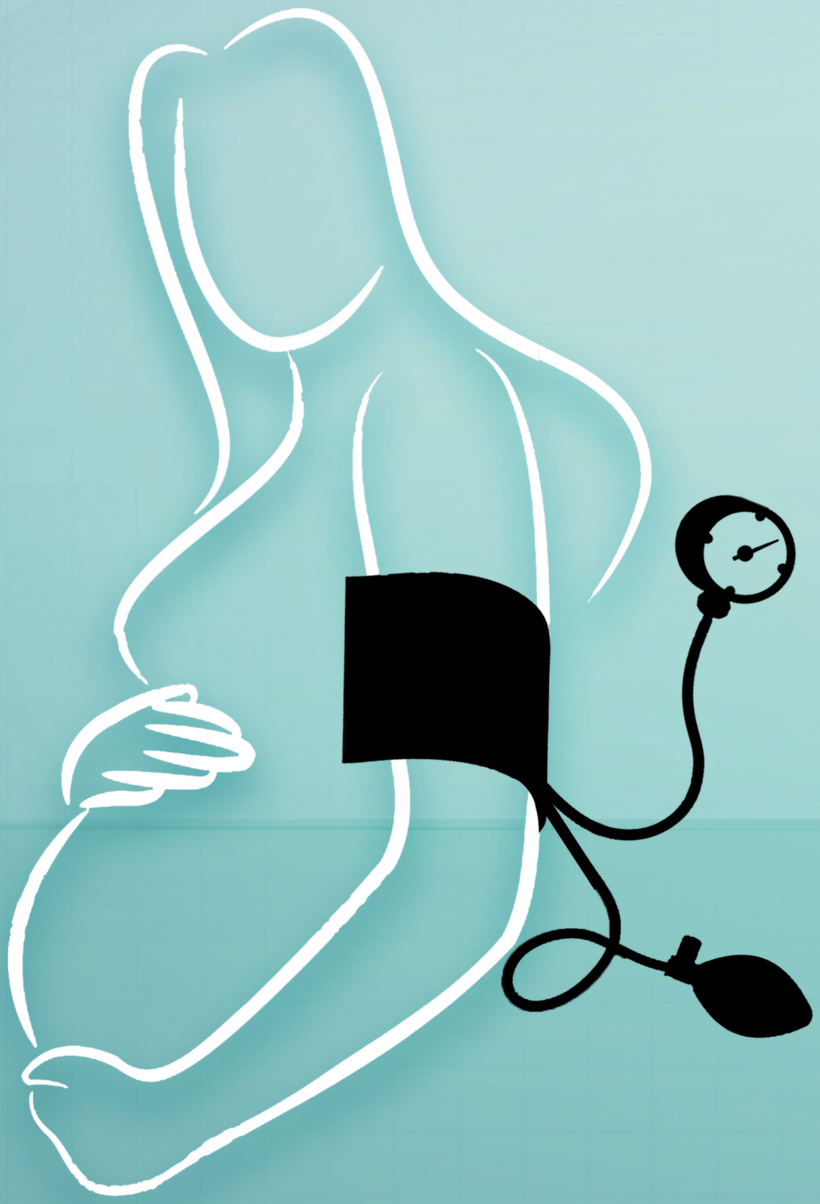
HYPERTENSIVE DISORDERS OF PREGNANCY:

EVIDENCE AND IMPLEMENTATION IN A LOW RESOURCE SETTING



Edward Antwi

Hypertensive disorders of pregnancy: evidence and implementation in a low resource setting

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Utrecht University, the Netherlands
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CHAPTER 1

General introduction

HYPERTENSIVE DISORDERS OF PREGNANCY AND MATERNAL MORTALITY

Reduction of maternal mortality remains one of the world's major global priorities for improving health, considering that an estimated 303,000 women die annually from complications of pregnancy and childbirth worldwide (1). Most of these deaths occur in low-and middle-income countries (LMIC), especially in sub-Saharan Africa which accounts for about 66% of all global maternal deaths (1,2). The Millennium Development Goal (MDG)-5 aimed to reduce the maternal mortality ratio by 75% between 1990 and 2015 (3). Despite considerable progress the MDG target was not achieved, necessitating roll-over of the unfinished agenda into the Sustainable Development Goal-3 (4) target 3.1, which states that "by 2030, reduce the global maternal mortality ratio to less than 70 per 100,000 live births". The indicators for accessing this target are the "maternal mortality ratio (indicator 3.1.1.1)" and the "proportional births attended by skilled health personnel (indicator 3.1.2)". A major contributory factor to maternal mortality are the hypertensive disorders of pregnancy (HDPs) which account for about 14% of all global maternal deaths (5), second to haemorrhage which accounts for 24.5% of maternal deaths. In sub-Saharan Africa HDPs account for 16% of all maternal deaths (5). A study conducted between 2010 and 2011 at the Korle Bu Teaching Hospital, a tertiary level facility in Ghana, showed that HDPs were the leading causes of death having overtaken haemorrhage which used to be the major cause of maternal deaths in that hospital in the mid 1990s (6). Healthcare costs associated with these disorders are significant because of the prolonged stay in intensive care units by women having complications of HDPs and because of the long-term sequelae for both the pregnant women and their offspring (7). HDPs are also the main indication for preterm delivery, accounting for about 15% of all preterm deliveries and contributing to the burden of perinatal deaths (8-13). To date there is no known cure for these disorders and the definitive treatment remains the delivery of the fetus and the placenta (10).

The HDPs consist of gestational hypertension (also known as pregnancy induced hypertension), preeclampsia (de novo or superimposed on chronic hypertension) and chronic hypertension (14). They are characterized by elevated blood pressure after 20 weeks of gestation with or without proteinuria and multiple organ dysfunction (15-19).

Although there are global and national estimates for the burden of HDPs (20,21), the incidence across sub-national geographic areas has not been described. It is important to ascertain whether the rates of HDPs are uniform within countries. Mapping out the sub-national incidence rates across regions and districts could enable the identification of other contextual factors such as obesity, urbanization, diet, socio-economic status and other lifestyle behaviours that are associated with HDPs.

Risk factors known to be associated with HDPs include nulliparity, obesity, extremes of maternal age, multiple gestation, assisted reproductive techniques, family history of preeclampsia or gestational hypertension in a mother or sister, previous history of a hypertensive disorder of pregnancy, African descent, preexisting medical conditions such as diabetes mellitus, chronic hypertension, renal disease, vascular and connective tissue disorders and the antiphospholipid syndrome (16,22). Whereas some risk factors associated with HDPs such as racial or ethnic origin,

nulliparity and family history in a close relative are not amenable to change, others like age at conception and obesity can be modified to some extent.

PREDICTION MODELS AS TOOLS FOR REDUCING THE BURDEN OF HDPS

Knowledge on risk factors for HDPs assists to identify women at risk of developing HDPs early in pregnancy, ideally in the first trimester of pregnancy. Prediction models have been used to stratify pregnant women into risk categories. Women at high risk can be provided aspirin prophylaxis, shown in the ASPERE trial (23) and a Cochrane systematic review (24) to reduce the risk of preeclampsia given to at-risk pregnant women from 12 weeks of gestation. By identifying high at-risk women early in pregnancy, appropriate care and improved monitoring can be provided for them throughout the pregnancy.

Prediction models for HDPs generally use maternal clinical and demographic characteristics but increasingly are including serum biomarkers and uterine artery Doppler as predictors. The risk predictions obtained from models using only maternal clinical characteristics are modest and often do not discriminate well between those at high and low risk of the hypertensive disorders. Most prediction models for gestational hypertension and preeclampsia have also been developed and are used mostly in the European and North American populations (25). Very few of these models have been developed and applied in the African population. Apart from maternal clinical characteristics which are routinely measured in most settings, serum biomarkers and uterine artery doppler pulsatility index at present are not routinely measured in most low- and middle-income countries. This makes prediction models developed in Europe and North America at present not generalizable to many low resource settings.

AIMS AND OBJECTIVES OF THE WORK PRESENTED IN THE THESIS

The overall aim of this thesis therefore was to explore the extent and variations in hypertensive disorders of pregnancy as a major cause of maternal mortality in Ghana, a low resource setting, and to provide options for a simple prediction model for women at high risk which can support efforts to reduce morbidity and mortality due to gestational hypertension in Ghana.

Specific Objectives were:

1. To explore and describe variation of the incidence of gestational hypertension across rural and urban contexts in Ghana;
2. To document the current state of knowledge of prediction models for gestational hypertension and preeclampsia;
3. To develop and validate a prediction model for gestational hypertension before 20 weeks of pregnancy based on clinical data;

4. To validate the added benefit of improving prediction by including biomarkers in a clinical data based prediction model;
5. To analyze the implications of using a prediction model for the management of gestational hypertension and prevention of morbidity and mortality related to gestational hypertension in the lower middle income country context of Ghana.

METHODS

The methods employed are summarized in Table 1 by study questions and objectives.

Table 1 | Summary of methods by objectives, study question and corresponding chapters in this thesis.

Chapter	Objective	Study Question	Methods
(2)	*Specific Objective 1:* To explore and describe variation of the incidence of gestational hypertension across rural and urban contexts in Ghana	Are there sub-national (small area) geographical variations in the incidence of PIH in Ghana?	A comparative analysis of clinical records data from antenatal clinics in districts in the highly urbanized (90% urban) Greater Accra region in the South of Ghana and the predominantly rural (16.3% urban) Upper West region in the North of Ghana
(3)	*Specific Objective 2:* To document the current state of knowledge on prediction models for gestational hypertension and preeclampsia.	What prediction models are currently available for gestational hypertension?	A systematic review of prediction models for gestational hypertension and preeclampsia.
(4)	*Specific Objective 3:* To develop and validate a prediction model for gestational hypertension before 20 weeks of pregnancy based on clinical data	Is it possible to develop an accurate predictive model of gestational hypertension to support case management based on clinical data alone in an LMIC context?	Prospective cohort study of pregnant women
(5)	*Specific Objective 4:* To validate the added benefit of improving prediction by including biomarkers in a clinical data based prediction model.	To what extent does addition of biomarker improve the predictive value of the clinical data model?	Prospective cohort study of pregnant women
(6)	*Specific Objective 5:* To analyze the implications for the management of gestational hypertension and prevention of morbidity and mortality related to gestational hypertension in the LMIC context of Ghana	What are the applied implications of the study findings for reducing maternal morbidity and mortality in an LMIC context?	Review and synthesis of the data from the four sub-studies

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CHAPTER 2

Measuring regional and district variations in the incidence of pregnancy induced hypertension in Ghana: challenges, opportunities and implications for maternal and newborn health policy and programmes

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ABSTRACT

Introduction Local area variations in morbidity and mortality due to hypertensive disorders of pregnancy have implications for policy and program design and implementation. High quality routine health management information system (HMIS) data can make measurement and analysis simpler and less expensive than the use of special surveys.

Objectives The objectives were to assess the quality of HMIS data needed for assessments of local area variation in pregnancy induced hypertension (PIH) incidence and to describe district and regional variations in PIH incidence.

Methods A retrospective review of antenatal and delivery records of 2,682 pregnant women in ten district hospitals in the Greater Accra and Upper West regions of Ghana was conducted in 2013. Quality of HMIS data was assessed by completeness of reporting. The incidence of PIH was estimated for each district.

Results Key variables for routine assessment of PIH such as blood pressure at antenatal visits, weight and height were 95% to 100% complete. Fundal height, gestational age and blood pressure at delivery were not consistently reported. The incidence of PIH was significantly different between Greater Accra region (6.1%) and Upper West region (3.2%). Prevalence of obesity among pregnant women in Greater Accra region (13.9%) was significantly higher than that of women in Upper West region (2.2%).

Conclusions More attention needs to be given to understanding local area variations in PIH and possible relationships with urbanization and lifestyle changes that promote obesity, to inform maternal and newborn health policy. This can be done with good quality routine HMIS data.

Key Words: Routine data, decision making, maternal and newborn health, pregnancy induced hypertension, local area variation.

INTRODUCTION

Hypertensive disorders of pregnancy (HDPs) are important causes of maternal and perinatal morbidity and mortality globally. They include pregnancy-induced hypertension (PIH), pre-eclampsia, eclampsia and the HELLP (Hemolysis, Elevated Liver enzymes, Low Platelets) syndrome. A World Health Organization (WHO) systematic review concluded that with 50,000 annual deaths, hypertensive disorders are one of the major causes of maternal mortality, particularly in low- and middle-income countries (LMICs). In that report, hypertensive disorders of pregnancy were the third leading cause of maternal deaths (9.1%) in Africa and the leading cause of death in Latin America and the Caribbean, accounting for 25.7% of mortality (1).

The underlying causes of HDPs are not fully understood but hypothesized to be related to poor placentation and feto-maternal interactions (2). A number of individual risk factors are known to be associated with the condition (3;4) including maternal age, obesity, ethnicity, nulliparity, multiple pregnancy, diabetes mellitus, and family history of hypertension and PIH.

In Ghana, HDPs are the third leading cause of maternal deaths (9%) after haemorrhage (22%) and induced abortion (11%) (5). However the incidence of HDPs does not appear to be uniform across the country. The Ghana Maternal Health Survey conducted in 2007 found that in highly urbanized Accra, the capital city, hypertensive disorders of pregnancy were more common, accounting for 19% of all maternal deaths (5). A retrospective study of maternal deaths at the Komfo Anokye Teaching Hospital in Kumasi, Ghana between January 2008 and June 2010 found that hypertensive disorders of pregnancy were the leading cause of institutional mortality, accounting for 26.4% of all maternal deaths (6), and having overtaken haemorrhage as the major cause of death in pregnant women.

There is very little information about the extent of and the reasons why there would be rural urban and other geographic area variation in the incidence and prevalence of the condition in sub-Saharan African countries. It is possible that in addition to individual factors, there may be environmental and contextual risk factors such as urbanization and lifestyle factors associated with the condition.

Observations of variations in the incidence and prevalence of HDPs are not new, but the data is mainly from other parts of the world. A WHO study on the geographic variation of the incidence of hypertension in pregnancy in Asia found that it varied by a factor of 25 between countries (7). The study concluded that there are genuine differences in the incidence of HDPs in the populations of South East Asia and that these are not caused by underlying differences in the baseline blood pressures (BP) in these populations. A similar study is not available for Sub-Saharan Africa or for individual countries within the region despite it being important to understand the extent of any geographical variations in HDPs prevalence and factors contributing to such variation. It has implications for the development and implementation of clinical and programmatic interventions that can contribute to the reduction of HDPs to maternal, fetal and newborn morbidity and mortality.

Antenatal and delivery data management at the health facility level in Ghana

All antenatal and delivery information in Ghana is kept in the individual maternal health record book of each woman. This includes personal information, information on services received including

laboratory results. The maternal record books are not retained in the clinic as the women take them home with the advice to carry them to any clinic they may need to visit. At each visit, the attending nurses at the antenatal clinic and labour wards enter key information about the woman's care into the antenatal register or the delivery register. Which of the data entered into the maternal health record book is extracted into the antenatal and the delivery register is determined at the national level and conveyed to frontline staff in all health facilities. It is also integrated into the design of the antenatal and delivery registers. Thus any patient information, which is not required to be entered into these registers, is effectively lost to routine HMIS data once patients leave the clinic with their records.

The availability of high quality routine health management information system (HMIS) data can make mapping of local area variations in the incidence of a condition such as PIH, as well as tracking changes over time, a relatively simple task. It is however uncertain whether the quality of the routine HMIS data permits its use for such a purpose. We decided to carry out an initial exploration to answer some of these questions.

Aims of the study

Our study had two aims. The first was to assess the availability and completeness of district and facility level routine HMIS data in Ghana that would enable a mapping of PIH incidence on a routine basis. The second was to describe the extent to which the data allows to study variation in the incidence of PIH between urban and rural districts in Ghana and explore some of the possible maternal, contextual and environmental factors that might explain these variations.

