is even acknowledged by healthcare providers (15) and has a known detrimental effect on patient compliance and trust in their providers (45-46). In the long term, the quality of patient-provider interactions has the ability to strongly influence future health-seeking behaviors (37).

Prior studies on the emotional burden of preeclampsia and eclampsia have demonstrated women feeling scared, unprepared, guilty, and with a high sense of self-blame regarding their diagnosis of preeclampsia (31, 47), all of which are consistent with the sentiments expressed by our study participants. These studies have shown a direct link in lack of knowledge to those feelings of self-blame, as many women do not know the diagnostic causes of preeclampsia and often feel there was something they should have done better or differently to prevent it. Many women incorrectly believe changing their diet or reducing emotional stress could have prevented preeclampsia, leading to significant feelings of self-blame (47).

The lack of knowledge compounded by negative interactions with healthcare providers contribute to the emotional state of this already vulnerable population. Consistent with a few of our interviews, one study found that having a trusting and continuous relationship with their healthcare provider and feeling informed about their condition positively impacts a woman's experience with preeclampsia (31). While our data acknowledges there are many systemic barriers for healthcare providers (Figure 3), this presents an opportunity for increased education of preeclampsia to the general population. As suggested by our participants, this may imply more educational material provided in other forms, such as through television, the internet, or social media.

Ultimately, it is important to acknowledge the emotional impact of preeclampsia/eclampsia, especially due to the fact that many women feel a sense of unpreparedness and self-blame. As demonstrated by our data and several other studies, these feelings may be positively modified by informative interactions with healthcare providers to promote patient knowledge, empowerment, and agency. This further has the ability to impact life-long patient health-seeking behaviors.

Our study fills an important gap in the literature by exploring the patient perspective on preeclampsia and eclampsia in a low-resource setting. Nonetheless, this study has several limitations. First, our study was conducted at a single tertiary hospital in Ghana. While our qualitative study design precludes traditional discussion of generalizability, the Korle Bu Teaching Hospital provides care for women from urban Accra, as well as referrals from peri-urban and rural areas throughout southern Ghana. Participants represented a wide range of ages, parity, education level, and primary language of healthcare conversations, which supports the diversity of responses that were included and the likelihood that these findings are indeed valid. Second, interviews were conducted in an inpatient hospital setting, which may have made participants feel uncomfortable sharing responses that were critical of their healthcare providers or facility. To limit this bias, interviews were conducted by research assistants not connected with the healthcare team and the informed consent process included reassurance that participation would have no impact on their medical care. Third, there is not a direct translation of the clinical term "preeclampsia" or "eclampsia" in Twi/Akan, which is a primary local language spoken by many participants in our study. This may contribute to challenges for providers in providing clear counseling and to women's lack of understanding of their condition. However, similar themes were seen across all participants, including those whose healthcare counseling and study interview was conducted in English.

Conclusion

We demonstrate that women with preeclampsia and eclampsia experience common themes of low knowledge about their diagnosis, inadequate counseling by healthcare providers, and emotional distress. Women recognize barriers to communication with their providers, including high patient volume and limited time and number of providers. Women want to be more informed about their diagnosis, and some attribute their non-compliance with medical recommendations to the quality of counseling they receive. This connection is especially important, because occurrence of preeclampsia or eclampsia is a risk factor for recurrence in future pregnancies and negative experiences may impact future health-seeking behaviors. These findings highlight the need for improved models of counseling and health education that support patients, particularly those with recurring pregnancy complications like preeclampsia and eclampsia. Women's acknowledgement of provider barriers also suggests that future studies on the provider perspective of counseling could be helpful in creating and implementing improved models of counseling and health education. Understanding the patient perspective on preeclampsia and eclampsia helps inform the patient's understanding of their diagnosis, their experience with obstetric care, and their attitudes toward future engagement in the healthcare system.

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10

GENERAL DISCUSSION

Authorship statement

I had the idea and set-up of the general discussion; I conducted the literature search andwrote the general discussion. During the whole process I asked for and implemented input and feedback from my supervisors. The general discussion represents my opinion and viewwhich may be different from that of my supervisors

Magnesium sulfate treatment protocols in clinical practice – the search for an optimal dosing regimen.

Magnesium sulfate therapy has been the cornerstone of seizure prophylaxis in preeclampsia and eclampsia for decades. Though the mechanism of action of magnesium sulfate in seizure prophylaxis for preeclampsia and eclampsia is poorly understood, it has proven clinical efficacy: compared to placebo, magnesium sulfate lowers risk for eclampsia with 58% in patients with preeclampsia.[1] It is the recommended anti-convulsant of choice by the World Health Organization (WHO) for the prevention of seizures in preeclampsia and eclampsia.[2]

Despite several decades of experience with its use, and the wide clinical acceptance of magnesium sulfate for seizure prophylaxis in hypertensive disorders, several dosing regimens exists - with most dosing protocols in current clinical practice being empirical and lacking the evidence of standard exposure-response studies.[3,4] The most widely accepted treatment regimens are the Zuspan and Pritchard regimens.[1,3,4] In most LMICs, the intramuscular (Pritchard) regimen and its modifications are commonly used because of limited material and human resources for administration and monitoring of the in such settings.[4] The search for the minimum effective dose of magnesium sulfate for seizure prophylaxis in clinical practice has seen several modifications done to the standard Pritchard or Zuspan regimens with almost all variations reducing the dose and or duration of treatment.[5–11] The reasons for these variations have been cost, maternal safety and availability of resources.[12] The safety concerns were confirmed in the Magpie trial, when the prevalence of composite side effects (such as flushing, nausea/vomiting, respiratory depression, reduced/absent tendon reflexes etc) was 24% in patients receiving standard doses magnesium sulfate compared to 5% in patient on placebos.[1]

This thesis defines in a chapter 2 a new intramuscular regimen of magnesium sulfate for seizure prophylaxis in preeclampsia with severe features and eclampsia, the Beyuo regimen, which is a modification of Prichard regimen with a shorter duration of treatment compared to the standard Prichard regimen.[13] This was subsequently tested in a randomized trial in chapter 3.[14] The Beyuo regimen has a fixed duration of treatment, which is 12 hours from the timing of diagnosis, irrespective of the timing delivery or the last fit.[13] This is in contrast to the Pritchard regimen which has a minimum duration of 24 hours if initiated after delivery of the last fit and can have an extended duration if initiated before delivery or if the last fit occurred before delivery because it stipulates 6 maintenance doses be given after delivery or the last fit, whichever comes later[12]. The Beyuo regimen is distinct from other shorter duration regimens that define the period of maintenance in relation to the postpartum period, as all such regimens could potentially be administered for longer periods in the event of antepartum initiation of therapy. Whereas all other regimens define the duration of treatment in relation to postpartum period, ie 12-hours post-delivery or 24-hours post-delivery, the Beyuo regimen defines a fixed 12-hour total duration of treatment inclusive of antepartum therapy (if initiated before delivery). This

novel regimen has demonstrated comparable clinical efficacy in seizure prophylaxis with the Pritchard regimen. In addition to the shorter duration which obviously translates to less cost, we demonstrated fewer side effects, shorter duration of urethral catheterization and shorter hospital stay.