For the second aim, we hypothesized that there are statistically significant variations in incidence of PIH across regions and districts in Ghana with the incidence of PIH being higher in highly urbanized areas compared to less urbanized and rural areas. We further theorized that these variations would possibly be explained in part by a higher prevalence of obesity in higher incidence PIH geographic localities. This is because urbanization is often accompanied by changes in critical lifestyle factors known to favour obesity.

METHODS

The study was a retrospective record review of antenatal clinic (ANC) and delivery records of 2,682 pregnant women using district hospitals in the Greater Accra (n=1,578) and Upper West (n=1104) regions of Ghana in the first half of 2012. We used antenatal clinic records since based on community surveys and routine health management information system data we consider that they are reasonably representative of the population of pregnant women in the community

With regard to ANC coverage rates, the Ghana Maternal Health Survey, 2007 (5) reported ANC coverage for the various regions in Ghana ranging from 91.7% to 98.7% and reported ANC coverage of 96.4% and 94.3% for the Greater Accra and the Upper West regions, respectively. The 2008 and the 2014 Ghana Demographic and Health surveys (8;9) providing aggregate regional data, show over 95% antenatal clinic attendance across the country, including the two regions studied. Routine

health management information system data of the Ghana Health Service similarly show over 95% antenatal clinic attendance at the aggregate regional level. Routine Ghana Health Service data on district level show district by district variation ranging from 56.4% to 135.5% in the Upper West region and 45.4% to 172.1% in the Greater Accra region (10). The district by district variation in ANC coverage is in part accounted for by women crossing borders to use clinics in neighbouring districts rather than lower community based use rates of antenatal care, resulting in ANC coverage rates exceeding 100% for some districts.

For all pregnant women, individual patient data were obtained for the first ANC to give baseline characteristics of the women at the onset of their pregnancy and for subsequent ANC visits to delivery where available. In addition, to facilitate explanation of the findings, observation within the clinics and unstructured discussions and conversations with the staff were conducted.

We purposively selected the Greater Accra and the Upper West regions for the conduct of this study based on the Ghana Statistical Service data that showed that Greater Accra is the most urbanized region in Ghana (90.5% urbanization) with lowest aggregate poverty levels (12% poverty prevalence) and Upper West is the least urbanized region in Ghana (16.3% urbanization) with some of the highest aggregate poverty levels (88% poverty prevalence) (11;12). The two extremes of rural and urban were chosen to assess the theory that variations in PIH across Ghana may in part be explained by urbanization and the accompanying lifestyles changes that favour the development of obesity.

Within each region, the inclusion criteria for districts in the study were that the district should have a district hospital and the hospital management team should agree to participate in the study. Out of eleven districts in the Upper West Region, eight met the inclusion criteria and formed the sampling frame. Five districts were randomly selected through balloting. Of the sixteen districts in the Greater Accra Region, nine met the inclusion criteria and constituted the sampling frame out of which five were randomly selected through balloting. The selection of five districts per region was based on resources available to conduct the study and the need to have a minimum of four units of randomization (district with a district hospital) in each region.

Within each district, the inclusion criterion for women in the study were pregnant women presenting with normal blood pressure at the district hospital antenatal clinic visits before 20 weeks of gestation for a routine antenatal rather than a referred antenatal visit. The exclusion criteria were pregnant women in the selected districts with pre-existing hypertension or who developed hypertension before 20 weeks of gestation. The primary outcome measure, pregnancy induced hypertension, was defined as systolic BP (SBP) of 140mmHg or more and/or a diastolic BP (DBP) of 90mmHg or more on at least two occasions, four hours apart, and present for the first time after 20 weeks of pregnancy (13).

Data on pregnant women who attended the health facility from 1st January 2012 to 30th June 2012 were extracted from the antenatal and maternity registers and recorded on a checklist. These registers are facility level summary listings of key clinical variables and information on all pregnant women who have used the antenatal clinic and delivered at their facility. Data on weight, height, gestational age, fundal height, weight and blood pressure at first and subsequent antenatal visits were obtained from the antenatal register. Body mass index (BMI) was calculated by dividing the

weight in kilograms by the squared height in metres of the woman. Data on mode of delivery, and delivery outcome was obtained from the maternity/delivery register. Additionally, we searched the laboratory registers of the hospitals to obtain data on urine testing for protein and the delivery records and nurses notes for data on blood pressure measurements at delivery.

Data analysis

Data was analyzed using IBM SPSS Statistics 20 (IBM Corporation, New York City, USA, 2011). In the analysis we compared characteristics of pregnant women from the Upper West and Greater Accra regions. Data on categorical variables were presented by frequencies and percentages. Continuous data were presented as means with standard deviation (SD).

Student's T-test was used to assess whether there were significant differences in means between the pregnant women in the two regions and reported significant with a p-value of <0.05. The WHO BMI classification of underweight<18.5, normal weight 18.5 -24.9, overweight 25.0 -29.9 and obese ≥30 was used to categorise women in the study (14). The Chi-Square test was used to assess differences in categorical variables between the two regions. Analysis of covariance was used to test whether there were differences in BMI, SBP and DBP between districts and the regions after adjusting for gestational age. To estimate the incidence of PIH, the numerator was the number of pregnant women who developed PIH and the denominator was the total number of pregnant women in the study. Logistic regression was used to assess the relationship between BMI and PIH and expressed as relative risk (RR) with 95% confidence interval.

Ethical approval

Ethical approval for the study was given by the Ghana Health Service Ethical Review Committee. (GHS-ERC: 13/07/13). In addition, permission to conduct the study was also given by the hospitals.

RESULTS

Routine HMIS Data availability and completeness

Key variables needed to assess the incidence of PIH were collected by all hospitals participating in the study. There was however variation in the completeness of the recordings. Age, parity, blood pressure at antenatal clinic, weight and height records were 95% to 100% complete in the facility-based records. Completeness of data on blood pressure at delivery, fundal height and gestational age at first visit varied across districts. Urine protein was not recorded in most hospitals. Details for data completeness are shown in Figures 1 and 2.

Background characteristics of the women in the study, variations in PIH and BMI

Table 1 summarizes the demographic and obstetric characteristics of the women in the study by region of residence at the first antenatal care visit. The average age was about 27 years in both regions. There were statistically significant differences between the women in the two regions on all the other variables.

There was a higher proportion of women with a parity of three or more in the Upper West (58%) compared to the Greater Accra region (42%), p<0.001. The mean weight of the women in Greater Accra region was 63.1 kg (SD 12.7) compared to 58.1 kg (SD 8.2) in the Upper West region. There was a significant difference between the mean BMI of women in Upper West (22.4 kg/m^2 (SD 2.9)) and those in Greater Accra (24.7 kg/m^2 (SD 4.7)), p <0.001. About 13.9% (n=212) of women in Greater Accra were obese compared to 2.2% (n=24) in the Upper West region (p<0.001). Women who were overweight comprised 12.8% and 26.6% of antenatal clinic attendants in the Upper West and Greater Accra regions, respectively.

Both the mean systolic and diastolic blood pressures at the first antenatal visit were slightly higher for women in Greater Accra region than in Upper West region. Women in Greater Accra had a higher gestational age at the time of first antenatal care visit compared to women in the Upper West region.

After adjusting for the effect of gestational age, there were still significant differences between BMI, systolic and diastolic blood pressures respectively of women in the Upper West and Greater Accra regions (p<0.001), and between the districts in each region (p<0.001). The incidence of PIH among ANC attendants in the Upper West region ranged from 0.65% in Wa West to 6.5% in Nandom, with a regional mean of 3.2%. The incidence in Greater Accra region ranged from 4.3% in Ada East to 9.0% in La Dadekotopon with a regional mean of 6.1% (Table 2). The difference in the incidence of PIH between Greater Accra region and Upper West region was statistically significant (p< 0.001) as was the incidence of PIH between all the districts. Because of the incompleteness of blood pressure at delivery data, incidence of PIH manifesting for the first time at delivery could not be estimated and therefore also overall incidence of PIH – both occurring during pregnancy and at delivery could not be estimated.

Table 3 shows that obese women had a nearly 2-fold increased risk of developing PIH compared to normal weight women (OR=1.85, 95% CI 1.00-3.43, p=0.05). Overweight was not associated with increased risk of PIH (OR=1.41, 95% CI 0.78-2.54, p=0.25).

DISCUSSION

The findings confirm our hypothesis that there are variations in the incidence of PIH between rural and urban areas of Ghana and that some of the variation may be associated with variation in risk factors for hypertension in general such as obesity. Significant differences in mean systolic and diastolic blood pressures of women in the two regions were observed, with average blood pressures being higher in the urbanized Greater Accra region compared to the Upper West region.

The higher percentage of obese women in Greater Accra corresponded with a higher incidence of PIH in Greater Accra. Urbanization is among the population changes that have been documented to contribute to overweight and obesity in LMICs. Urbanization is known to be associated with lifestyle changes such as diet and decreased levels of physical activity that put people at increased risk of overweight and obesity (15-19). In 2013 the prevalence of overweight and obesity among women in West Africa ranged from 12.4% in Chad to 55.7% in Mauritania. Ghana registered a prevalence

of overweight among women of 38.4% and of obesity of 14.0% (18). Higher obesity rates among women (up to 37.1%) has been documented in other studies in the urban Greater Accra Region (20;21). Apart from the mother, the foetus is also put at risk by obesity, since maternal obesity is a known risk factor for adverse pregnancy outcomes (22-24).

Though there is limited data on local area variations in PIH incidence within the countries of sub-Saharan African or even between countries, data from other parts of the world suggest that it is an area of work worth further exploration in sub-Saharan Africa. Kaaja et al (25) documented regional differences in the prevalence of preeclampsia in Finland. The Northern, Eastern and Southern parts of Finland had rates of 13.9%, 11.1% and 7.9% respectively. These regional differences remained significant after adjustment for several maternal factors such as age at first birth, current age, parity, BMI, diabetes, hypertension, coronary artery disease and mothers' myocardial infarction. Differences in preeclampsia rates were attributed to the risk factors of coronary artery disease among women in Finland.

The incompleteness of critical HMIS data such as blood pressure at delivery limits the strength of the study and therefore our ability to be conclusive beyond doubt from the routine HMIS. Several of the gaps in the HMIS data availability could be attributed to the design of the antenatal and delivery registers, which have not made provision for these variables.

There were however a few other reasons for data incompleteness. Although staff were aware of existing protocol requirements, routine dipstick test for urine protein was often not done for pregnant women in the Upper West region because of stockout and non availability of test kits. In the Greater Accra region routine testing of urine protein was done by the midwives at the antenatal clinic. Here too, one clinic reported occasional stock out of urine dipsticks. When this happened, pregnant women were asked to test their urine at private laboratories. In both regions the urine protein results were not recorded in the antenatal register again because it is not one of the variables in the register. Where the tests had been done at the hospital's laboratory it was sometimes possible to extract the result from the laboratory register. Yet even this had limitations since most of the laboratories did not have good records of the tests done. In instances in the Greater Accra region where the test was done at private laboratories, the option to confirm from the laboratory register was not available.

There were several reasons for the low percentage of fundal height recording even though that variable was in the register. In some clinics the fundal height was simply not recorded in the antenatal register. In other clinics the fetal heart rate was recorded rather than fundal height although the register had a foot note explaining the abbreviation "fht" as fundal height.

All the health facilities did not record the blood pressure of the women at delivery in the delivery/maternity register because there is no column for it. It was however recorded on the delivery sheets and in the nurses' notes. Accessing these documents was difficult because in some facilities the delivery sheets could not be traced.

These challenges can be addressed by changing national level requirements, recognizing the importance of PIH in maternal outcomes. Addressing the gaps in the quality of the routine HMIS is likely to be an effective approach to ensure the needed routine monitoring as well as producing the evidence base related to local area variations in PIH incidence. In the study setting the interventions

that need to be put in place to enable the use of routine HMIS data for such purposes are fairly simple and inexpensive and likely to be more cost effective than the use of special surveys. Interventions such as expanding the range of variables that are captured in the antenatal and delivery registers can make a major difference in the quality of the evidence available to inform decision making.

Addressing stock out and non-availability of urine protein testing strips is also a step that can make a difference not only to data quality but also to the health and outcome of pregnant women and newborns. The policy of allowing pregnant women to take their maternal health record books home was to ensure continuity of care in a setting in which women sometimes move from one clinic to another in the course of a pregnancy; and also where patient records storage is poor in facilities. Given that this situation has not changed, key information in the book should be extracted and kept in the routine HMIS records of the clinic.

This study has shown statistically significant variations of PIH between districts and between the two regions. Maternal health policies and programmes should pay more attention to collecting evidence on local variations in maternal health conditions and take account of these local variations in the planning and delivery of health services.

Using a retrospective record review, the study was limited by the information obtained and recorded in the antenatal clinic and delivery registers. Hence detailed risk factor information such as family history of hypertensive disorders in pregnancy, chronic hypertension, diabetes, twin pregnancies, and personal lifestyle conditions such as smoking, dietary habits and physical activity could not be ascertained.

Our data collection was health facility rather than community based. However, it is reasonable to assume that the women in the study are representative of women in the community because the Ghana Demographic and Health Surveys (Table 4) show more than 95% of Ghanaian women attend antenatal care (8;9).

Conclusion

There are significant variations in the incidence of PIH across districts in Ghana. More attention needs to be given to mapping and understanding local area variations in PIH within countries as well as between countries in sub-Saharan Africa. Possible relationships with urbanization and lifestyle changes that promote obesity should be investigated in detail to provide information to inform maternal and newborn health policy and program decisions. This can be done with HMIS data, but interventions need to be put in place to improve the data completeness.

Attention also needs to be paid to quality of antenatal and delivery care inputs such as preventing stock out of reagents to test for urine protein. Despite high antenatal care coverage in the study setting (over 95%) and high skilled attendance at delivery, the quality of the service received can limit the impact on outcomes if these issues are not addressed.

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APPENDICES | TABLES AND FIGURES

Table 1 | Demographic and obstetric characteristics of 2,682 pregnant women by region of residence in Ghana at the first antenatal care visit.

Variable (mean (SD))	Greater Accra region N=1578	Upper West region N=1104	P-value
Mean Age (years)	27.2 (5.8)	27.3 (6.3)	0.608
Gestational Age (weeks)	13.9 (4.4)	11.7 (6.8)	<0.001
Mean Height (cm)	159.7 (6.4)	160.9 (6.3)	<0.001
Mean Weight (kg)	63.1 (12.7)	58.1 (8.2)	<0.001
Mean BMI (kg/m^2)	24.7 (4.7)	22.4 (2.9)	<0.001
Systolic BP (mmHg)	107.6 (11)	102.7 (9.7)	<0.001
Diastolic BP (mmHg)	64.5 (9)	62.9 (8.1)	<0.001
Parity			
0	491 (60.8%)	317(39.2%)	<0.001
1-2	804 (66.1%)	412 (33.9%)	
≥ 3	275(42.0%)	374(58.0%)	
BMI Category			
Overweight (25.0 -29.9 kg/m^2)	406 (26.6%)	139 (12.8%)	<0.001
Obese (≥30 kg/m^2)	212 (13.9%)	24 (2.2%)	

Table 2 | Incidence of pregnancy-induced hypertension across districts in the Upper West and Greater Accra regions of Ghana.

Region	District*	Type of district	Rate of PIH (%)	95% Confidence Interval
Upper West	–	-	3.2	3.19-3.21
	Lawra	Rural	4.1	4.07-4.13
	Jirapa	Rural	0.97	0.96-0.98
	Wa West	Rural	0.65	0.64-0.66
	Nandom	Rural	6.5	6.46-6.54
	Sissala West	Rural	5.9	5.87-5.93
Greater Accra	–	–	6.1	6.09-6.11
	Ledzokuku Krowor	Urban	5.6	5.58-5.63
	La Dadekotopon	Urban	9.0	8.96-9.04
	Ada East	Rural	4.3	4.28-4.32
	Ga West	Mostly urban with rural areas	5.8	5.77-5.83
	Shai Osu Doku	Mostly rural but urbanizing	6.6	6.57-6.63

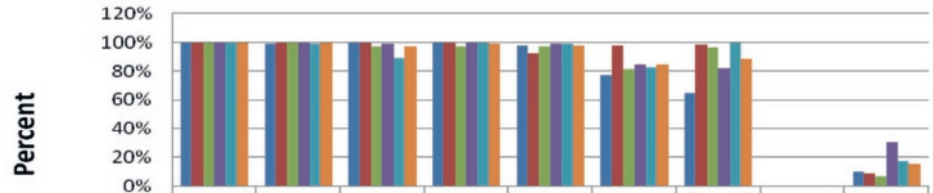
**Source:* GHANADISTRICTS.com accessed at www.ghanadistricts.com/districts on 20/12/2014.

Table 3 | Association between Body Mass Index (BMI) category and pregnancy-induced hypertension in 2,682 women in Ghana.

BMI category	Crude Odds Ratio (95% CI.)	P-value
Normal weight (Reference)	–	–
Underweight(<18.5 kg/m^2)	2.65 (1.38-5.08)	0.003
Overweight (25.0 kg/m^2-29.9 kg/m^2)	1.41 (0.78-2.54)	0.25
Obese (≥30 kg/m^2)	1.85 (1.00-3.43)	0.05

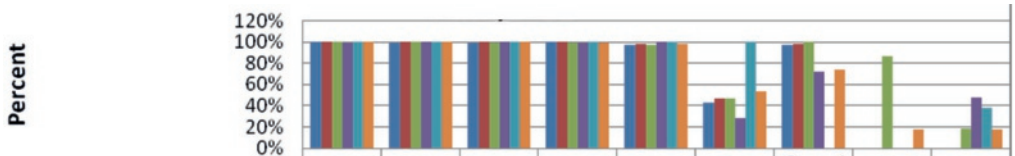
Table 4 | Antenatal coverage by socio-demographic variables, Ghana Demographic and Health Survey 2003, 2008 and 2014.

Variable		GDHS 2003 (ANC coverage (%))	GDHS 2008 (ANC coverage (%))	GDHS 2014 (ANC coverage (%))
	Upper West	90.9	95.7	98.3
Region	Greater Accra	96.3	97.6	98.5
	Rural	88.6	93.9	96.0
Residence	Urban	97.9	97.8	98.8
	No Education	86.1	93.5	94.1
	Primary	92.6	93.5	95.9
Education level	Middle/JHS	96.9	97.6	99.2
	Secondary+	100	98.9	99.9
	Lowest	83.3	92.5	94.0
	Second	91.3	93.2	95.6
Wealth quintile	Middle	94.7	96.1	98.2
	Fourth	95.3	97.7	99.4
	Highest	98.2	99.1	99.7
Mothers age at birth(years)	<20	93.8	97.3	97.8
	20-34	92.7	95.5	97.6
	35-49	88.6	94.3	96.3



	Age	Parity	BP	Weight	Height	Fundal height	Gestational age	Urine protein	BP at delivery
Ada East Hospital	100%	98.90%	100%	99.70%	97.70%	77.40%	64.70%	0	9.90%
Shai Osu Doku Hospital	100%	100%	100%	100%	92.30%	97.80%	98.40%	0	8.60%
Ga West Hospital	100%	99.70%	97.60%	97.30%	97.30%	81.60%	96.90%	0	6.60%
La General Hospital	100%	100%	99%	100%	99.40%	84.90%	82.40%	0	30.40%
LEKMA Hospital	100%	99.20%	89%	100%	99.20%	82.90%	99.50%	0	17.50%
Greater Accra Region	100.00%	99.60%	97.10%	99.40%	97.70%	84.90%	88.40%	0	15.40%

Figure 1 | Completeness of reporting of antenatal and delivery variables by health facility in Greater Accra region (GAR), January to June, 2012.



	Age	Parity	BP	Weight	Height	Fundal height	Gestational age	Urine protein	BP at delivery
Wa West Health Centre	100%	99.40%	99.40%	100%	96.80%	42.90%	97.40%	0	0
Jirapa District hospital	100%	100%	100%	100%	98.50%	47.10%	98.50%	0	0
Lawra District hospital	100%	100%	98.90%	98.90%	97.20%	46.90%	100%	86.60%	18.40%
Nandom District hospital	99.40%	100%	100%	98.80%	100%	28.40%	71.60%	0	47.90%
Sissala West District hospital	100%	100%	100%	100%	100%	100%	0	0	37.50%
Upper West Region	100%	99.90%	99.70%	99.50%	98.50%	53.10%	73.50%	17.30%	17.40%

Figure 2 | Completeness of reporting of antenatal and delivery variables by health facility in Upper West region (UWR), January to June, 2012.

CHAPTER 3

Systematic review of prediction models for gestational hypertension and preeclampsia

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ABSTRACT

Background Prediction models for gestational hypertension and preeclampsia have been developed with data and assumptions from developed countries. Their suitability and application for LMICs have not been tested. This review aimed to identify and assess the methodological quality of prediction models for gestational hypertension and pre-eclampsia with reference to their application in low resource settings.

Methods Using combinations of keywords for gestational hypertension, preeclampsia and prediction models seven databases were searched to identify prediction models developed with maternal data obtained before 20 weeks of pregnancy and including at least three predictors (Prospero registration CRD 42017078786). Prediction model characteristics and performance measures were extracted using the CHARMS, STROBE and TRIPOD checklists. The National Institute of Health quality assessment tools for observational cohort and cross-sectional studies were used for study quality appraisal.

Results We retrieved 3,706 articles out of which 32 articles were eligible for review. Thirty of these were cohort studies; two were nested case control studies. Seventy-seven percent of all the prediction models combined biomarkers with maternal clinical characteristics. Body mass index (BMI) was the most frequently used predictor (17/32). Biomarkers used as predictors in most models were pregnancy associated plasma protein-A (PAPP-A) and placental growth factor (PlGF). Six of the prediction models had been externally validated; three studies were conducted in a low-and middle income country (LMIC).

Conclusions Most of the studies fell short of reporting according to the criteria for developing or validating a prediction model. Only six out of 32 prediction models had been externally validated, hampering their generalizability to other populations. To improve on the methodological rigour and reporting of prediction modeling studies, TRIPOD, STROBE and CHARMS guidelines should be adhered to. The use of biomarkers, though enhancing performance of prediction models, may limit the applicability of prediction models in most LMIC because these biomarkers are currently not routinely measured in these settings. This suggests investment in research to develop affordable easy to use uterine artery Doppler imaging equipment and diagnostic assays for serum biomarkers.

Keywords: Prediction models, CHARMS Checklist, Systematic review, RIsk of bias assessment.

BACKGROUND

Hypertensive disorders of pregnancy (HDPs) are important causes of maternal morbidity and mortality globally but the burden is greatest in low- and middle-income countries (LMIC) (1-3). These disorders of pregnancy include gestational hypertension, preeclampsia and eclampsia and are characterized by an increase in blood pressure and multi-organ derangements which range from mild to severe (4). There is no known cure but daily administration of aspirin early in the first trimester has been shown to reduce the incidence and the severity of preeclampsia (5-8). Preeclampsia is a major indication for preterm delivery, accounting for about 15% of all preterm deliveries (9-13) and is a cause of increased healthcare costs through the prolonged stay of the mother or newborn in intensive care units (14).

Prediction models provide estimates of the probability or risk of the future occurrence of a particular outcome or event in individuals at risk of such an event (15). Prediction models have also been used to identify women at high risk of developing HDPs later in pregnancy so as to provide for closer monitoring from early pregnancy onwards, including aspirin prophylaxis (5-8) which has been shown to reduce the risk of developing preeclampsia.

The aim of this systematic review was to evaluate the performance of multivariate prediction models to address the question of the effectiveness of prediction models in identifying pregnant women at risk of gestational hypertension and preeclampsia. Study objectives were to identify prediction models for gestational hypertension and preeclampsia; assess the methodological quality of the studies to develop and externally validate the prediction models using the CHARMS (16) checklist; and to identify prediction models that can be applied in low and middle income country settings.

METHODS

This study was conducted using the checklist for critical appraisal and data extraction for systematic reviews of prediction modelling studies (CHARMS) (16), strengthening the reporting of observational studies in epidemiology (STROBE) (17) and the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) (18) checklists. The Population, Intervention, Comparator and Outcome (PICO) format for the review was as follows: P (pregnant women), I (prediction models), C (none) and O (gestational hypertension or preeclampsia). The study protocol was registered with the Prospero International Prospective Register of Systematic Reviews (CRD 42017078786).

Search strategy

A comprehensive systematic literature search was conducted in PubMed/Medline, Embase, Cochrane Library, Web of Science and CINAHL databases from 1960 through 18 September 2017 (DLV,EA). The MeSH database, EMTREE subject headings and CINAHL subject headings were used to construct the search strategy along with author keywords and general keywords. This search method was

chosen to allow ease in replication of the search. In addition, a manual search (also referred to as an electronic hand search) was conducted in a number of journals from 10th September through 25th September, 2017 (see Appendix 1). Finally, grey literature was searched using the New York Academy of Medicine Grey Literature, OCLC's OAISTER, and Open Grey databases.

The full search strategy is presented in Appendix 1.

Eligibility/Inclusion criteria

Cohort studies, nested-case control studies and randomized controlled trials were eligible for inclusion in the study. Case-control, cross-sectional, animal studies, bio-molecular studies, letters, reviews and case reports were excluded because for prediction modeling studies we require absolute risks whereas case-control or cross-sectional studies only give relative risks. The primary outcomes for the included studies were gestational hypertension and preeclampsia.

Definition of terms

Gestational hypertension was defined as elevated systolic blood pressure equal to or greater than 140 mmHg and/or diastolic blood pressure equal or greater than 90 mmHg on at least two occasions four hours apart and appearing for the first time after 20 weeks of gestation without proteinuria (4). Pre-eclampsia was defined as gestational hypertension with proteinuria of 300 mg or more in a 24-hour urine sample or spot urine protein/creatinine ratio of 30 mg/mmol (4). Pre-eclampsia was further divided into early-onset preeclampsia (occurring before 34 weeks gestation) and late-onset preeclampsia (occurring after 34 weeks gestation) as an outcome by some studies (19-24).

A prediction model (25) was defined as a logistic regression formula with three or more predictors that could be used to estimate risk probabilities for individual patients or to distinguish between groups of patients of different risks.

Screening methods for study identification

Two reviewers (EA, MAC) independently assessed the titles and abstracts of the search results to select relevant papers for further screening. After removal of duplicates, the articles were obtained for screening/reading of the full text after which eligible papers were selected for inclusion in the systematic review. Discrepancies between the reviewers were resolved through consensus.

Data extraction and management

Data extraction of the identified studies was done by using the CHARMS checklists (EA). Extracted data were checked (MAC) and disagreements were resolved by consensus (EA,MAC). In case of disagreement a third reviewer (KKG) was consulted. Studies were analysed qualitatively given the large variability of the studies included.

The following categories were extracted: authors, journal, year of publication, region or place where study was conducted, period of data collection, study design, inclusion and exclusion criteria, the sample size of the derivation cohort and/or the validation cohort, the gestational age at which women were enrolled into the study and the number of outcomes. Other information extracted were the number and types of predictors, the target population for whom the prediction model is

intended for, the handling of missing data, the modeling method used, the model selection method, the handling of continuous data, the method used for internal validation and whether or not an external validation was done.

Quality assessment

Quality of the studies was assessed using the CHARMS, STROBE and TRIPOD checklists and the National Institute of Health (NIH) (26) quality assessment tools for observational cohort and cross-sectional studies was independently assessed by two authors (EA, MAC). The NIH quality assessment tools focus on concepts that are key for critical appraisal of the internal validity of a study. The tool uses a 14-item checklist to assess the study design, inclusion criteria, outcome and variable description and collection and loss to follow up among others. Each item is scored as yes, no or other (not reported, not applicable or cannot determine). The tool also provides guidance on grading the studies as good, fair or poor. The studies were finally graded for risk of bias as "low" if risk of bias was unlikely, "moderate" if there were no essential flaws, but not all criteria had been satisfied and "high" if there were flaws in one or more important items. We adapted the tool and used 13 out of the 14 items, because one item, "*for exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?*" was not relevant to our review.

RESULTS

The flow chart for selection of the studies is shown in Figure 1 (Appendix 3). The search yielded 4,062 papers. After removing 361 duplicates, 3701 papers were screened further for relevance and 174 papers selected for full text assessment. Finally 32 papers, published between 2000 and 2017, were selected for the review.

Prediction models for gestational hypertension and pre-eclampsia.

All thirty-two studies (14,19-21,23,24,27-52) included in this review were conducted between 2000 and 2017. Table 1 gives an overview of important parameters of the selected studies. Ten studies were conducted in the United Kingdom (20,21,27,33-35,44,48,53,54), eight in the United States of America (23,28,31,38,46,50-52), four in Australia (20,30,33,48) and three each in Italy (14,37,45) and New Zealand (20,33,48). Two studies were done in the Netherlands (19,32) and Ireland (33,48) with one each in Japan (42), Chile (24), Spain (36), Germany (49), Ghana (47), Norway (41) and Brazil (43).

Most of the studies were prospective cohort studies (25/32=78.1%), four were retrospective cohort studies (12.5%), two were nested-case control studies (6.3%) and one study combined a retrospective and prospective cohort design for data collection. All the prediction models were derived through logistic regression.

The gestational age at inclusion into the studies ranged between eight and twenty weeks. All the gestational ages were confirmed by ultrasound. The sample size for the studies ranged between 173 and 35,948. The events per variable in the studies ranged between 2.1 and 88.2.

Seventy seven percent of all the prediction models combined biomarkers with maternal clinical characteristics. Body mass index (BMI) was the most frequently used predictor (17/32). Other maternal clinical predictors used in the models were first trimester systolic blood pressure and diastolic blood pressure, mean arterial pressure, maternal ethnicity, parity, previous history of preeclampsia, family history of hypertension, family history of preeclampsia, history of smoking and history of gestational diabetes mellitus. The following biomarkers were included: uterine artery pulsatility index (UtA PI, 13/32), pregnancy associated plasma protein-A (PAPP-A) (12/32) and placental growth factor (PlGF) (12/32). The following predictors were used less than ten times in the studies under review: free beta human chorionic gonadotropin (fβ-HCG), alpha feto protein (AFP), soluble fms-like tyrosine kinase-1 (sFlt-1), placental protein 13 (PP13), A disintegrin and metalloproteinase 12 (ADAM12), soluble endoglin (sEng) and vascular endothelial growth factor (VEGF). The frequency of predictor variables in the models is shown in Figure 2 (Appendix 3).

Methodological quality of the studies to develop or validate prediction models using the CHARMS, STROBE and TRIPOD checklists

Source of data

All the studies indicated the type of study design used to obtain data for the prediction modeling. Thirty were cohort studies whilst two were nested case-control studies.

Participants

All the studies indicated the participant eligibility and recruitment criteria, including the study location, number of centres and the inclusion and exclusion criteria.

Outcomes to be predicted

All the studies gave a standard definition for the outcome(s) to be predicted. Most of the studies had a single outcome while eight studies had two or more outcomes.