In clinical practice, however, implementation of the Beyuo regimen must consider the local setting because this regimen was tested in a setting where most patients with the diagnosis of preeclampsia with severe features or eclampsia proceed rapidly to delivery with the median initiation of loading dose-to-delivery time of 14.6 hours.[14] In LMIC settings such as the Korle Bu Teaching Hospital (KBTH) in Ghana where the trial took place, the cost associated with use of longer duration regimen of magnesium sulfate, such as the personnel and monitoring required to safely administer magnesium sulfate, may be significant. The additional benefits of preventing additional injections to reduce side effects, the discomfort to patients and risk of non-compliance to such longer duration protocols may be incentives for the use of shorter duration protocols such as the Beyuo regimen.

The attempts to devise a safe and effective protocol that is acceptable to caregivers and patients resulted in several varied treatment regimens evaluated in clinical studies.[6,10,11,17–19] To date the optimum regimen remains elusive. Sadly, many of these protocols, though they demonstrated some clinical efficacy, have never gained wide clinical acceptance.[6,10,11,17–19] Thus, beyond the generation of evidence from RCTs for optimal regimens, the acceptance and uptake into clinical guidelines and practice is an essential bottleneck. This has called into question the life cycle of clinical treatment regimens. Like the drug development process, the journey of new treatment regimens for existing drugs or variations to standard surgical procedures or techniques - from the conception stage, through development and testing in clinical trials, and ultimately translating into accepted clinical practice appears to be a difficult one. Many potential regimens or new techniques fail to reach their intended destination - wide clinical usage and adoption into practice guidelines. Their “valley of death” is the stage between clinical trial and the transition into clinical acceptance in the form of guidelines /protocols as has been identified in other disciplines of medicine.[18] The reasons most new regimens do not traverse this “valley of death” may include the fact that the study results may not be generalizable, the study sample size may be considered too small to influence a policy change or the barriers to implementation in the clinical setting. To overcome the barrier of lack of generalizability, larger and multi-center studies involving different populations are recommended to evaluate new clinical regimens such as the Beyuo regimen.

To bridge the valley of death, we propose a critical evaluation of new and existing clinical treatment regimens or techniques through the plan-do-check-act (PDCA) cycle (figure 1 below), as a promising strategy.[19] For existing regimens and techniques, the review will assess their relevance to contemporary practice and the data supporting their continuing use. As we discovered in the case of magnesium sulfate, some of the widely accepted

and practiced regimen are at best empirical and lacking robust scientific basis for their adoption.[3] For new regimens, this evaluation could unveil the facilitators and barriers to progression into clinical acceptance as well as their adherence in practice guidelines during the implementation phase.

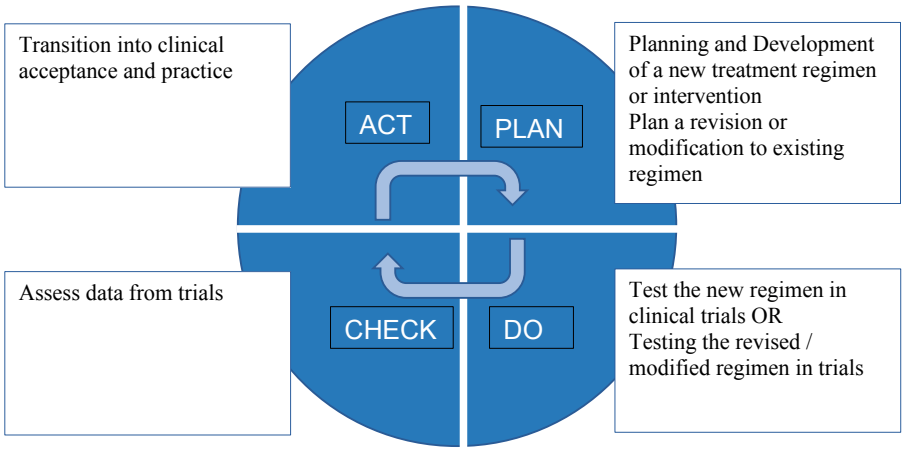

Figure 1: PDCA cycle applied to treatment regimens

In general, implementation and adherence to evidence-based interventions, clinical guidelines, and protocols in most LMICs and to some extent in some high-income-countries (HICs) has been low[20,21,22] . More specifically, clinical audit of protocols in a LMIC revealed variable adherence to clinical protocols in the management of preeclampsia with severe features and eclampsia[23]. Unpublished hospital data across many referral hospitals in Ghana assessed prior to the development of the Beyuo regimen revealed very poor adherence to the standard Pritchard regimen, with many centers practicing a modification of the regimen where patients received only six maintenance doses irrespective of the timing of initiation or delivery. This has been confirmed by Browne et al in their study that revealed poor adherence of 45% to the specific component of the Pritchard regimen requiring continuation of the maintenance doses for 24 hours after delivery[23]. Challenges with the implementation of clinical protocols identified in LMICs include health system level barriers (lack of material and financial resources, human resources, communication/information sharing, and policy issues), provider level barriers (inadequate training, knowledge, and skills; lack of access to or awareness of protocols; and attitudes and beliefs) and patient /community level barriers (training /knowledge/ skills, poor access/awareness, and attitudes/beliefs)[21]. Unlike the barriers, the study across LMICs found facilitators to be very variable across countries with only improved monitoring and evaluation systems staying consistent as a facilitator of implementation of protocols[21]. The Beyuo regimen was developed through the bottom-up approach in a LMIC, Ghana, through multidisciplinary team participation, patient involvement and review

of local protocols. This bottom-up approach has been demonstrated as a facilitator for successful implementation[20]. It is therefore anticipated that acceptance will be high with improved adherence during implementation in this setting. Despite the anticipated ease of clinical acceptance of the Beyuo regimen in LMICs due do its development process and its fixed and short duration of treatment, broader stakeholder engagement including patients, nurses, midwives, and clinicians is highly recommended to policy makers and clinical leaders as an enabler to promote adoption into guidelines and subsequent adherence during clinical use.

We recommend the adoption of the Beyuo regimen for settings like ours, alongside continuous monitoring, and evaluation of this protocol for adherence. Larger multinational randomized controlled trials (RCTs) are recommended to further evaluate this regimen and other shorter duration regimens via the IV route (a modification of the Zuspan regimen) in settings using mainly the IV route. Further, subjecting these new regimens to dose-response studies is recommended to explain the pharmacokinetic profile and provide a better understanding of the mechanism of action of magnesium sulfate in seizure prophylaxis.

Contextualization of positive pregnancy experience of preeclampsia and eclampsia in LMICs

The World Health Organization (WHO) has advocated for a positive pregnancy, delivery and postpartum experience for all women across the globe through policy changes and evidence based recommended interventions.[24,25] It is expected that within the context of well-resourced and functional health systems, application of the recommendations of the WHO will result in positive antenatal and intrapartum experience of care that will transition successfully into a positive postpartum experience for individual women, their families, and their communities at large. A lot of research work has been done on the implementation of the WHO recommendations for a positive pregnancy experience especially in the context of health system strengthening and respectful maternal care.[26–30] There is, however, dearth in the literature on the barriers to successful implementation of positive pregnancy experience recommendations in the context of complicated high-risk pregnancies such as preeclampsia and eclampsia receiving care in resource limited settings.

Effective communication and respectful maternity care have been identified as pillars to providing intrapartum care for a positive experience .[25] Effective communication, providing information and adequate counselling from caregivers are expected to result in women having sufficient knowledge of their diagnosis and management.[25] It has been established that women who suffered preeclampsia with severe features and eclampsia have very low knowledge of their pathologies.[31]

The inadequate counselling provided by caregivers coupled with the low patient knowledge of their condition in this setting has led to self-blame and emotional distress reported by women.[31,32]

The perceived caregiver barriers to patient-centered antenatal and intrapartum care of pregnancies complicated by preeclampsia and eclampsia, for a positive pregnancy experience as observed by patients in LMICs, include poor communication, amongst other reasons due to too few staff for crowded clinics and wards and staff attitudes.[31,33] The recognition of these barriers from our research provides the basis for the application of a health systems approach (figure 2) to minimizing or eliminating the barriers.

In LMICs, the burden of hypertensive disorders in pregnancy is significant with complications of preeclampsia and eclampsia becoming the leading cause of maternal deaths.[34–36] Unfortunately, most LMICs have under-resourced and weak health systems that are overburdened with other infectious diseases as well an ever-increasing burden of hypertensive disorders of pregnancy (HDPs). To achieve the desired outcome of a positive pregnancy experience by individuals and overall reduced national burdens of the morbidities and mortalities associated with pregnancies, a health-systems building blocks approach must be applied to the specific causes of maternal morbidities and mortalities such as hypertensive disorders and hemorrhage.

Figure 2: Health systems approach to the management of HDPs in LMICs.

Community and patient level factors influencing positive experience of pregnancies complicated by HDPs in LMICs.

At the community and patient levels, it has been established that for LMICs such as Ghana, women with HDPs have a nearly three-fold increased odds of developing eclampsia if the women get pregnant at age less than 20 years or is pregnant with twins.[37] The variation in the health-seeking behavior between the extremes of age may explain this observation. Whereas women with advanced maternal age in pregnancy are usually perceived as at increased risk of complications, may seek care more frequently and receive improved monitoring and interventions; the younger aged women perceived as at low risk for complications may lose these benefits because they tend to be poor clinic attenders and may not receive improved care. Delaying pregnancy in very young people is important to reduce the incidence of eclampsia in LMICs. In patients with the identified risk factors of younger age and twin gestation, quality antenatal care (including aspirin and calcium supplementation) and early diagnosis as well as initiation of prompt management of hypertensive disorders can prevent eclampsia, improve pregnancy outcomes, and ensure a positive pregnancy experience. When eclampsia does occur, it happens mostly antepartum, at a location outside the health facility and is witnessed by a family member.[37] Community engagement by healthcare providers and empowerment of

women and their social support network on the need to prevent eclampsia through quality antenatal care, first responder care for fits in pregnant women and psycho-social support for family members who witness eclampsia are appropriate interventions. Among women with HDPs, obesity and chronic hypertension are protective against the development of eclampsia.[37] This protection could stem from the effective management of the chronic hypertension and the increased surveillance of the risks posed by obesity in pregnancy. This may suggest that early diagnosis and management of gestational hypertension may reduce its risk of eclampsia to the risk level posed by chronic hypertension, implying a role for quality antenatal care.

Though universally recommended, evidence-based evaluation of the relationship between number of antenatal visits and pregnancy outcomes have been varied. Whiles some studies demonstrate a relationship between fewer antenatal clinic visits and worse pregnancy outcomes, including low birthweight, preterm birth, and neonatal death,[38–40] others failed to show improved outcomes,[41] especially in populations considered low risk[42]. A Cochrane Review demonstrated that there was no adverse perinatal outcomes when number of visits was reduced in high income countries, but in LMIC significantly higher rates of perinatal mortality occurred,[43] In women with preeclampsia and eclampsia in a LMIC (Ghana), where nearly 50% of women achieved the adequate number of prenatal visits recommended by the WHO for their gestational age at delivery, frequent visit reduced poor neonatal outcome but was not sufficient to improve adverse maternal outcomes.[44] The quality of antenatal care appears to be a significant factor in determining pregnancy outcomes. It has been demonstrated that receiving antenatal care at a tertiary facility and by a specialist obstetrician confers protective benefits and these factors may be proxy for quality of care, reflecting settings of improved monitoring, institution of preventive measures such as aspirin and calcium supplementation, earlier detection of hypertensive disorders, and improved overall management.

Improving the quality of antenatal care, minimizing antenatal risk indicators, empowering the patients and their communities with knowledge on preeclampsia and ultimately improving the outcomes of pregnancy to both mother and baby ensures that women and their families have a positive experience of pregnancies.

Recommendation for future research

1. Further research is recommended to subject the Beyuo regimen and other varying duration regimens to further randomized controlled trials in different populations to achieve the optimal duration of therapy. Along with these trials should be standard dose-response studies comparing these regimens to explain their pharmacokinetic profiles.
2. To improve adherence to clinical protocols and guidelines more qualitative explorative studies are recommended to evaluate healthcare worker specific factors serving as barriers and enablers to adoption and implementation of evidence-based guidelines in the LMIC setting.
3. Research into innovative techniques and avenues for patient education on preeclampsia such as peer-education by survivors and group antenatal care within the LMIC context should be explored.
4. To improve provider counselling on HDPs, future research should evaluate the provider barriers and enablers to effective patient counseling and education on preeclampsia in LMICs.

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SUMMARY OF THESIS

Hypertensive disorders in pregnancy continue to be associated with severe adverse pregnancy outcomes in low resource settings despite recommendations and interventions instituted to reverse the trend. Ensuring women with these complicated pregnancies have a positive experience of the pregnancy and postpartum period is particularly challenging in low- and middle-income countries (LMIC), partly because of the health systems challenges and the severity of disease burden that these systems are expected to manage. This thesis aimed to optimize the care and patient experience of preeclampsia in low resource settings.