Candidate predictors

All the studies defined and described the candidate predictors and the methods for their measurement. The timing of predictor measurements was also provided in all studies. Handling of predictors in the modeling process was described by 30 out of the 32 studies. Nine of the studies categorized continuous variables whilst 19 studies kept continuous variables linear.

Sample size

All studies provided the number of participants and the number of outcomes. Only seven of the studies explicitly estimated the sample size before the onset of the study. The number of outcomes in relation to the number of candidate predictors (events per variable) were deduced from the data and ranged between 2.1 and 88.2.

Missing data

The number of participants with any missing value for each predictor was not provided by the studies. Five of the studies did not indicate how missing data were handled. Complete case analysis was used by 22 out of the 32 studies whilst five studies imputed missing data using the single regression imputation method (19,32), expectation maximization method (33,48) and multiple imputation (47).

Model development

All the studies selected candidate predictors for inclusion in the model through univariate analysis using a pre-determined p-value. Logistic regression was used to derive all the prediction models. For selection of predictors during multivariable modeling, one study used the stepwise forward selection method, 12 studies used the stepwise backward selection method and two studies used stepwise selection without further specification. One study (46) applied the Lasso regression approach whilst 13 studies did not state the method used for deriving the model.

Model performance

Discrimination of the prediction models, depicted by the c-statistic or the area under the receiver operating characteristic (ROC) curve was reported by 27 (84.4%) of the studies while calibration was reported by four (12.5%) studies. Classification measures were reported by 30 (94%) of the studies (Table 1).

Model evaluation

Internal and external validation

Internal validation was reported by nine out of 32 studies, using bootstrapping (19,47), cross validation (14,20,40,46,48), split sample (55) and back propagation of error method for artificial neural networks (45). Seven out of the 32 prediction models were externally validated.

Risk of bias assessment

Risk of bias refers to the extent that flaws in the design, conduct, and analysis of the primary prediction modelling study lead to biased, often overly optimistic, estimates of predictive performance measures such as model calibration, discrimination, or (re)classification (usually due to overfitted models).

Figure 3 (Appendix 3) shows a chart of the risk of bias assessment on 13 domains. Most of the studies had a low risk of bias. The major source of bias related to sample size estimations, only stated in detail by seven out of 32 studies. Details of the risk of bias assessment are presented in Table 2 (Appendix 2)**.**

Prediction models applicable in low and middle income settings

Apart from one model each from Brazil (43) and Chile (24), both Upper middle income countries in Latin America, and one model from Ghana (47), all the other models in the literature that met our inclusion criteria were developed in high income countries of Europe, Japan, Australia, New Zealand and the United States of America.

DISCUSSION

We set out to review the evidence in the published literature on the performance of multivariate prediction models for gestational hypertension and preeclampsia to assess the effectiveness of prediction models in identifying pregnant women at risk for gestational hypertension and preeclampsia. The specific objectives of this study were to identify prediction models for gestational hypertension and preeclampsia in the literature, assess the methodological quality of the prediction modeling studies by applying the CHARMS checklist and identify prediction models that can be applied in low and middle income country settings.

Prediction models for gestational hypertension and preeclampsia

Our study identified 32 prediction models for gestational hypertension and preeclampsia, most of which had been developed and validated in high-income countries in Europe, Australia and the USA. Only three of such studies had been conducted in a low and middle income country setting. Most of the prediction models were developed in single centres but a few had been developed using data from multiple centres in one or more countries.

Methodological quality of prediction modeling studies

The STROBE (Strengthening the reporting of observational studies in epidemiology), TRIPOD (Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis) and the CHARMS checklists have outlined steps for developing and validating prediction models. The CHARMS checklist in particular provides guidance as to the items to extract when conducting a systematic review of prediction studies. An assessment of the methods used in model development in the studies evaluated in this review showed gaps in application of recommendations in the CHARMS, TRIPOD and STROBE checklists. The following domains of the CHARMS checklist were not adequately addressed in most of the studies: the source of data, study participants, outcome(s) to be predicted, candidate predictors, sample size, missing data, model development, model performance, model evaluation, results, interpretation and discussion. For example continuous predictors were dichotomized in some of the studies despite evidence and recommendations to the contrary (56-59). Bias in predictor selection is known to occur when continuous predictors are categorized. Again, categorizing continuous variables assumes that there is a stepwise change in risk from one cut-off point to another. Bodnar et al (60) have demonstrated a dose-dependent relationship between pre-pregnancy BMI and the risk of preeclampsia. As BMI increases, so does the risk of preeclampsia. Therefore categorizing the predictor variable makes the functional relationship between the continuous variable (predictor) and the outcome variable linear, hence nonlinear transformations such as restricted cubic splines or fractional polynomials cannot be applied (56,61,62).

To prevent overestimation of risks by prediction models, it is recommended that the number of outcomes in relation to the number of predictors (events-per-variable) should be at least ten to one (63,64). This requires an adequate sample size that ensures that there are enough outcomes in the study. Hence sample size estimation is an important methodological consideration so that at the onset of the study an adequate events-per-variable can be assured and thereby prevent

overestimation of the predictive performance of the models (overfitting). Unfortunately, most of the studies under review did not report on sample size estimation. An adequate sample size also minimizes predictor selection bias. Predictor selection bias tends to be greater in smaller datasets when the events-per-variable ratio is small, especially when there are weak predictors in the dataset (16).

Information on missing data should be reported as part of the results of the studies. This includes the number of participants with any missing value (including values for both predictors and outcomes), number of participants with missing data for each predictor and how the missing data were handled, for example by complete case analysis, imputation or other methods. Information about missing data gives an idea as to the extent of bias, dependent on the reasons for the missing data. Where data were not missing completely at random, the prediction estimates are likely to be biased (58,65-69). Missing data are seldom missing completely at random and may often be related to other observed participant data. Consequently, participants with completely observed data are likely to be different from those with missing data. Complete-case analysis which was the commonest method used to handle missing data in most studies deletes participants with a missing value from the analysis, thereby resulting in loss of information from a subset of the study population. This may result in over or under estimation of the predictive effect and reduced performance in an external population.

Prediction model performance is one of the important domains to be reported on (65). Model performance indicators include calibration, discrimination and classification. It is recommended that discrimination and calibration should always be reported for prediction models. Discrimination indicates how well the prediction model distinguishes between two outcomes such as disease or non-disease and is assessed using the c-statistic or the area-under-the-curve (AUC) of a receiver operating characteristic curve (70-72). The AUC ranges from 0.5 to 1 and represents the prediction model's ability to correctly classify a randomly selected individual as being from one of two hypothetical populations (72-75). An AUC value of 1.0 is considered perfect, 0.9-0.99 excellent, 0.8-0.89 good, 0.7-0.79 fair and 0.51-0.69 poor. An AUC of 0.5 is considered non-informative. The AUC in the studies under review ranged between 0.65 and 0.98. Apart from the study by Kuijk et al (19) which had an AUC of 0.65, all the other studies reported AUC greater than or equal to 0.70, indicating good to excellent discrimination. Calibration refers to how well the predicted risks compare to the observed outcomes. Usually this is evaluated in a calibration plot by graphically plotting observed against predicted event rates (16,61,76). Calibration plots may be supplemented by the Hosmer-Lemeshow test, which is a formal statistical test to determine whether calibration is adequate. Unfortunately, most of the studies under review did not report the calibration plot. This shortcoming leaves room for uncertainty in applying the model in clinical practice because one cannot determine the probability range within which the model works well. Both discrimination and calibration are essential in determining model performance.

Prediction model evaluation can be undertaken by internal validation (using the same dataset as that used to develop the model) and external validation (using a different dataset to that used in developing the model). The external dataset should be collected using the same predictor and outcome definitions and measurements. Again most of the studies did not report whether or not

internal validation had been performed thus breaching an important methodological consideration. Most of the studies did not follow the guidelines in the TRIPOD, STROBE and CHARMS checklists. A possible explanation may be that some of the studies were conducted prior to the development of these guidelines so the investigators may not have had the benefit of these methodological guidelines.

Prediction models applicable in low-and-middle income settings

Only three of the studies had been conducted in a low-and-middle income country setting (24,43,47). Given contextual differences between high and low-and-middle income countries, many of the prediction models under review which have been developed in high income countries at present may not be applicable in most low-and-middle income countries. Most of these prediction models included biomarkers and uterine artery pulsatility index as predictors in addition to maternal clinical characteristics (20,21,23,24,27,28,30,36-41,44,46,48-53,55). At present uterine Doppler measurement and serum biomarker assays are not widely available in many low-and-middle income countries. Therefore prediction models using biomarkers and uterine artery pulsatility index may not be routinely applied in these settings.

Generally, prediction models developed in one setting have to be externally validated in new populations to assess their performance before applying them in clinical decision-making. The model intercept and the regression coefficients often have to be updated to fit the new context or population to which the prediction model is being applied to. Thus prediction models developed elsewhere may be updated for use in other settings provided the predictors and outcome are the same. In situations where a prediction model includes variables which cannot be measured in the setting where the model is to be applied, that model cannot be used in that population. Consequently most prediction models developed in high income countries and including variables like serum biomarkers and uterine artery pulsatility index are at present not applicable in most low-and-middle income countries where the burden of hypertensive disorders of pregnancy is greater. This means that prediction models using maternal clinical characteristics, and which generally do not give optimum predictions remain the option until such time that new diagnostics which are affordable and easy to apply in low resource areas become available

Conclusion

Most of the prediction models included biomarkers and uterine artery pulsatility index as predictors. However these predictors are currently not measured in many low-and-middle income countries. This limits the use of such models in LMIC settings where they are most needed because of their high burden of hypertensive disorders of pregnancy. To optimize the use of prediction models as a tool for improving maternal health, we recommend that further research to develop affordable, easy to use diagnostic assays for serum biomarkers should be undertaken. As has been done with the development of low-cost, portable and robust equipment for ultrasonography, uterine artery Doppler imaging equipment could also be developed to make the service more accessible and affordable.

To improve on the methodological rigour and reporting of prediction modelling studies, the TRIPOD, STROBE and CHARMS checklists should be adhered to by investigators.

LIST OF ABBREVIATIONS

HDPs	Hypertensive disorders of pregnancy
LMIC	Low and middle income country
CHARMS	Checklist for critical appraisal and data extraction for systematic reviews of prediction modelling studies
STROBE	Strengthening the reporting of observational studies in epidemiology
TRIPOD	Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis
BMI	Body mass index
UtA PI	Uterine artery pulsatility index
PAPP-A	Pregnancy associated plasma protein-A
PlGF	Placental growth factor
fβ-HCG	Free beta human chorionic gonadotropin
AFP	Alpha feto protein
sFlt-1	Soluble fms-like tyrosine kinase
PP13	Placental protein 13
ADAM12	A disintegrin and metalloproteinase 12
sEng	Soluble endoglin
VEGF	Vascular endothelial growth factor

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Authors' contributions

EA designed study. EA, DLV and SM collected data. EA, MAC, KKG analysed the data. EA wrote the initial draft of the manuscript. KKG, IAA, KAK, DEG, DLV and MAC provided scientific guidance and were also actively involved in the preparation and review of the manuscript. All authors read and approved the final manuscript.

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APPENDIX 1

Search strategy

(gestational hypertension OR pregnancy induced hypertension OR pregnancy transient hypertension OR maternal hypertension) and (pre-eclampsia OR preeclampsia OR pre-eclamptic OR pregnancy toxemia OR pregnancy toxemias OR edema proteinuria hypertension gestosis OR eph complex OR eph toxemia OR eph gestosis OR proteinuria edema gestosis) and (prediction models OR prediction model OR prediction OR predictive OR forecasting OR probability learning OR decision support technique OR decision support technique OR decision support model OR decision support models OR decision analysis OR decision analyses OR clinical prediction rule OR clinical prediction rules) AND (risk OR risks OR probability OR probabilities OR causality OR causation OR enabling factor OR enabling factors OR predisposing factors OR predisposing factors)

(pre-eclampsia OR preeclampsia OR pre-eclamptic OR pregnancy toxemia OR pregnancy toxemias OR edema proteinuria hypertension gestosis OR eph complex OR eph toxemia OR eph gestosis OR proteinuria edema gestosis) and (prediction models OR prediction model OR prediction OR predictive OR forecasting OR probability learning OR decision support technique OR decision support technique OR decision support model OR decision support models OR decision analysis OR decision analyses OR clinical prediction rule OR clinical prediction rules) AND (risk OR risks OR probability OR probabilities OR causality OR causation OR enabling factor OR enabling factors OR predisposing factors OR predisposing factors)

Hand search of the following journals

Ultrasound Obstet Gynecol, Hypertension, Am J Obstet Gynecol, BJOG, Pregnancy Hypertens, BMC Pregnancy Childbirth, Prenat Diagn, Acta Obstet Gynecol Scand, Arch Gynecol Obstet, Euro J Obstet Gynecol Reprod Biol, Fetal Diagn Ther, J Matern Fetal Neonatal Med, Placenta, Am J Perinatol, J Hum Hypertens, BMC Womens Health, BMJ, Biomark Med, Clin Exp Obstet Gynecol, J Soc Gynecol Investig, JAMA, Lancet, PLoS One and Reprod.

Keywords and subject heading terms and their combinations used in the searches

"Gestational hypertension", "pregnancy hypertension", "pregnancy-induced hypertension", "pregnancy transient hypertension", "maternal hypertension", "pre-eclampsia", preeclampsia", "pre-eclamptic", "pregnancy toxemia", "pregnancy toxemias", "edema", "hypertension", "hypertension", "edema", "proteinuria", "gestosis", "EPH Complex", "EPH toxemia", "EPH gestosis", "proteinuria edema hypertension gestosis", "prediction models", "prediction", "predictive", "forecasting", "probability learning", "decision support techniques", "decision aids", "decision support model", "decision support models", "decision analysis", "decision analyses", "clinical prediction rule", "clinical prediction rules", "risk", "risks", "probability/ies", "causality", "causation", "enabling factor", "enabling factors", "predisposing factors", "predisposing factor" and "human".

APPENDIX 2 | TABLES

Table 1 | Overview of prediction models

Publication	Study design	Centre	Study population	Outcome	Women, n (outcome events; predictors)	Number of events per variable	Predictors	Type of model
Mello et al, 2002 (14)	Prospective cohort	Single	Italian (Caucasian)	Preeclampsia	187 (47; 8)	5.9	maternal characteristics	Logistic regression
Becker, 2011 (25)	Retrospective cohort	Single	German (Caucasian)	Preeclampsia, Preterm delivery, Intrauterine fetal growth restriction, placental abruption, intrauterine fetal death. Early neonatal fetal death (within first week of postnatal life).	15,855 (172; 6)	28.7	maternal characteristics, uterine artery pulsatility index	logistic regression
Myatt et al, 2012 (26)	Prospective (nested)cohort	Multicentre	American (Multi racial)	Preeclampsia	2,394 (176; 7)	25.1	maternal characteristics, serum biomarkers	Logistic regression
Goetzinger et al, 2010 (27)	Retrospective cohort	Single	American (Multi racial)	Preeclampsia	3716 (293; 5)	58.6	maternal characteristics, serum biomarkers	Logistic regression
Odibo et al, 2011 (28)	Retrospective cohort	Single	American (Multi racial)	Preeclampsia	452 (42; 6)	7	maternal characteristics, serum biomarkers	Logistic regression
O'Gorman et al, 2014 (29)	Prospective cohort	Single	United Kingdom (Multi racial)	Preeclampsia	35,948 (1058; 15)	70.5	maternal characteristics, serum biomarkers, uterine artery pulsatility index	Logistic regression

Table 1 | *Continued*

Publication	Study design	Centre	Study population	Outcome	Women, n (outcome events; predictors)	Number of events per variable	Predictors	Type of model
Paré et al, 2014 (30)	Prospective cohort	Multicentre	American (Multi racial)	Outcomes: Preeclampsia, gestational hypertension, HELLP† syndrome, eclampsia.	2,637 (431; 8)	29.6	maternal characteristics, serum biomarkers, uterine artery pulsatility index	Logistic regression
Moon et al, 2015 (31)	Prospective cohort	Single	United Kingdom (Multi racial)	Preeclampsia	1177 (102; 11)	9.3	maternal characteristics, serum biomarkers, uterine artery pulsatility index	Logistic regression
Park et al, 2013 (32)	Prospective study	Multicentre	Australian (Multi racial)	Preeclampsia	3066 (83; 7)	11.9	maternal characteristics, serum biomarkers, uterine artery pulsatility index	Logistic regression
Stamilio et al, 2000 (33)	Retrospective cohort	Single	American (Multi racial)	Severe preeclampsia	1998 (49; 4)	12.2	maternal characteristics, serum biomarkers.	Logistic regression
Van Kuijk et al, 2014 (35)	Combined prospective and retrospective cohort	Multicentre	Dutch (Multi racial)	Early onset preeclampsia	229(15; 5)	3	Maternal characteristics	Logistic regression
Kenny et al, 2014 (36)	Prospective cohort	Multicentre	New Zealand, Australia, United Kingdom, Ireland (Multi racial)	Preeclampsia	3529 (278; 5)	55.6	maternal characteristics, serum biomarkers, uterine artery pulsatility index	Logistic regression

Table 1 | *Continued*

Publication	Study design	Centre	Study population	Outcome	Women, n (outcome events; predictors)	Number of events per variable	Predictors	Type of model
Poon et al, 2010 (37)	Prospective cohort	Single	United Kingdom (Multi racial)	Preeclampsia	8366 (165; 8)	20.6	Maternal characteristics	Logistic regression
Poon et al, 2009 (19)	Prospective cohort	Single	United Kingdom (Multi racial)	Preeclampsia	7797 (157; 8)	19.6	maternal characteristics, serum biomarkers, uterine artery pulsatility index	Logistic regression
Herraiz et al, 2009 (39)	Prospective cohort	Single	Spanish (Multi racial)	Preeclampsia	152 (20; 4)	5	maternal characteristics, serum biomarkers, uterine artery pulsatility index	Logistic regression
Di Lorenzo et al, 2012 (40)	Prospective cohort	Single	Italian (Multi racial)	Preeclampsia, gestational hypertension	2118 (preeclampsia(25), gestational hypertension (46); 8)	3.1	maternal characteristics, serum biomarkers, uterine artery pulsatility index	Logistic regression
Goetzinger et al, 2014 (41)	Prospective cohort	Single	American (Multi racial)	Preeclampsia	578(49; 6)	8.1	maternal characteristics, serum biomarkers, uterine artery pulsatility index	Logistic regression
Crovetto et al, 2014 (20)	Prospective cohort (nested case-control)	Single	Spanish (Multi racial)	Preeclampsia	5759 (112; 10)	11.2	maternal characteristics, serum biomarkers, uterine artery pulsatility index	Logistic regression

Table 1 | *Continued*

Publication	Study design	Centre	Study population	Outcome	Women, n (outcome events; predictors)	Number of events per variable	Predictors	Type of model
Gallo et al, 2016 (43)	Prospective cohort	Multicentre	United Kingdom (Multi racial)	Preeclampsia	7748 (268; 11)	24.4	maternal characteristics, serum biomarkers, uterine artery pulsatility index	Logistic regression
Skråstad et al, 2014 (44)	Prospective cohort	Single	Norway	Preeclampsia	541 (21; 11)	1.9	maternal characteristics, serum biomarkers, uterine artery pulsatility index	Logistic regression
Muto et al, 2016 (45)	Prospective cohort	Single	Japanese	Preeclampsia, gestational hypertension.	1986 (50; 6)	8.3	maternal characteristics.	Logistic regression
Antonio et al, 2017 (46)	Prospective cohort	Single	Brazilian (Multi racial)	Preeclampsia, gestational hypertension.	617 (34; 4)	8.5	maternal characteristics, biomarkers, Uterine artey pulsatility index.	Logistic regression
van Kuijk et al, 2011 (17)	Prospective cohort	Multicentre	Dutch (Multi racial)	Preeclampsia	407 (28; 5)	5.6	maternal characteristics, fasting blood glucose.	Logistic regression
Gabbay-Benziv et al, 2016 (21)	Prospective cohort	Multicentre	American (Multi racial)	Preeclampsia	2433 (108; 5)	21.6	maternal characteristics, biomarkers.	Logistic regression
Poon et al, 2008 (38)	Prospective cohort	Single	United Kingdom (Multi racial)	Preeclampsia, gestational hypertension	5193 (104; 5)	5	maternal characteistics	Logistic regression

Table 1 | *Continued*

Publication	Study design	Centre	Study population	Outcome	Women, n (outcome events; predictors)	Number of events per variable	Predictors	Type of model
Allen et al, 2017 (47)	Prospective cohort	Single	United Kingdom (Multi racial)	Preeclampsia, gestational hypertension, small-for-gesttaional age.	1045 (56; 5)	11.2	maternal characteristics, biomarkers.	Logistic regression
Parra-Cordero et al, 2013 (22)	Nested case-control (prospective cohort)	Single	Chilean	Preeclampsia	2619 (83; 4)	20.7	maternal characteristics, biomarkers, Uterine artey pulsatility index.	Logistic regression
Mello et al, 2001 (48)	Prospective cohort	Single	Italian (Caucasian women)	Preeclampsia	303 (76; 9)	8.4	maternal characteristics, hematological and biochemical indices.	Logistic regression
Myers et al, 2013 (18)	Prospective cohort	Multicentre	United Kingdom, New Zealand, Australia (Multi racial)	Preterm preeclampsia	3529 (55; 7)	7.9	maternal characteristics, biomarkers, Uterine artey pulsatility index.	Logistic regression
Baschat et al, 2014 (49)	Prospective cohort	Multicentre	American (Multi racial)	Preeclampsia	2441 (108; 5)	21.6	maternal characteristics, biomarkers, Uterine artey pulsatility index.	Logistic regression
Antwi et al, 2017 (50)	Prospective cohort	Multicentre	Ghanaian	Gestational hypertension	2529 (261; 6)	43.5	maternal characteristics, serum biomarkers.	Logistic regression

Table 1 | *Continued*

Publication	Study design	Centre	Study population	Outcome	Women, n (outcome events; predictors)	Number of events per variable	Predictors	Type of model
North et al, 2011 (51)	Prospective cohort	Multicentre	New Zealand, Australia, United Kingdom, Ireland (Multi racial)	Preeclampsia	3529(186; 13)	14.3	maternal characteristics, uterine artery pulsatility index	Logistic regression

† hemolysis, elevated liver enzymes and low-platelet count (HELLP) syndrome.

Table 1 | Overview of prediction models (Continued)

Publication	Internal validation	External validation	Calibration (P-value Hosmer-Lemeshow test or calibration plot)	Discrimination (AUC)	Prediction rule/ score chart/ nomogram	Handling of missing values	Model selection: Stepwise selection, Univariate P-values, No selection	Handling of continuous data: Kept linear, Categorized, Dichotomized	Model performance: ROC curve, AUC or c-statistic, PPV, NPV, Sensitivity, Specificity, Hosmer-Lemeshow goodness-of fit test
Mello et al, 2002 (14)	Yes	No	No	Yes	No	Not stated	Stepwise selection	Categorized	Yes
Becker, 2011 (25)	Not stated	Yes	No	No	Model formula with regression coefficients, algorithm	Not stated	not stated	Categorized	No
Myatt et al, 2012 (26)	Not stated	No	No	Yes	No	Complete case analysis	Stepwise backward selection	Kept linear	Yes
Goetzinger et al, 2010 (27)	Not stated	No	No	Yes	Model formula with regression coefficients	Complete case analysis	Stepwise backward selection	Categorized	Yes

Table 1 | *Continued*

Publication	Internal validation	External validation	Calibration (P-value Hosmer-Lemeshow test or calibration plot)	Discrimination (AUC)	Prediction rule/ score chart/ nomogram	Handling of missing values	Model selection: Stepwise selection, Univariate P-values, No selection	Handling of continuous data: Kept linear, Categorized, Dichotomized	Model performance: ROC curve, AUC or c-statistic, PPV, NPV, Sensitivity, Specificity, Hosmer-Lemeshow goodness-of fit test
Odibo et al, 2011 (28)	Not stated	No	No	Yes	Model formula with regression coefficients	Complete case analysis	Stepwise backward selection	Kept linear	Yes
O'Gorman et al, 2014 (29)	Not stated	No	No	Yes	Model formula with regression coefficients	Complete case analysis	Stepwise backward selection	Kept linear	Yes
Paré et al, 2014 (30)	Not stated	No	No	No	Model formula with regression coefficients	Not stated	Stepwise backward selection	Kept linear	No
Moon et al, 2015 (31)	Not stated	No	No	Yes	Model formula with regression coefficients	Complete case analysis	stepwise backward selection	Not stated	Yes
Park et al, 2013 (32)	Not applicable. External validation of a previously developed prediction model.	Yes	No	Yes	Model formula with regression coefficients	Complete case analysis	not stated	Kept linear	Yes
Stamilio et al, 2000 (33)	Not stated	No	No	Yes	Model formula with regression coefficients	Complete case analysis	stepwise backward selection	Categorized	Yes

Table 1 | *Continued*

Publication	Internal validation	External validation	Calibration (P-value Hosmer-Lemeshow test or calibration plot)	Discrimination (AUC)	Prediction rule/ score chart/ nomogram	Handling of missing values	Model selection: Stepwise selection, Univariate P-values, No selection	Handling of continuous data: Kept linear, Categorized, Dichotomized	Model performance: ROC curve, AUC or c-statistic, PPV, NPV, Sensitivity, Specificity, Hosmer-Lemeshow goodness-of fit test
Van Kuijk et al, 2014 (35)	Not stated	Yes. External validation of a previously developed prediction model	Hosmer-Lemeshow goodnesss-of-fit test.	Yes	Model formula with regression coefficients, score chart.	Regression imputation	Not applicable	Categorized	Yes
Kenny et al, 2014 (36)	Yes	No	No	Yes	Model formula with regression coefficients	Imputation by expectation maximization method, complete case analysis for uterine artery pulsatility index	Stepwise backward selection	Kept linear	Yes
Poon et al, 2010 (37)	Not stated	No	No	Yes	Model formula with regression coefficients	Complete case analysis	not stated	Kept linear	Yes

Table 1 | *Continued*

Publication	Internal validation	External validation	Calibration (P-value Hosmer-Lemeshow test or calibration plot)	Discrimination (AUC)	Prediction rule/ score chart/ nomogram	Handling of missing values	Model selection: Stepwise selection, Univariate P-values, No selection	Handling of continuous data: Kept linear, Categorized, Dichotomized	Model performance: ROC curve, AUC or c-statistic, PPV, NPV, Sensitivity, Specificity, Hosmer-Lemeshow goodness-of fit test
Poon et al, 2009 (19)	Not stated	No	No	No	model formula with regression coefficients	Complete case analysis	Not stated	Kept linear	Yes
Herraiz et al, 2009 (39)	Not stated	External validation of a previously developed prediction model	No	Yes	Model formula with regression coefficients	Not stated	Not applicable	Kept linear	Yes
Di Lorenzo et al, 2012 (40)	Not stated	No	No	Yes	Model formula with regression coefficients	Complete case analysis	Step down procedure	Kept linear	Yes
Goetzinger et al, 2014 (41)	Not stated	Yes	Yes	Yes	Model formula with regression coefficients	Complete case analysis	Stepwise backward selection	Categorized	Yes
Crovetto et al, 2014 (20)	Not stated	No	No	Yes	Model formula with regression coefficients	Not stated	Stepwise forward selection	Kept linear	Yes
Gallo et al, 2016 (43)	Cross validation	No	No	Yes	Model formula with regression coefficients	Complete case analysis	Not stated	Kept linear	Yes

Table 1 | *Continued*

Publication	Internal validation	External validation	Calibration (P-value Hosmer-Lemeshow test or calibration plot)	Discrimination (AUC)	Prediction rule/ score chart/ nomogram	Handling of missing values	Model selection: Stepwise selection, Univariate P-values, No selection	Handling of continuous data: Kept linear, Categorized, Dichotomized	Model performance: ROC curve, AUC or c-statistic, PPV, NPV, Sensitivity, Specificity, Hosmer-Lemeshow goodness-of fit test
Skråstad et al, 2014 (44)	Not stated	Yes. Study externally validated a previously developed prediction model	No	Yes	Fetal Medicine Foundation algorithm	Complete case analysis	Not stated	Kept linear	Yes
Muto et al, 2016 (45)	Not stated	No	No	No	Model formula with regression coefficients	Complete case analysis	Not stated	Categorized	Yes
Antonio et al, 2017 (46)	Not stated	No	No	Yes	Model formula with regression coefficients	Complete case analysis	Not stated	Kept linear	Yes
van Kuijk et al, 2011 (17)	Boot-strapping	No	Hosmer-Lemeshow goodness-of-fit test	Yes	Model formula with regression coefficients	Single regression imputation	Not stated	Kept linear	Yes
Gabbay-Benziv et al, 2016 (21)	Not stated	No	No	Yes	Prediction rule	Complete case analysis	Not stated	Categorized	Yes
Poon et al, 2008 (38)	Not stated	No	No	Yes	Model formula with regression coefficients	Complete case analysis	Not stated	Kept linear	Yes

Table 1 | *Continued*

Publication	Internal validation	External validation	Calibration (P-value Hosmer-Lemeshow test or calibration plot)	Discrimination (AUC)	Prediction rule/ score chart/ nomogram	Handling of missing values	Model selection: Stepwise selection, Univariate P-values, No selection	Handling of continuous data: Kept linear, Categorized, Dichotomized	Model performance: ROC curve, AUC or c-statistic, PPV, NPV, Sensitivity, Specificity, Hosmer-Lemeshow goodness-of fit test
Allen et al, 2017 (47)	Not stated	No	No	Yes	Model formula with regression coefficients	Complete case analysis	Stepwise selection	Kept linear	Yes
Parra-Cordero et al, 2013 (22)	Not stated	No	No	Yes	Model formula with regression coefficients	Complete case analysis	Not stated	Kept linear	Yes
Mello et al, 2001 (48)	Cross validation	No	No	Yes	Model formula with regression coefficients	Complete case analysis	not stated	Categorized	Yes
Myers et al, 2013 (18)	Cross validation	No	No	Yes	Not provided	Complete case analysis	Stepwise selection (forward selection followed by series of backward selection)	Age and blood pressure kept linear, BMI categorized	Yes
Baschat et al, 2014 (49)	Cross validation	No	No	Yes	Model formula with regression coefficients	Complete case analysis	Lasso logistic regression	Categorized	Yes
Antwi et al, 2017 (50)	Boot-strapping	Yes	Yes	Yes	Model formula with regression coefficients, score chart	Multiple imputation	stepwise backward selection	Kept linear	Yes
North et al, 2011 (51)	10-fold cross validation	No	Yes	Yes; AUC=0.710 (0.706 to 0.714)	Model formula with regression coefficients	Imputation by expectation maximization method	Stepwise backward selection	Kept linear, BMI categorized	Yes

† hemolysis, elevated liver enzymes and low-platelet count (HELLP) syndrome.

Table 2 | Quality assessment of prediction model studies using the National Institute of Health criteria.