S**ection 1** comprises of chapters 2 and 3, and focusses on the therapeutic backbone of seizure prophylaxis in the management of preeclampsia and eclampsia, magnesium sulfate and its treatment regimens.

We defined in **chapter 2,** a novel treatment regimen of magnesium sulfate which differed from the most widely accepted and practiced Pritchard regimen in most low resource settings. With a global consensus that magnesium sulfate is the anti-convulsant of choice in seizure prophylaxis in preeclampsia and eclampsia, a clinical equipoise has arisen on the optimal duration and dose of treatment. The novel mainly intramuscular *Beyuo* regimen is:

Loading dose: IV 4 grams of MgSO4 and 10mg IM MgSO4 (5 gram in each buttock) given at the time of antepartum, intrapartum, or postpartum diagnosis of eclampsia or preeclampsia with Severe Features.

Maintenance doses: IM 5 grams MgSO4 every 4 hours for a total of THREE doses over TWELVE hours starting at the time of diagnosis of eclampsia or preeclampsia with Severe Features

In **chapter 3**, we evaluated the *Beyuo* regimen with a shorter fixed maintenance duration of 12 hours, against the Prichard regimen with a longer variable maintenance duration of at least 24 hours in an open label randomized control (**Mo**dified versus standard **P**ritchard regimen in **E**clampsia **P**rophylaxis (**MOPEP**)) trial at a large tertiary hospital in Ghana, the Korle Bu Teaching Hospital. 1176 participants with preeclampsia with severe features (including 116 with an admission diagnosis of eclampsia) were randomized into the Pritchard regimen arm (n=584) and the Beyuo regimen arm (n=592). We found no difference in occurrence of seizure between the 24-hour group (n=9, 1.5%) versus the 12-hour group (n=5, 0.9%), (p=0.28, RR 0.55, 95% CI 0.19–1.64). Participants in the 12-hour group had a shorter period of inpatient admission and urethral catheterization, with fewer side effects from magnesium sulfate. We conclude that compared with 24 hours, 12 hours of intramuscular magnesium sulfate showed similar rates of seizures,

with fewer side effects and shorter inpatient admission. Therefore, the Beyuo regimen is the preferable preventive eclampsia intervention in LMICs. Whiles we recommend this regimen for adoption into institutional and national practice guidelines in Ghana, further trials of this regimen in different countries and populations may be required to validate it for different populations.

In **section 2**, we assessed the outcomes of pregnancies complicated by preeclampsia in a tertiary hospital in Ghana and the underlying factors associated with these outcomes. Eliciting the factors associated with adverse maternal and perinatal outcomes can provide guidance for effective interventions within the resource constraints in LMICs to improve outcomes and facilitate a positive experience of pregnancies complicated by preeclampsia and eclampsia. In **chapter 4** we assessed the factors associated with the occurrence of eclampsia in at out study site, the KBTH. This study was nested in the MOPED trial and analyzed data of the 1176 women with preeclampsia with severe features and eclampsia. About 10% of the study sample (n=116, 9.9%), had a diagnosis of eclampsia. Most women with eclampsia experienced their first seizure antepartum (68.7%), in a location outside a health facility (56.5%) and witnessed by a family member (55.9%). Women with eclampsia had a median of 1 seizure (IQR 1.0, 2.0). Only 15 (12.9%) had a prior diagnosis of preeclampsia. There was a nearly three-fold increased odds of a diagnosis of eclampsia in women aged < 20 (aOR 2.75, 95% CI 1.10-6.89) and those with twin pregnancy (aOR 2.59, 95% CI 1.26-5.32). Lower odds of eclampsia were observed with age older than 35 (aOR 0.32, 95% CI 0.15-0.67), obesity (aOR 0.44, 95% CI 0.25-0.77), and chronic hypertension (aOR 0.38, 95% CI 0.17-0.86). We conclude that in women with preeclampsia or eclampsia, younger age and twin pregnancy are associated with three-fold increased odds of eclampsia, while older age, obesity, and chronic hypertension were associated with lower odds of eclampsia. These lower odds may be due to the increased vigilance and monitoring of the women in this risk profile, implying a critical role for quality prenatal care.

In **chapter 5** we evaluated the neonatal outcomes of preeclampsia and eclampsia from mothers involved in the MOPEP trial. From the prospectively collected data, we observe that there were 1218 babies born to the 1176 women in our study. Median gestational age at delivery was 36.6 weeks (IQR 33.3, 38.9). Median birthweight was 2.3kg (IQR 1.6, 3.0), with 227 (19.0%) birthweights less than 1500g. Fifteen percent of neonates had an APGAR score <7 at 5 minutes and 147 (12.1%) were stillbirths. Of livebirths, half (n=522, 50.2%) were admitted to the NICU and 7.3% (n=89) died prior to discharge. A composite of poor neonatal outcomes was experienced by 57.9% (n=704) of babies and was twice as likely with a maternal diagnosis of eclampsia (OR 1.91, p=0.04). For each increasing week of gestational age, the probability of a poor neonatal outcome is reduced by 39% (OR 0.61, p<0.0001). We conclude that preeclampsia with severe features and eclampsia are associated with poor neonatal outcomes in our setting. Pregnancies complicated by eclampsia were twice as likely to have poor neonatal outcomes.

Having established in chapter 4 the factors associated with occurrence of eclampsia in a LMICs such as Ghana and evaluated the neonatal outcomes of preeclampsia and eclampsia in chapter 5, we assessed the impact of antenatal care on severe maternal and neonatal outcomes in pregnancies complicated by preeclampsia and eclampsia in chapter 6. This was a secondary analysis nested in a randomized control trial. Participants were adult pregnant women with preeclampsia or eclampsia at a tertiary hospital in Ghana. Measures of antenatal care utilization included timing of first visit, number of total visits, facility type, provider type, and referral status. Based on World Health Organization recommendations, pregnancies were categorized by ≥ four visits, ≥ eight visits, and adequate visits for gestational age at delivery. Outcomes were a composite of maternal complications (occurrence of pulmonary edema, acute kidney injury, ICU admission or maternal death) and a composite of poor neonatal outcomes (stillbirth, birthweight less than 1500 grams, five-minute APGAR below 7, NICU admission, death before discharge. Multivariate logistic regressions identified associations with antenatal care factors.