Study	Research question or objective in this paper clearly stated?	Study population clearly specified and defined?	Participation rate of eligible persons at least 50%?	Study subjects recruited from the same or similar populations (including the same time period)? Inclusion and exclusion criteria prespecified and applied uniformly to all participants?	Sample size justification, power description, or variance and effect estimates provided?	Exposure(s) of interest measured prior to the outcome(s) being measured?	Sufficient time frame to reasonably expect to see an association between exposure and outcome if it existed?	Exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Exposure(s) assessed more than once over time?	Outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	Outcome assessors blinded to the exposure status of participants?	Loss to follow-up after baseline 20% or less?	Key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?
G.Mello et al 2002 (7)	Yes	Yes	Yes (100%)	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes (0)	Yes
Becker (62)	Yes	Yes	Yes (100%)	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes (0)	Yes
Myatt L. et al (63)	Yes	Yes	Yes (100%)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes (1.9%)	Yes
Goetzinger et al (64)	Yes	Yes	Yes (100%)	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes (7%)	Yes
Odibo et al (65)	Yes	Yes	Yes (94.8%)	Yes	NR	Yes	Yes	Yes	Yes	Yes	Cd	Yes (5.2%)	Yes
O'Gorman et al (40)	Yes	Yes	Yes (100%)	Yes	NR	Yes	Yes	Yes	Yes	Yes	CD	Yes (0)	Yes
Paré et al (41)	Yes	Yes	Yes (100%)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	CD	No	Yes
Moon et al (66)	Yes	Yes	Yes (100%)	Yes	CD	Yes	Yes	Yes	Yes	Yes	CD	Yes (1.9%)	Yes
Park et al (43)	Yes	Yes	Yes (98.1%)	Yes	No	Yes	Yes	Yes	Yes	Yes	CD	Yes (1.9%)	Yes
Kuijk et al (45)	Yes	Yes	Yes (100%)	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes (0)	Yes

Table 2 | *(Continued)*

Study	Research question or objective in this paper clearly stated?	Study population clearly specified and defined?	Participation rate of eligible persons at least 50%?	Study subjects recruited from the same or similar populations (including the same time period)? Inclusion and exclusion criteria prespecified and applied uniformly to all participants?	Sample size justification, power description, or variance and effect estimates provided?	Exposure(s) of interest measured prior to the outcome(s) being measured?	Sufficient time frame to reasonably expect to see an association between exposure and outcome if it existed?	Exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Exposure(s) assessed more than once over time?	Outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	Outcome assessors blinded to the exposure status of participants?	Loss to follow-up after baseline 20% or less?	Key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?
Stamilio et al (44)	Yes	Yes	Yes (100%)	Yes	No	Yes	Yes	Yes	Yes	Yes	CD	Yes (0)	Yes
Kenny et al (46)	Yes	Yes	Yes (99%)	Yes	No	Yes	Yes	Yes	Yes	Yes	CD	Yes (1%)	Yes
Poon, et al (47)	Yes	Yes	Yes (100%)	Yes	No	Yes	Yes	Yes	Yes	Yes	CD	Yes (0)	Yes
Poon et al (35)	Yes		Yes (91.9%)	Yes	No	Yes	Yes	Yes	Yes	Yes	CD	Yes (8.1%)	Yes
Herraiz et al (49)	Yes	Yes	Yes (87.9%)	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes (12.1%)	Yes
Di Lorenzo et al (50)	Yes	Yes	Yes (98%)	Yes	No	Yes	Yes	Yes	Yes	Yes	CD	Yes (2.4%)	Yes
Goetzinger et al (51)	Yes	Yes	Yes (98%)	Yes	No	Yes	Yes	Yes	Yes	Yes	CD	Yes (2%)	Yes
Crovetto et al (52)	Yes	Yes	Yes (100%)	Yes	No	Yes	Yes	Yes	Yes	Yes	CD	Yes (0)	Yes
Gallo et al (53)	Yes	Yes	Yes (100%)	Yes	No	Yes	Yes	Yes	Yes	Yes	CD	Yes (0)	Yes
Skrastad et al (54)	Yes	Yes	Yes (96.6%)	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes (3.4%)	Yes

Table 2 | *(Continued)*

Study	Research question or objective in this paper clearly stated?	Study population clearly specified and defined?	Participation rate of eligible persons at least 50%?	Study subjects recruited from the same or similar populations (including the same time period)? Inclusion and exclusion criteria prespecified and applied uniformly to all participants?	Sample size justification, power description, or variance and effect estimates provided?	Exposure(s) of interest measured prior to the outcome(s) being measured?	Sufficient time frame to reasonably expect to see an association between exposure and outcome if it existed?	Exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Exposure(s) assessed more than once over time?	Outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	Outcome assessors blinded to the exposure status of participants?	Loss to follow-up after baseline 20% or less?	Key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?
Muto et al (55)	Yes	Yes	Yes (100%)	Yes	No	Yes	Yes	Yes	Yes	Yes	CD	Yes (0)	Yes
Antonio et al (56)	Yes	Yes	87.6%	Yes	Yes	Yes	Yes	Yes	Yes	Yes	CD	Yes (12.4%)	Yes
Kuijk et al (33)	Yes	Yes	Yes (100%)	Yes	No	Yes	Yes	Yes	Yes	Yes	CD	Yes (0)	Yes
Gabbay-Benziv et al (37)	Yes	Yes	Yes (100%)	Yes	No	Yes	Yes	Yes	Yes	Yes	CD	Yes (0)	Yes
Poon et al (48)	Yes	Yes	Yes (92.9%)	Yes	No	Yes	Yes	Yes	Yes	Yes	CD	Yes (7.1%)	Yes
Allen et al (57)	Yes	Yes	Yes (83.6%)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	CD	Yes (16.4%)	Yes
Parra-Cordero et al (38)	Yes	Yes	Yes (100%)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	CD	Yes (0)	Yes
Myers et al (34)	Yes	Yes	Yes (99%)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	CD	Yes (1%)	Yes
Mello et al (58)	Yes	Yes	Yes (100%)	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes (0)	Yes

Table 2 | *(Continued)*

Study	Research question or objective in this paper clearly stated?	Study population clearly specified and defined?	Participation rate of eligible persons at least 50%?	Study subjects recruited from the same or similar populations (including the same time period)? Inclusion and exclusion criteria prespecified and applied uniformly to all participants?	Sample size justification, power description, or variance and effect estimates provided?	Exposure(s) of interest measured prior to the outcome(s) being measured?	Sufficient time frame to reasonably expect to see an association between exposure and outcome if it existed?	Exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Exposure(s) assessed more than once over time?	Outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	Outcome assessors blinded to the exposure status of participants?	Loss to follow-up after baseline 20% or less?	Key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?
Baschat et al (59)	Yes	Yes	Yes (100%)	Yes	No	Yes	Yes	Yes	Yes	Yes	CD	Yes (0)	Yes
Antwi et al (60)	Yes	Yes	Yes (100%)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes (0)	Yes
North et al (61)	Yes	Yes	Yes (94.8%)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes (5.2%)	Yes

CD- Could not be determined; NR- Not reported

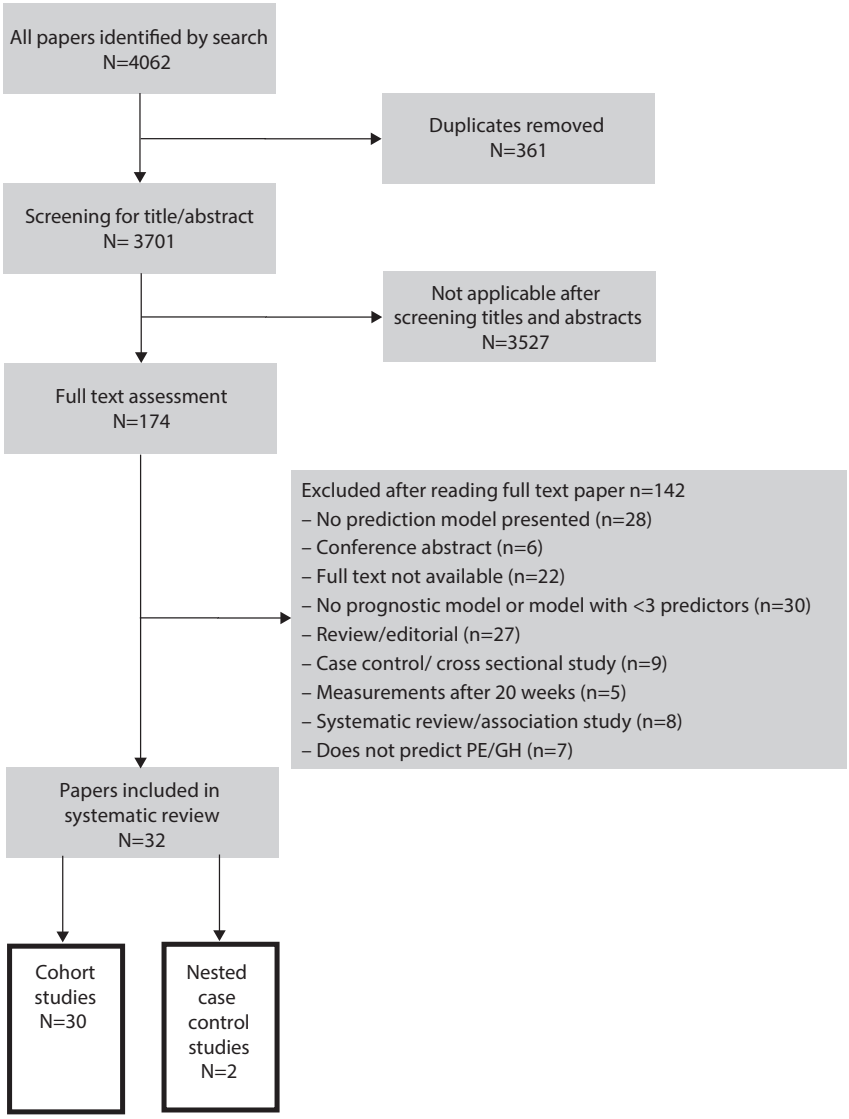

Figure 1 | Flow chart for selection of studies for inclusion in systematic review

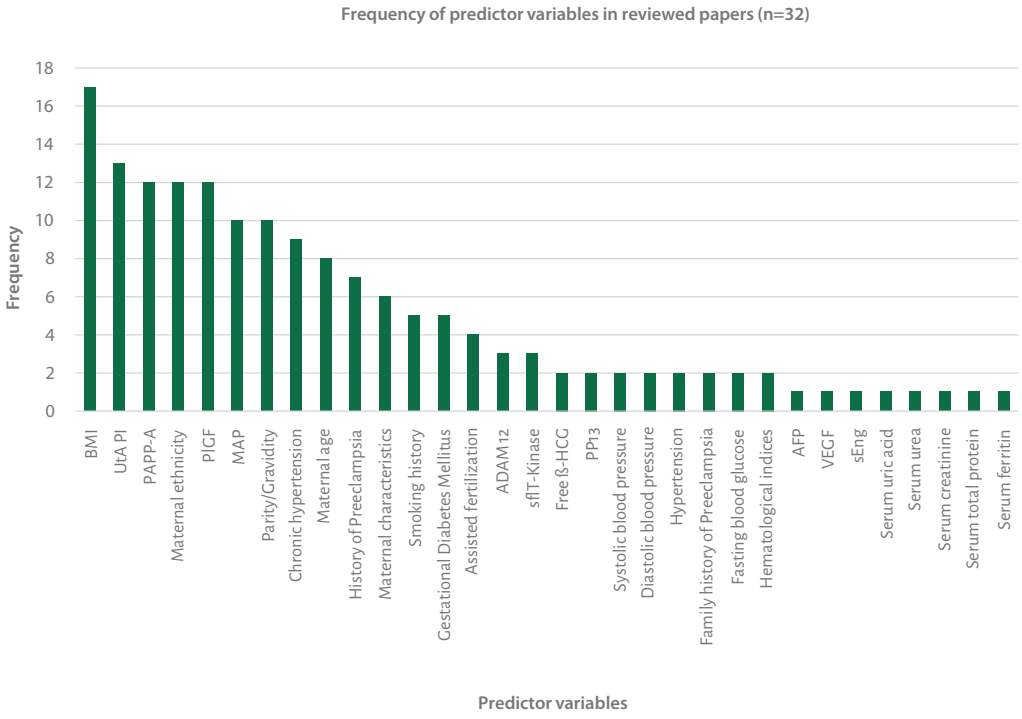

Figure 2 | Type and frequency of predictor variables used in the prediction studies

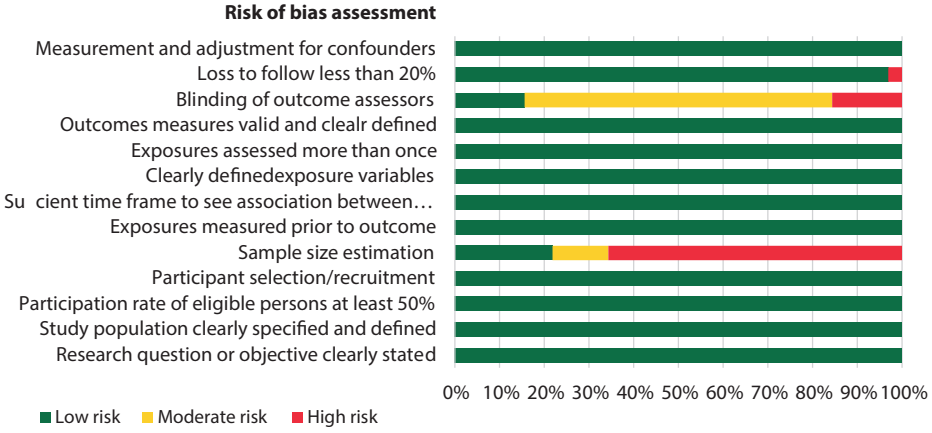

Figure 3 | Risk of bias assessment chart

CHAPTER 4

Development and validation of a prediction model for gestational hypertension in a Ghanaian cohort

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ABSTRACT

Objective To develop and validate a prediction model for identifying women at increased risk of developing gestational hypertension (GH) in Ghana.

Design A prospective study. We used frequencies for descriptive analysis, Chi square test for associations and logistic regression to derive the prediction model. Discrimination was estimated by the c-statistic. Calibration was assessed by calibration plot of actual versus predicted probabilities.

Setting Primary care antenatal clinics in Ghana.

Participants Two thousand five hundred and twenty nine pregnant women in the development cohort and 647 pregnant women in the validation cohort. Inclusion criterion was women without chronic hypertension.

Primary outcome Gestational hypertension.

Results Predictors of GH were diastolic blood pressure, family history of hypertension in parents, history of GH in a previous pregnancy, parity, height and weight.
The c-statistic of the original model was 0.70 (95% CI: 0.67-0.74) and 0.68 (95% CI: 0.60-0.77) in the validation cohort. Calibration was good in both cohorts. The negative predictive value (NPV) of women in the development cohort at high risk of GH was 92% compared to 94% in the validation cohort.

Conclusion The prediction model showed adequate performance after validation in an independent cohort and can be used to classify women into high, moderate or low risk of developing GH. It contributes to efforts to provide clinical decision-making support to improve maternal health and birth outcomes.

Key words: Predictors, Gestational hypertension, Prediction model, Hypertensive disorders of pregnancy, Risk scores.

INTRODUCTION

Hypertensive disorders of pregnancy (HDPS), which include gestational hypertension (GH), pre-eclampsia, eclampsia and the haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome are the third leading cause of maternal deaths globally (1), with most of these deaths occurring in low- and middle-income countries (LMICs). The International Society for the Study of Hypertension in Pregnancy (ISSHP) classifies HDPSs as chronic hypertension, gestational hypertension, pre-eclampsia-de novo or superimposed on chronic hypertension and white coat hypertension (2). HDPSs are the leading cause of maternal death in Latin America and the Caribbean accounting for 25.7% of mortality; in Africa they rank third (9.1%) (3). In Ghana, 14% of all female deaths are pregnancy related with HDPSs being the third leading cause of maternal deaths (9%) after haemorrhage (22%) and induced abortion (11%) (4).

The underlying causes of HDPSs are not fully known (5),however accurate prediction of women at increased risk of HDPS could lead to better antenatal care (ANC) and a reduction of complications from the condition.

Clinical prediction models estimate the probability of individuals having certain health conditions or obtaining defined health outcomes (6-9). They combine two or more items of patient data to predict clinical outcome and prior to application in clinical practice should be externally validated (6-12). The main approaches to predicting the occurrence of GH include the use of maternal clinical characteristics, Uterine Artery Doppler and biomarkers (13-15). Although a number of prediction models for HDPS, mainly pre-eclampsia and eclampsia have been developed in high-income countries, they may not be suitable for low- and middle-income countries because of differences in the availability and the cost of diagnostic tools (16).

The aim of this study was to develop and externally validate a contextual appropriate and low cost clinical prediction model for GH based on maternal characteristics obtained at the first antenatal care visit for use in primary care settings in Ghana and potentially other LMIC.

METHODS

Study design and population

(i) Development cohort

The prediction model was developed in a prospective cohort of 2,529 pregnant women attending antenatal care in primary care setting in six hospitals in the Greater Accra region of Ghana between February and May 2010. The eligibility criterion was pregnant women without chronic hypertension. The exclusion criteria were a history of hypertension or having hypertension before 20 weeks gestation as per blood pressure (BP) measurements. After potential participants had given written informed consent, they were enrolled and followed up at ANC visits until they delivered. Ethical approval for the study was granted by the Ethical Review Committee of the Ghana Health Service (Ethical Clearance ID No: GHS-ERC 02/1/10).

Sample size estimation was based on the incidence of HDPSs in the Ghanaian population and on the principle of ten outcome events per variable (17). The Ghana Maternal Health Survey of 2007 (3) had estimated that 9% of all maternal deaths were due to HDPS. Using an estimated incidence of GH of 10% in the study population and for 10 predictors, we aimed to enrol 2500 women but actually enrolled 2,529.

Data was obtained from the women's medical records as measured by the midwives during routine antenatal care. The midwives had been given standardized training in data collection. Candidate predictors were selected based on a review of the literature on variables known to be associated with GH (18-22). Information on the following predictors: maternal age, diabetes mellitus (confirmed diagnosis of diabetes mellitus), family history of hypertension (confirmed diagnosis of hypertension in parents or siblings), family history of diabetes (confirmed diagnosis of diabetes in parents or siblings), and family history of multiple pregnancies were obtained during the first antenatal clinic visit. Blood pressure (measured with a mercury sphygmomanometer), height (measured in centimetres with a stadiometer), weight (measured in kilogrammes with a bathroom scale) and urine protein (defined as 2+ or more on urine dipstick) were also obtained during the first and subsequent antenatal clinic visits. Pregnancy outcomes were obtained from the hospital maternity register.

(ii) Validation cohort

For external validation of the derived prediction model, data from 647 adult pregnant women recruited as part of a prospective cohort study conducted between July 2012 and March 2014 at Ridge Regional Hospital and Maamobi General Hospital in Accra were utilized. These hospitals provide primary antenatal care similar to that received by the women in the derivation study. Ethical approval for the validation study was granted by the Ethical Review Committee of the Ghana Health Service (GHS-ERC 07/09/11). The inclusion criteria were women less than 17 weeks pregnant and 18 years or older with no pre-existing hypertension. Pregnant women were included in the study after they had given written informed consent and were interviewed by trained research assistants using a structured questionnaire for socio-demographic characteristics and obstetric history. Weight, height, blood pressure, urine protein at the initial and subsequent ANC visits was obtained from the maternal health record books. Pregnancy outcomes were obtained from the hospital maternity register. Data was entered by trained data clerks using EpiDataEntry (EpiData Association, Odense, Denmark, 2010) and validated by double entry, cleaned and checked for missing data.

Outcome

The outcome, GH, was defined as a systolic BP of 140mmHg or more and or a diastolic BP of 90mmHg or more on at least two separate occasions, and present for the first time after 20 weeks of pregnancy (23). In both cohorts blood pressure measurements were taken using a mercury sphygmomanometer by trained midwives. The appropriate adult-sized cuff was placed on the bare left upper arm with the woman comfortably seated and her back supported and the legs uncrossed. The arm was at the level of the heart and neither the patient nor the observer talked during the measurement. Korotkoff phase V sounds were used (24). Two readings were taken at interval of

five minutes and the average used to represent the woman's B. The sphygmomanometers at the clinics are calibrated periodically to ensure accurate readings. The gestational age at which GH was diagnosed is available for both cohorts.

Data analysis

The mean and standard deviation of continuous predictors were calculated for women who developed GH and those who did not. Means were compared using the independent T-test; percentages for categorical data were assessed by Chi-square test. Missing data were imputed by multiple imputation using "Multivariate Imputation by Chained Equations (MICE)" function in R (25). Missing values were imputed 10 times and Rubin's rule (26), was applied to pool results over the ten imputed datasets. Predictors that were related to GH by a pre-determined p-value of 0.20 or less were selected and used in a multivariable logistic regression model. Stepwise backward selection using $p<0.20$ was used to derive the model which was internally validated using the bootstrapping technique. Parity was included in the model while systolic blood pressure dropped out of the model. The resulting shrinkage factor after bootstrapping was used to adjust the regression coefficients, thus correcting for model overfitting.

The performance of the models in the development and validation cohort was assessed by discrimination and calibration. Discrimination is the ability of the model to distinguish between women who develop GH and those who do not and was assessed using the c-statistic. The c-statistic or area under the receiver operating characteristic curve (AUC) ranges from 0.5 (no discrimination) to 1.0 (perfect discrimination) (12). Calibration of the model was assessed by the calibration plot of actual probabilities versus predicted probabilities.

For application of the model, a score chart was derived using the regression coefficients of the predictors. The total score of each woman was related to her risk of developing GH. Cut-off points based on a total score of less than one, between two and six and equal or greater than seven were used to classify women into low, moderate and high risk of GH respectively. The sensitivity, specificity, negative and positive predictive values of the cut-off points were calculated.

Reporting and analysis of study results was conducted according to the TRIPOD checklist (27) statistical data analysis was done by use of SPSS software (version 20.0, IBM SPSS Statistics Inc., Chicago, Illinois, USA) and R statistical software (version 3.1.0 (2014-04-10)).

RESULTS

Table 1 describes the baseline characteristics of the development and validation cohorts at the first ANC visit.

Development Cohort

Women with and without GH differed with respect to age (28.9 (SD 5.9) years vs. 28.0 (SD: 5.8) years, p=0.01). There was no difference in mean height between women who developed GH and those without GH (159.9 cm (SD 6.7) vs. 160.6 cm (SD 7.4), p=0.19). The mean weight differed between

women with and without GH (73.3 kg (SD 19.0) vs. 66.2 kg (SD 13.2), p<0.001). The mean diastolic blood pressure also differed between women who developed GH and those who did not (71.9 mmHg (SD 11.6) vs. 66.2 mmHg (SD 9.1), p<0.001).

About 27% of women with GH had a parent with hypertension compared to 17.2% of women without GH (p<0.001). Furthermore 15.3% of women with GH had a history of GH in a previous pregnancy compared to 1.0% of women without GH (p<0.001).

Validation cohort

Mean age of women who developed GH (29.8 (SD 5.6) years) was higher than in those who did not. (28.2 (SD 5.0) years, p=0.053). There was no difference in mean height between women with and without GH (161.4 cm (SD 9.5) vs. 161.1 cm (SD 7.5), p=0.75). However there was a difference in the mean weight of women with and without GH (74.0 kg (SD 14.8) vs. 65.9 kg (SD 7.5), p<0.001). The mean diastolic blood pressure differed between women who developed GH and those who did not (75.2 mmHg (SD 12.6) vs. 69.1 mmHg (SD 10.5), p<0.001), as did mean systolic blood pressure (115.6 mmHg (SD 14.5) vs. 111.6 mmHg (SD 12.2), p=0.046).

Of the women who developed GH, 29.2% reported a family history of hypertension in parents compared to 3.6% of those who did not (p=0.02). Percentage of women with previous history of GH did not materially differ between those who developed GH and those who did not.

Table 2 shows the adjusted Odds ratios of predictors of gestational hypertension in the development cohort. These are maternal height, weight, diastolic blood pressure, a history of hypertension in the parents, a previous history of GH in the mother and parity. The c-statistic of the model was 0.70 (95% CI: 0.67 - 0.74).

The final prediction model was:
Logit (GH)=-1.53 -0.031*Height+0.38*Hypertension in parents+2.26*Previous GH + 0.024*Weight + 0.041*Diastolic BP - 0.10*Parity.

The c-statistic after external validation was 0.68 (95% CI: 0.60-0.77).

Figure 1 shows the calibration plot for the development cohort. The calibration plot shows a good fit for probabilities between 0.1 and 0.16 where most of the events occur.

Figure 2 shows the calibration plot in the validation cohort. The plot shows a good fit for probabilities between 0.04 and 0.16, where most of the events occur.

Table 3 presents the score chart for obtaining the total risk score of each woman.

Table 4 shows the categorization of the development cohort into low, moderate and high risk. Three hundred and one women were classified as being at high risk of developing GH and 82 of them eventually developed GH giving a positive predictive value (PPV) of 27.2% and a negative predictive value of 92.0%. The likelihood ratio positive was 1.22 for low risk and 3.24 for moderate risk while the likelihood ratio negative was 0.32 for low risk and 0.76 for moderate risk.

Table 5 presents information on the categorization of the validation cohort into low, moderate and high risk of GH. Twelve women were classified as high risk and 4 of them eventually developed GH, giving a PPV of 33.3% and a negative predictive value of 94.0%. The likelihood ratio positive

was 1.15 for low risk and 7.31 for moderate risk while the likelihood ratio negative was 0.50 for low risk and 0.92 for moderate risk. Table 6 shows the number of observations and missing values (with percentage missing) for the development and validation cohorts. Table 7 compares characteristics of women in the development and validation cohorts before and after imputation.

DISCUSSION

We developed and externally validated a simple prediction model for GH in two different cohorts of pregnant women attending ANC clinics in similar settings in line with the general recommendation that before being applied in clinical practice, prediction models should be externally validated (6-12). The c-statistic of the model in the original cohort (0.70 (95% CI: 0.67-0.74)) was only slightly reduced (0.68 (95% CI: 0.60-0.77)) after external validation, consistent with findings from other studies (28-31). Nijdam et al (32) in the Netherlands derived a prediction model for identifying nulliparous women who developed hypertension before 36 weeks of gestation using systolic blood pressure, diastolic blood pressure and weight. The AUC of the original model of 0.78 (95% CI: 0.75-0.82) reduced to 0.75 (95% CI: 0.68-0.81) after external validation. The small decrease in c-statistic in our study implies that the model predicts well based on data routinely collected as part of antenatal care and can be applied to the pregnant women in the study setting.

Most prediction models for HDPSs, such as the SCOPE model (16), have focussed on pre-eclampsia and eclampsia which are severer forms of the disorder. However milder forms such as GH are also associated with less favourable pregnancy outcomes. Given that GH can be managed to prevent progression to severer forms, a model that identifies women at risk is useful.

A limitation of our study was the application of clinical characteristics only, excluding biomarkers and Uterine Artery Doppler in our prediction model. This is because of the non- routine use of these parameters in ANC in the Ghanaian setting. Both approaches are expensive and the equipment for analysing these biomarkers is generally not available in many low resource settings. However, future research could assess the added value of these biomarkers as recent systematic review for first trimester prediction of preeclampsia showed that a combination of Uterine Artery Doppler, maternal characteristics and two or more biomarkers yielded detection rates of 38% to 100% (13). The best rates were reported for the combination of Inhibin A, PLGF, PAPP-A, Uterine Artery Doppler and maternal characteristics (13). The difficulty of predicting GH using only maternal clinical characteristics has been pointed out (33), however, the feasibility of applying these models in low resource settings currently remains limited due to constraints in the availability of diagnostic equipment and the high cost of the tests which are beyond the means of most people who require them. Thus despite the increased predictive value of adding biomarkers to the predictive model; the need to derive reasonably accurate prediction models that use variables, which are routinely easy to obtain for low resource settings is important.

In the development cohort, 301 (11.9%) women were classified as being at high risk of developing GH. Eighty two of them eventually developed GH giving a PPV of 27.2% and NPV of 92%. In the validation cohort, 12 (1.9%) women were classified as being at high risk of GH and 4 of them

developed the condition. The PPV was 33.3% and the NPV 94%. Classifying women into different risk categories allows for closer monitoring of pregnant women at high risk. This will include more frequent ANC visits or referral for specialist care.

Given that the addition of biomarkers in the screening of women could enhance the identification of those at high risk of GH, future research should explore the added value of biomarkers in the early identification of pregnant women at increased risk of HDPSs in LMICs. Such studies should be accompanied by comparative cost effectiveness of the routine data only predictive models and the models that combine routine data and biomarkers to provide essential health technology assessment information for future decision making. In the interim however, despite the fact that the modest PPV in both the development and validation cohorts show the limitation and difficulty of predicting GH using only demographic and clinical characteristics the model has the potential of identifying pregnant women at increased risk of GH for subsequent care and monitoring. Its further validation and use is worth serious consideration in low resource settings.

Conclusion

We developed and validated a prediction model for GH at the first ANC visit using maternal data prospectively collected in a LMIC setting. Our results are easily converted into a simple user friendly clinical decision making support tool for use in antenatal clinics in low resource settings that enables frontline providers of maternal health services to use a score chart to quickly categorize women into different risk levels. The strength of this model is the use of a few maternal clinical variables already routinely obtained by care-givers during routine ANC. Such a simple predictive model to aid frontline providers of maternal care to estimate the probability of GH later on in the pregnancy and take relevant precautions is potentially life-saving. Obtaining the information does not involve expensive procedures such as Uterine Artery Doppler (34). The application of the model at the ANC should aid in the early detection of women at risk of GH and contribute to efforts to provide clinical decision making support to improve maternal health outcomes. We would recommend its validation in other low-income settings as well as implementation research to inform implementation, monitoring and evaluation at scale in Ghana.

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Contributors

EA designed the study, collected data, carried out data analysis and wrote the initial draft of the manuscript. RHHG assisted with data analysis. DEG, RHHG, IA, KAK, KK-G, JLB and AF provided scientific guidance and were also actively involved in the preparation and review of the manuscript and approved it.

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APPENDICE | TABLES AND FIGURES

Table 1 | Characteristics of the development and validation cohort at first antenatal visit stratified by gestational hypertension.