Antenatal care was initiated at a median of 16.0 weeks gestation (IQR 11.7-21.0). The median number of antenatal visits was 5.0 (IQR 3.0-7.0), with 72.9% attending ≥ four visits, 19.4% attending ≥ eight visits, and 54.9% attending World Health Organization-defined adequate visits. Care was most frequently provided in a government polyclinic (n=522, 47.2%) and by a midwife (n=704, 65.1%). After adjusting for age, parity, body mass index, insurance status, and gestational age at delivery, the odds of experiencing a poor neonatal outcome was lower in women who received their antenatal care at a tertiary level hospital (aOR 0.67, 95% CI 0.46 - 0.99, p = 0.04), by a specialist OBGYN (aOR 0.61, 95% CI 0.42 - 0.87, p = 0.004), and who attended ≥ 8 antenatal visits (aOR 0.69, 95% CI 0.47 – 0.99, p = 0.049). Compared to attendants, referrals had twice the odds of a maternal complication (aOR 2.00 p = 0.01) and poor neonatal outcome (aOR 1.69, p = 0.003). We conclude that fewer complications are seen in Ghanaian women with preeclampsia and eclampsia who receive antenatal care at tertiary facilities. Attending eight or more antenatal visits reduced the odds of poor neonatal outcomes, however, did not impact serious maternal complications. Quality of antenatal care is essential, not just quantity.

In the **third section** of the thesis, we looked at the patient perspective of preeclampsia and its care a tertiary hospital in Ghana. We assessed in **chapter 7,** the preeclampsia knowledge among postpartum women managed for preeclampsia and eclampsia at Korle Bu Teaching Hospital in Accra. We surveyed postpartum women diagnosed with preeclampsia or eclampsia between 2–5 days after delivery. Provider counseling on diagnosis, causes, complications, and future health effects of preeclampsia/eclampsia was quantified on a 4-point scale ('Counseling Composite Score'). Participants also completed an objective knowledge assessment regarding preeclampsia /eclampsia, scored from 0 to 22 points ('Preeclampsia/Eclampsia Knowledge Score' (PEKS)). While 74% of women reported having a complication during pregnancy, only 32% of participants with preeclampsia were able to correctly identify their diagnosis, and no participants

diagnosed with eclampsia could correctly identify their diagnosis. Thirty-one percent of participants reported receiving no counseling from providers, and only 11% received counseling in all four categories. Even when counseled, 40–50% of participants reported incomplete understanding. Out of 22 possible points on a cumulative knowledge assessment scale, participants had a mean score of 12.9 ± 0.38. Adjusting for age, parity, and the number of antenatal visits, higher scores on the knowledge assessment are associated with more provider counseling (β 1.4, SE 0.3, $p < 0.001$) and higher level of education (β 1.3, SE 0.48, $p = 0.008$). We conclude that counseling by healthcare providers is associated with higher performance on a knowledge assessment about preeclampsia/eclampsia. Patient knowledge about preeclampsia/eclampsia is important for efforts to encourage informed healthcare decisions, promote early antenatal care, and improve self-recognition of warning signs—ultimately improving morbidity and reducing mortality.

Subsequently, self-blame and the perceived causes of preeclampsia in urban Ghana was explored in **chapter 8.** We conducted a postpartum survey of 150 participants who were diagnosed with preeclampsia, 133 (88.7%) and eclampsia, 17 (11.3%) in their just ended pregnancy. Regarding perceptions of self-blame, 10 (6.8%) participants were told by healthcare providers that the development of preeclampsia/eclampsia was their fault, 26 (17.5%) believed it was their fault, and 58 (38.7%) believed they could have done something differently to prevent it. The predictors of self-blame (believing it was their fault) included a woman being told preeclampsia was her fault (OR 7.6, 95% CI 1.3–45.5, $P<0.05$), and a woman believing there was something she could have done to prevent preeclampsia (OR 10.0, 95% CI 2.6–38.9, $P<0.05$). Self-blame was independent of diagnosis (preeclampsia versus eclampsia), delivery outcome (live birth versus stillbirth), and education level. Self-blame was also independent of perceived provider counseling and the participant's score on the knowledge assessment. We assert that regardless of perceived quality of intrapartum care, self-blame may be an important aspect of the patient experience of preeclampsia/eclampsia and is dependent on whether a patient is told that development of the condition is her fault. Understanding the patient experience can help develop counseling tools and policies that support women affected by preeclampsia/eclampsia to improve their overall experience of care.

We explored women's knowledge, attitudes, and experiences with preeclampsia in Ghana in **chapter 9.** We used grounded theory to explore patients' experience of preeclampsia and eclampsia in a low-resource setting. Postpartum women diagnosed with preeclampsia or eclampsia at Korle Bu Teaching Hospital in Ghana were interviewed with semi-structured and open-ended questions regarding participant understanding of their diagnosis of preeclampsia and eclampsia; counseling from their healthcare providers; and experiences with their delivery, monitoring, and treatment. A total of 45 women were interviewed, 88.9% with preeclampsia and 11.1% with eclampsia. Major themes identified include participants' low general knowledge of their diagnosis, inadequate counseling from healthcare providers, and resulting emotional distress. Women desire

more information regarding their diagnosis and associate their health-seeking behaviors with counseling they receive from healthcare providers. Women also acknowledge the systemic barriers that make patient care and counseling challenging for providers, especially in low- and middle-income countries. Our findings highlighted the global need for improved models of counseling and health education for women with pregnancies complicated by preeclampsia and eclampsia.

Chapter 10 discusses the future of preeclampsia care in LMICs such as Ghana and makes recommendations on how to optimize the care for women whose pregnancies are complicated by severe preeclampsia and eclampsia to promote a positive pregnancy experience.

Key Recommendations

1. The adoption of the shorter duration but effective regimen (the Beyuo regimen) of magnesium sulfate administration is recommended for seizure prophylaxis in preeclampsia with severe features and eclampsia in LMICs with similar settings such as Ghana. This could improve patient compliance, increase protocol adherence, reduce side effects, shorten hospital stay and ultimately improve the patient experience of care. Continuous monitoring and evaluation of the Beyuo regimen is required to promote implementation adherence.
2. Enhanced education of all persons especially women in the reproductive years on HDPs and the need for prevention of eclampsia through quality antenatal care should be prioritized in LMICs. In Ghana stakeholder engagement should lead to the identification of specific translation for preeclampsia and eclampsia in various local languages.
3. We recommend community engagement and education on the prevention and early recognition of eclampsia. Community level first aid management of eclampsia and safe transportation of women eclampsia to the nearest health facility should be emphasized in these engagements. Hospitals receiving patients who fit in the community should engage and offer psychological support for the women as well as community members who witnessed and assisted in providing first aid to the patient.
4. Further studies assessing the implementation and compliance with evidence based antenatal care practices and intervention LMICs are recommended for health system managers to evaluate why high frequency of antenatal contacts are not translating to quality of care and reduction in adverse maternal outcomes

Appendices

Samenvatting

Hypertensieve aandoeningen in de zwangerschap zijnin lage- en middelinkomens landen (LMIC) geassocieerd met ernstige nadelige zwangerschapsuitkomsten, ondanks aanbevelingen en interventies om de trend te buigen. Met name in LMICs is het, doordat er beperkte middelen voorhanden zijn, een uitdaging om voor vrouwen die lijden aan hypertensieve aandoeningen in de zwangerschap een positieve ervaring van de zwangerschap en kraamperiode te bieden. Dit is ten dele te wijten aan de uitdagingen in de gezondheidssystemen en de relatief grote ziektelast die deze systemen verduren. Dit proefschrift heeft als doel de zorg voor en de ervaring van patiënten met pre-eclampsie in lage inkomenslanden te optimaliseren.

Deel één bestaat uit de hoofdstukken 2 en 3 en richt zich op de preventie van eclampsiemet magnesiumsulfaat en de behandelingsschema's daarvan bij (pre-)eclampsie. In **hoofdstuk 2** stellen wij een alternatief behandelingsschema voor, dat verschilt van het in LMICs veel gebruikte Pritchard-protocol. Met de wereldwijde consensus dat magnesiumsulfaat het middel van eerste keuze is in preventie van eclampsie bij (pre-)eclampsie is er een vraagontstaan wat betreft de optimale dosering en duur van de behandeling. Het nieuwe, voornamelijk intramusculaire, Beyuo-protocol is als volgt:

Oplaaddosis: 4 gram $MgSO_4$, intraveneus (i.v.) toe te dienen in combinatie met in totaal 10 milligram $MgSO_4$ intramusculair (i.m.) verdeeld over twee injecties (één in elke bil) op het moment van ante-, intra- of postpartum diagnose van ofwel eclampsie, ofwel ernstige pre-eclampsie.

Onderhoudsdosering: 5 gram $MgSO_4$ i.m. elke 4 uur met in totaal van 3 doses over 12 uur gerekend vanaf het moment van de diagnose eclampsie of ernstige pre-eclampsie.

In **hoofdstuk 3** vergelijken wij het Beyuo-protocol met het Pritchard-protocol middels een open-label gerandomiseerd gecontroleerd onderzoek getiteld: *Modified versus standard Pritchard regimen in Eclampsia Prophylaxis (MOPEP)*. Het Beyuo-protocol wijkt af van het Pritchard-protocol door een kortere onderhoudsbehandeling van standaard 12 uur, waar het Pritchard-protocol wordt gekenmerkt door een langere onderhoudsbehandeling van ten minste 24 uur. Het onderzoek vond plaats in het *Korle Bu Teaching Hospital (KBTH),* een groot tertiair ziekenhuis in Accra, Ghana. Er werden 1176 patiënten met ernstige pre-eclampsie geïncludeerd, waarvan, bij opname, 116 met de diagnose eclampsie. Zij werden gerandomiseerd naar ofwel de Pritchard-arm (n=584), ofwel de Beyuo-arm (n=592). Wij vonden geen verschil in het optreden van eclampsie tussen de Pritchard-groep (n=9, 1,5%) en de Beyuo-groep (n=5, 0,9%), (p=0,28, RR 0,55, 95% CI 0,19-1,64). Patiënten in de Beyuo-groep hebben een kortere opnameduur, hebben voor kortere tijd een urinekatheter en ondervinden minder bijwerkingen van magnesiumsulfaat. Wij concluderen dat er geen significant verschil is in het optreden van eclampsie tussen de

groepen die tot 12, respectievelijk 24 uur of langer intramusculair met $MgSO_4$ behandeld werden, maar wel met minder bijwerkingen en een kortere ziekenhuisopname in de Beyuo-arm. Daarom is het Beyuo-protocol te verkiezen boven het Pritchard-protocol in de preventie van eclampsie in LMICs. Hoewel wij dit schema aanbevelen voor opname in de institutionele en nationale praktijkrichtlijnen in Ghana, zijn verdere trials van dit schema in verschillende landen en populaties nodig om het voor verschillende andere populaties te valideren.

In deel twee evalueren we de uitkomsten van door pre-eclampsie gecompliceerde zwangerschappen en de onderliggende factoren die hiermee geassocieerd worden in een tertiair ziekenhuis in Ghana (KBTH). Het identificeren van de ongunstige prognostische factoren voor maternale en perinatale uitkomsten kan bijdragen aan de totstandbrenging van effectieve interventies teneinde een positieve zwangerschapservaring voor deze groep vrouwen te realiseren, rekening houdend met de beperkte middelen in LMICs.

In **hoofdstuk 4** evalueren we de factoren die geassocieerd zijn met het optreden van eclampsie in het KBTH. Dit onderzoek was onderdeel van de MOPED-studie en analyseert gegevens van de 1176 vrouwen met ernstige pre-eclampsie en eclampsie. Ongeveer 10% van de onderzoekspopulatie (n=116, 9,9%) was gediagnosticeerd met eclampsie. Bij de meeste vrouwen met eclampsie, uit zich dit met: een eerste eclampsie antepartum (68,7%); buiten een gezondheidsinstelling (56,5%); in de aanwezigheid van een familielid (55,9%). Vrouwen met eclampsie hebben gemiddeld 1 aanval (IQR 1,0, 2,0). Slechts 15 vrouwen (12,9%) zijn eerder in de zwangerschap gediagnosticeerd met pre-eclampsie. De kans op eclampsie is ongeveer 3 maal hoger bij vrouwen jonger dan 20 jaar (aOR 2,75, 95% CI 1,10-6,89) en ruim 2.5 keer hoger bij vrouwen met een tweelingzwangerschap (aOR 2,59, 95% CI 1,26-5,32). Lagere kansen op lampsie werden waargenomen bij vrouwen ouder dan 35 jaar (aOR 0,32, 95% CI 0,15-0,67), vrouwen met obesitas (aOR 0,44, 95% CI 0,25-0,77) en vrouwen met chronische hypertensie (aOR 0,38, 95% CI 0,17-0,86). Wij concluderen dat bij vrouwen met (pre-)eclampsie, jongere leeftijd en tweelingzwangerschap geassocieerd zijn met een ongeveer drievoudig verhoogde kans op eclampsie, terwijl oudere leeftijd, obesitas en chronische hypertensie geassocieerd waren met een lagere kans op eclampsie. Deze lagere kansen kunnen mogelijk verklaard worden door de verhoogde waakzaamheid en betere monitoring van de vrouwen met dit risicoprofiel, wat een cruciale rol impliceert voor hoogwaardige prenatale zorg.

In **hoofdstuk 5** evalueren we de neonatale uitkomsten van pre-eclampsie en eclampsie bij moeders die deelnemen aan de MOPEP-studie. Uit de prospectief verzamelde gegevens blijkt dat er in onze studie, 1218 baby's zijn geboren bij de 1176 vrouwen. De mediane zwangerschapsduur bij de bevalling iss 36,6 weken (IQR 33,3, 38,9 wkn). Het mediane geboortegewicht is 2,3 kg (IQR 1,6, 3,0 Kg), 227 neonaten (19,0%) hebben een geboortegewicht van minder dan 1500 g. 15% van de pasgeborenen heeft een APGAR score <7 na 5 minuten en 147 (12,1%) baby's zijn dood geboren. Van de levendgeborenen is

de helft (n=522, 50,2%) opgenomen op de NICU en 7,3% (n=89) overleed tijdens opname. Er is bij 57,9% (n=704) van de baby's sprake van een combinatie van slechte neonatale uitkomsten en er is tweemaal meer kansop een maternale diagnose van eclampsie (OR 1,91, CI=1,03-3.54). Voor elke toename van één week in zwangerschapsduur, neemt de kans op een slechte neonatale uitkomst met 39% af (OR 0,61, CI=0,57-0,65). Wij concluderen dat ernstige pre-eclampsie en eclampsie geassocieerd zijn met slechte neonatale uitkomsten in de onderzochte setting. Bij door eclampsie gecompliceerde zwangerschappen was de kans op slechte neonatale uitkomsten twee keer zo hoog.

Nadat we in hoofdstuk 4 de met eclampsie geassocieerde factoren identificeren en we in hoofdstuk 5 de neonatale uitkomsten van pre-eclampsie en eclampsie evalueren, beoordelen we in **hoofdstuk 6** de invloed van prenatale zorg op ernstige maternale en neonatale uitkomsten bij zwangerschappen gecompliceerd door (pre-)eclampsie.

Het betreft een secundaire analyse binnen een gerandomiseerd-gecontroleerd onderzoek. Deelnemers zijn volwassen zwangere vrouwen met (pre-)eclampsie in een tertiair ziekenhuis in Ghana (KBTH). Metingen van het gebruik van prenatale zorg bestaan uit: het tijdstip van het eerste bezoek, het totale aantal bezoeken, het type instelling die bezocht is, het type zorgverlener dat bezocht is en de verwijzingsstatus. Gebaseerd op aanbevelingen van de Wereldgezondheidsorganisatie (WHO) zijn patiënten ingedeeld in ≥4 bezoeken, ≥8 bezoeken en een volgens de WHO toereikend aantal bezoeken voor de zwangerschapsduur. Er werd gebruik gemaakt van de volgende samengestelde uitkomstmaten: maternale complicaties (optreden van longoedeem, acute nierschade, IC-opname of maternaal overlijden) en nadelige neonatale uitkomsten (doodgeboorte, geboortegewicht <1500 gram, vijf-minuten APGAR <7, NICU-opname, overlijden tijdens opname). We gebruiken multivariate logistische regressies om associaties met prenatale zorg te identificeren.

Prenatale zorg is gestart bij een zwangerschapsduur van mediaan 16,0 weken (IQR 11,7-21,0). Het mediaan aantal prenatale bezoeken iss 5,0 (IQR 3,0-7,0), waarvan 72,9% ≥4 bezoeken, 19,4% ≥8 bezoeken, en 54,9% een toereikend aantal bezoeken voor de zwangerschapsduur als aanbevolen door de WHO. De meeste prenatale zorg is verleend in een polikliniek van een ziekenhuis gefinancierd door de overheid (n=522, 47,2%) en door een verloskundige (n=704, 65,1%). De kans op nadelige neonatale uitkomsten is lager wanneer de zorg is verleend door een gespecialiseerde gynaecoloog (aOR 0,61 CI= 0,42- 0,87), en bij vrouwen die ≥8 bezoeken aflegden (aOR 0,69, CI = 0,47-0,99). vrouwen die verwezen worden naar het tertiaire ziekenhuis hebben tweemaal zoveel kans op een maternale complicatie (aOR 2,00, p = 0,01) en op een nadelige neonatale uitkomst (aOR 1,69, CI = 1,20-2,37) in vergelijking met vrouwen die niet vrwezen werden. Wij concluderen dat minder complicaties worden gezien bij Ghanese vrouwen met (pre-)eclampsie die prenatale zorg ontvangen in tertiaire instellingen. Het bijwonen van acht of meer prenatale bezoeken vermindert de kans op nadelige neonatale uitkomsten, maar heeftgeen invloed op ernstige maternale complicaties. De kwaliteit van prenatale zorg is essentieel, niet alleen de kwantiteit.

In het derde deel van het proefschrift hebben we gekeken naar het patiëntperspectief bij pre-eclampsie en de zorg voor pre-eclampsie-patiënten in een tertiair ziekenhuis in Ghana (KBTH). In **hoofdstuk 7** onderzoeken we de kennis over pre-eclampsie bij vrouwen die behandeld wordenvoor(pre-)eclampsie in het KBTH in Accra. We namen tussen 2-5 dagen na de bevalling vragenlijsten af bij vrouwen met de diagnose (pre-)eclampsie. Het advies van de zorgverlener over de diagnose, oorzaken, complicaties en toekomstige gezondheidseffecten van (pre-)eclampsie werd gekwantificeerd op een vierpuntenschaal ('Counseling Composite Score'). Deelnemers vulden daarnaast een objectieve kennisbeoordeling in met betrekking tot (pre-) eclampsie, met een score van minimaal 0 en maximaal 22 punten ('Preeclampsia/Eclampsia Knowledge Score' (PEKS)). Hoewel 74% van de vrouwen aangaf een complicatie te hebben gehad tijdens de zwangerschap, kon slechts 32% van de deelnemers met pre-eclampsie hun diagnose correct verwoorden, geen enkele deelnemer met eclampsie was hiertoe in staat. Eenendertig procent van de deelnemers gaf aan géén advies te hebben gekregen van de zorgverleners en slechts 11% kreeg advies in alle vier de categorieën. Zelfs als ze advies kregen, gaf 40-50% van de deelnemers aan dit onvolledig te begrijpen. Van de maximaal 22 punten op een cumulatieve kennisbeoordelingsschaal, hadden de deelnemers een gemiddelde score van 12,9 ± 0,38. Gecorrigeerd voor leeftijd, pariteit, en het aantal prenatale bezoeken, zijn hogere scores op de kennisbeoordeling geassocieerd met meer counseling door de zorgverlener (β 1,4, SE 0,3, $p < 0,001$) en een hoger opleidingsniveau (β 1,3, SE 0,48, $p = 0,008$). Wij concluderen dat counseling door zorgverleners geassocieerd is met hogere prestaties op een kennistoets over (pre-)eclampsie. Kennis van patiënten over pre-eclampsie is belangrijk voor het faciliteren van weloverwogen beslissingen in de gezondheidszorg, het bevorderen van vroege prenatale zorg en het verbeteren van zelfherkenning van waarschuwingssignalen - wat uiteindelijk de morbiditeit verbetert en de mortaliteit vermindert.

Vervolgens hebben wij in **hoofdstuk 8** schuldgevoelenscq zelfverwijt en de waargenomen oorzaken van zwangerschapsvergiftiging in een stedelijk gebied in Ghana onderzocht. We voerden een postpartum onderzoek uit onder 150 deelnemers die tijdens hun zwangerschap de diagnose pre-eclampsie (n=133, 88.7%) en eclampsie (n=17 11.3%) kregen. Wat betreft percepties van schuldgevoel, kregen 10 (6,8%) deelnemers van zorgverleners te horen dat de ontwikkeling van pre-eclampsie hun schuld was, 26 (17,5%) geloofden dat het hun schuld was, en 58 (38,7%) geloofden dat ze iets anders hadden kunnen doen om het te voorkomen. De voorspellers van zelfverwijt (geloven dat het hun schuld was) waren onder andere te horen krijgen dat de pre-eclampsie de schuld van de vrouw was (OR 7,6, 95% CI 1,3-45,5, P<0,05) en het geloof iets te kunnen doen om zwangerschapsvergiftiging te voorkomen (OR 10,0, 95% CI 2,6-38,9, P<0,05). Zelfverwijt werd niet geassocieerd met: diagnose (pre-eclampsie versus eclampsie), bevallingsresultaat (levendgeborene versus doodgeborene) of opleidingsniveau. Zelfverwijt bleek tevens niet afhankelijk van de ervaren counseling door de zorgverlener en de score van de deelnemer op de kennisbeoordeling. Wij stellen dat,

ongeacht de kwaliteit van de intra-partum zorg, zelfverwijt en schuldgevoel een belangrijk aspect kan zijn van de ervaring van de patiënt met (pre-)eclampsie en sterk is geassocieerd met het horen dat de ontwikkeling van de aandoening de schuld van de zwangere zelf is. Inzicht in de ervaring van patiënten kan helpen bij het ontwikkelen van hulpmiddelen en beleid om vrouwen met (pre-)eclampsie te ondersteunen bij het verbeteren van hun algehele ervaring van de zorg.

In **hoofdstuk 9** onderzoeken we de kennis, attitude en ervaringen van vrouwen met pre-eclampsie in Ghana. We hebben gebruik gemaakt van “grounded theory” om de ervaringen van patiënten met (pre-)eclampsie te onderzoeken in een situatie met weinig middelen voorhanden. Vrouwen gediagnosticeerd met (pre-)eclampsie in het KBTH in Ghana werden post-partum geïnterviewd aan de hand van semigestructureerde en open vragen over het begrip van hun diagnose van (pre-)eclampsie; counseling door hun zorgverleners en ervaringen met hun bevalling, monitoring, en behandeling. In totaal werden 45 vrouwen geïnterviewd, 88,9% met pre-eclampsie en 11,1% met eclampsie. Belangrijke thema’s die werden geïdentificeerd waren het gebrek aan kennis van de deelnemers over hun diagnose, inadequate counseling door zorgverleners en het daaruit voortvloeiende emotionele leed. Vrouwen willen meer informatie over hun diagnose en brengen hun ziektegedrag in verband met het advies dat ze van zorgverleners krijgen. Vrouwen erkennen daarnaast de systemische barrières die patiëntenzorg en counseling een uitdaging maken voor zorgverleners, vooral in lage- en middeninkomenslanden. Onze bevindingen benadrukken de wereldwijde behoefte aan betere modellen voor counseling en gezondheidsvoorlichting voor zwangeren met (pre-)eclampsie.

Hoofdstuk 10 bespreekt de toekomst van de zorg rondom (pre-)eclampsie in LMICs zoals Ghana en doet aanbevelingen over het optimaliseren van deze zorg om een positieve zwangerschapservaring te bevorderen.

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About the author

Dr. Titus Kofi Beyuo was born on the 14th of September 1981 to peasant farmers both of whom had no formal education. He is the last of nine children and only the second who had the opportunity to pursue formal education. He completed Pope John Secondary School and Minor Seminary where he served as the Senior Prefect for the school. He had his medical degree from the University of Ghana Medical School and having developed an interest in pharmacology whiles in medical school, he pursued a Master of Philosophy degree in Pharmacology from the University of Ghana. His specialist training was in Obstetrics and Gynaecology, and he is a Fellow of the Ghana College of Physicians and Surgeons and a Fellow of the West African College of Surgeons. He also studied health management and administration from the Ghana Institute Management and Public Administration (GIMPA)

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Dr. Beyuo has a passion for students and union politics having served in various capacities as the President of the University of Ghana Medical students Association, Vice President of the Federation of Ghana Medical student Associations, Leader for the Junior Doctors in Ghana and is currently the General Secretary of the Ghana Medical Association. He has served on some National Councils, Boards and Technical Committees in Ghana such as the Professional and Disciplinary Committee of the Governing Council of the Nurses and Midwifery Council, a Technical Working Group of the Ministry of Health on attraction and retention of health workers in deprived and underserved communities in Ghana and Salaries and Wages Negotiations Committee of the Ghana Medical Association.

Dr. Beyuo has love for mass media production and presentation having previously produced and hosted national award-winning television health programs and radio programs on health education such as the ‘Ask Your Doctor’ and ‘The OR Show’.

He is an entrepreneur who co-founded the Comprehensive Care group of companies with his wife. The group comprise of a hospital, a media company and a not-for-profit organization that provides free healthcare services to rural and underserved communities in Ghana. He is a farmer and loves to spend time at his piggery.

The Beyuo is a Christian and is married to Dr. Mrs. Vera Beyuo (a Paediatric Ophthalmologist) and they have four children, Benito, Titus, Jeremy, and Jesse.

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The Dutch Working Party 'International Safe Motherhood and Reproductive Health' aims to contribute to improvement of the reproductive health status of women around the globe, in particular by collaborating with local health workers (http://www.safemotherhood.nl). The Working Party is part of both the Dutch Society of Obstetrics and Gynaecology (NVOG) and the Dutch Society for International Health and Tropical Medicine (NVTG). The activities that are undertaken under the umbrella of the Working Party can be grouped into four pillars: education, patient care, research and advocacy.

Research activities are undertaken by (medical) students, Medical Doctors International Health and Tropical Medicine and many others. Some research activities develop into PhD-trajectories. PhD- candidates all over the world, Dutch and non-Dutch, work on finding locally acceptable and achievable ways to improve the quality of maternal health services, supervised by different members of the Working Party. Professor Jos van Roosmalen initiated the Safe Motherhood Series, which started in 1995.

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- Optimizing care and patient experience of preeclampsia in low- and and middle-income countries – the case of Ghana (**Titus Kofi Beyuo**), UMC Utrecht, the Netherlands, 2022