	Development Cohort				Validation Cohort			
Variable **Mean (SD), resp. N (%)**	**GH (Yes)** **N=261**	**GH (No)** **N=2268**	**O.R (95% CI)**	**P-value**	**GH (Yes)** **N= 42**	**GH (No)** **N= 605**	**O.R (95% CI)**	**P-value**
Age (years)	28.9 (5.9)	28.0 (5.8)	1.03(1.01-1.05)	0.013	29.8(5.6)	28.2(5.0)	1.06 (0.99-1.13)	0.053
Height (cm)	159.9 (6.7)	160.6 (7.4)	0.98 (0.97-1.01)	0.19	161.4(9.5)	161.1(7.5)	1.01(0.97-1.05)	0.757
Weight (kg)	73.3 (19.0)	66.2 (13.2)	1.03 (1.02-1.04)	<0.001	74.0(14.8)	65.9(7.5)	1.05(1.02-1.07)	<0.001
Systolic Blood Pressure (mmHg)	116.0 (15.2)	108.7(10.8)	1.05(1.04-0.06)	<0.001	115.6(14.5)	111.6(12.2)	1.02(1.00-1.046)	0.046
Diastolic Blood Pressure (mmHg)	71.9 (11.6)	66.2(9.1)	1.06 (1.05-1.08)	<0.001	75.2(12.6)	69.1(10.5)	1.05 (1.02-1.08)	<0.001
Gestational age (weeks)	21.9 (6.1)	20.5(6.9)	1.03 (1.01-1.05)	0.003	10.9(2.9)	11.4(2.9)	0.95(0.85-1.05)	0.298
Employed	243 (93.1%)	2092 (92.2%)	1.14 (0.69-1.88)	0.62	37 (88.1%)	523 (86.4%)	0.86 (0.33-2.26)	0.76
Married	194 (74.3%)	1775 (78.3%)	0.80 (0.60-1.08)	0.15	38(90.5%)	501(82.8%)	1.97(0.69-5.65)	0.21
Educational level								
None	30(11.8%)	230(10.4%)	Referent		4(9.5%)	60(9.9%)	Referent	
Primary	55 (21.7%)	424 (19.1%)	0.84(0.47-1.47)	0.53	4(9.5%)	75(12.4%)	1.89(0.41-8.75)	0.42
Junior High School	101(39.9%)	999 (44.9%)	0.83 (0.50-1.38)	0.47	20(47.6%)	260(43.0%)	1.51(0.33-6.97)	0.59
Senior High School	42 (16.6%)	410 (18.4%)	0.65 (0.41-1.03)	0.07	11(26.2%)	125(20.7%)	2.18(0.63-7.52)	0.217
Tertiary	25 (9.9%)	160 (7.2%)	0.66(0.39- 1.11)	0.12	3(7.1%)	85(14.0%)	2.49(0.68-9.20)	0.17
Family history of hypertension (Parents)	70 (26.8 %)	392 (17.2%)	1.75 (1.29-2.34)	0.001	5(29.2%)	22(3.6%)	3.45(1.24-9.62)	0.018
Previous history of GH	40 (15.3%)	23 (1.0%)	17.8 (10.4-30.2)	<0.001	1(2.4%)	20(3.3%)	0.72(0.09-5.49)	0.749

Table 2 | Adjusted Odds ratio of predictors of GH at the first antenatal care visit in a cohort of 2,529 pregnant women.

	Adjusted O.R (95% CI)	P-value
GH in a previous pregnancy	9.55 (5.42-16.84)	<0.001
Hypertension in parents	1.46 (1.06-2.02)	0.022
Diastolic BP (mmHg)	1.04 (1.03-1.06)	<0.001
Height (cm)	0.97 (0.95-0.99)	0.002
Weight (kg)	1.02 (1.01-1.03)	<0.001
Parity	0.90 (0.66-1.23)	0.51

Table 3 | Score chart for the risk of developing gestational hypertension in a cohort of pregnant women from Ghana.

Predictor	Score
History of hypertension in parents	No=0 Yes=4
GH‡ in a previous pregnancy	No=0 Yes=24
Diastolic blood pressure (mmHg)	≤60=0 61-70 = 1 71-80 = 2 81-90 = 3 ≥90 = 4
Height(cm)	≥ 161=0 56-160=1 151-155=2 ≤150=3
Weight (kg)	≤70=0 71-80=1 81-90=2 ≥91=3
Parity	0=1 ≥1=0

Table 4 | Categorization of development cohort into low, moderate and high risk.

	GH (Yes)	GH (No)	Sensitivity	Specificity	NPV	PPV	LR+	LR-
Low risk (N=587) (Score ≤ 1)	21 (3.6%)	566 (96.4%)	91.9%	25.0%	96.4%	12.4%	1.22	0.32
Moderate risk (N=1,641) Score (2-6)	158 (9.1%)	1,483 (90.9%)	31.4%	90.3%	92.0%	27.2%	3.24	0.76
High risk (N=301) (Score ≥ 7)	82 (27.2%)	219 (72.8%)						

GH, gestational hypertension; NPV, Negative predictive value; PPV, Positive predictive value; LR+, Likelihood ratio positive; LR-, Likelihood ratio negative.

Table 5 | Categorization of the validation cohort into low, moderate and high risk.

	GH (Yes)	GH (No)	Sensitivity	Specificity	NPV	PPV	LR+	LR-
Low risk (N=148)	5 (3.4%)	143 (96.6%)	88.1%	23.6%	96.6%	7.4%	1.15	0.50
Moderate risk (N=487)	33 (6.8%)	454 (93.2%)	9.5%	98.7%	94.0%	33.3%	7.31	0.92
High risk (N=12)	4 (33.3%)	8 (67.7%)						

GH, gestational hypertension; NPV, Negative predictive value; PPV, Positive predictive value; LR+, Likelihood ratio positive; LR-, Likelihood ratio negative.

Table 6 | Number of observations and missing values (with percentage missing) for the development and validation cohorts.

	Development cohort		Validation cohort	
Variable	**Number of observations**	**Missing (%)**	**Number of observations**	**Missing (%)**
Age	2514	15 (0.6)	647	0 (0)
History of hypertension in parents	2498	31(1.2)	647	0 (0)
Height	2435	94 (3.7)	646	1 (0.2)
Weight	2522	7 (0.3)	646	1 (0.2)
Systolic Blood Pressure	2523	6 (0.23)	646	1 (0.2)
Diastolic Blood Pressure	2522	7 (0.3)	646	1 (0.2)
Parity	2527	2 (0.08)	647	0 (0)
Previous history of gestational hypertension	2395	134 (5.3)	504	143 (22.1)

Table | Comparison of characteristics of women in the development and validation cohorts before and after imputation.

Variable	**Development cohort**	**Development cohort after imputation**	**Validation cohort**	**Validation cohort after imputation**
Age (years)	28.1 (5.8)	28.1 (5.8)	28.3 (5.1)	28.3 (5.1)
Height (cm)	160.5 (7.4)	160.5 (7.4)	161.1 (7.6)	161.1 (7.6)
Weight (Kg)	66.9 (14.1)	66.9 (14.1)	66.4 (12.9)	66.4 (12.9)
Diastolic BP (mmHg)	66.8 (11.6)	66.8 (11.6)	69.5 (10.7)	69.5 (10.7)
Systolic BP (mmHg)	109.4 (11.6)	109.4 (11.6)	111.9 (12.4)	111.9 (12.4)
History of hypertension in parents	462 (18.5%)	470 (18.5%)	27 (4.2%)	27 (4.2%)

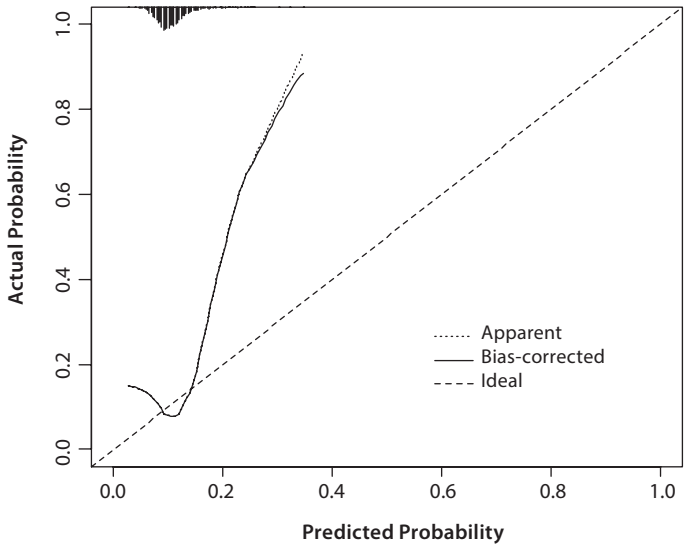

Figure 1 | Calibration plot for development cohort.

The dotted 45° line denotes the perfect agreement between predicted risk (x-axis) and observed risk (y-axis).The smoothed line approximates the agreement between predicted and observed risks across subgroups of pregnant women ranked by increasing predicted risks.

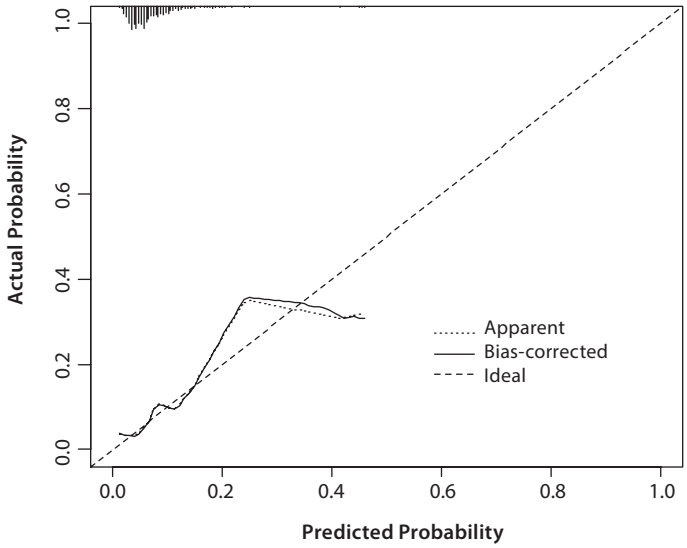

Figure 2 | Calibration plot for validation cohort.

CHAPTER 5

Improved prediction of gestational hypertension by inclusion of Placental Growth Factor and Pregnancy Associated Plasma Protein-A

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ABSTRACT

Introduction We assessed whether adding the biomarkers Pregnancy Associated Plasma Protein-A (PAPP-A) and Placental Growth Factor (PlGF) to maternal clinical characteristics improved the prediction of a previously developed model for gestational hypertension in a cohort of Ghanaian pregnant women.

Methods This study was nested in a prospective cohort of 1,010 pregnant women attending antenatal clinic in two public hospitals in Accra, Ghana. Pregnant women who were normotensive, at gestational age at recruitment of between 8 weeks and 13 weeks and provided a blood sample for biomarker analysis were eligible for inclusion. From serum, biomarkers PAPP-A and PlGF concentrations were measured by the AutoDELFIA immunoassay method and multiple of the median (MoM) values corrected for gestational age (PAPP-A and PlGF) and maternal weight (PAPP-A) were calculated. To obtain prediction models, these biomarkers were included with clinical predictors maternal weight, height, diastolic blood pressure, a previous history of gestational hypertension, history of hypertension in parents and parity in a logistic regression to obtain prediction models. The Area Under the Receiver Operating Characteristic Curve (AUC) was used to assess the predictive ability of the models.

Results Three hundred and seventy three women participated in this study. The area under the curve (AUC) of the model with only maternal clinical characteristics was 0.75 (0.64-0.86) and 0.89 (0.73-1.00) for multiparous and primigravid women respectively. The AUCs after inclusion of both PAPP-A and PlGF were 0.82 (0.74-0.89) and 0.95 (0.87-1.00) for multiparous and primigravid women respectively.

Conclusion Adding the biomarkers PAPP-A and PlGF to maternal characteristics in a prediction model for gestational hypertension in a cohort of Ghanaian pregnant women improved predictive ability. Further research using larger sample sizes in similar settings to validate these findings is recommended.

Key words: Prediction model, Gestational hypertension, Biomarkers, Hypertensive disorders of pregnancy.

INTRODUCTION

Hypertensive disorders of pregnancy (HDPS) are leading causes of maternal morbidity and mortality globally and affect about 5% to 10% of all pregnancies (1;2). The burden of these conditions is greatest in low and middle income countries (LMICs) (4;5). Early identification of pregnant women at risk of developing these conditions results in better monitoring and management to minimize complications to the mother and the fetus. Prediction models have been used to identify women at high risk of HDPSs, particularly preeclampsia (3-6). In addition, prevention interventions could be started such as calcium and aspirin supplementation that have been shown to reduce the risk of HDPSs, particularly preeclampsia (7-12). For example, in the ASPRE (Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention) trial with risk selection based on screening, a reduction in the incidence of preterm preeclampsia in the aspirin arm by 62% was observed (12).

PAPP-A is a protease that is involved in the local release of insulin-like growth factors. Low first trimester levels of PAPP-A is associated with hypertensive disorders of pregnancy (13-15). Placental growth factor (PlGF) is an angiogenic factor and low concentrations have been observed in pregnant women who develop preeclampsia. Suboptimal secretion of PlGF between 8 to 14 weeks gestation as a result of placental dysfunction has been associated with disorders such as preeclampsia, intrauterine growth restriction, small-for-gestational age and still births (16).

The aim of this study was to assess whether the addition of the biomarkers, placental growth factor (PlGF) and pregnancy-associated protein A (PAPP-A) to a previously developed prediction model (17) based on maternal clinical characteristics (diastolic blood pressure, family history of hypertension in parents, history of gestational hypertension (GH) in a previous pregnancy, parity, height and weight) improved prediction of gestational hypertension.

METHODS

Study design and study population

This study was nested in a prospective cohort of 1010 of adult pregnant women with a singleton pregnancy and without known pre-existent hypertension recruited between July 2012 and March 2014 at Ridge Regional Hospital and Maamobi General Hospital in Accra. Accra, the capital city of Ghana is cosmopolitan with high, middle and low-income persons from different ethnic backgrounds living and working in the city (26). Persons from all the social strata access health services, including antenatal and delivery care in these public hospitals. These hospitals were also chosen because they have a high attendance so the recruitment of pregnant women into the study could be completed in a shorter time. Eligibility criteria for this study were gestational age at enrollment of between between 8 weeks and 13 weeks based on ultrasound scan. This specific subset of women was selected based on evidence that prediction with these biomarkers is most appropriate at this gestational age (7-10;18-20). Women with gestational age at enrollment of less than 8 weeks or more than 13 weeks (n=411), without PlGF MoM values (n=95) or women without outcome data (n=131) were excluded.

We used the principle of 10 outcome events per variable for logistic and Cox regression analysis (21-24) to obtain a sample size adequate for our analysis. With an incidence of gestational hypertension of 10% in the Ghanaian population (25), and 8 variables in the prediction model, a sample size of 393 women was considered adequate for the analysis.

The women were included in the study after they had given written informed consent and were interviewed by trained research assistants using a structured questionnaire for socio-demographic characteristics and obstetric history. They were followed up at each antenatal clinic visit till they delivered. None of the women who developed gestational hypertension progressed to preeclampsia. Pregnancy outcomes were obtained at delivery and from the hospital maternity register.

Variables

Independent variables

Maternal weight (measured in kilogrammes with a bathroom scale), height (measured in centimeters with a stadiometer), blood pressure (measured in millimeters of mercury) and urine protein (defined as 2+ or more on urine dipstick) were obtained at the initial and subsequent antenatal clinic visits from the maternal health record books.

Blood pressure measurements were performed by trained midwives using a mercury sphygmomanometer. The appropriate adult sized cuff was placed on the bare left upper arm with the woman comfortably seated and with her back supported and legs uncrossed. The arm was at the level of the heart and neither the patient nor the observer talked during the measurement. Korotkoff phase V sounds were used (27). Two readings were taken at interval of five minutes and the average used as the woman's blood pressure.

PAPP-A and PlGF assay

Blood specimen was obtained from women on the day of their enrollment into the study by a phlebotomist. After the blood had coagulated, it was centrifuged to obtain the serum which was stored at a temperature of -20^{o}C in a freezer at the Maamobi General Hospital. Serum samples from the Ridge Hospital were stored temporarily in a fridge at 4^{o}C and transported daily in a cold box with ice packs to the laboratory at Maamobi General Hospital for storage. The frozen serum samples were air-freighted on dried ice to the Dutch Institute for Public Health and Environment (RIVM) in the Bilthoven, the Netherlands, where they were stored at a temperature of -80^{o}C until they were analyzed for PlGF and PAPP-A. PAPP-A and PlGF concentrations were determined using commercially available immunoassays and the AutoDelfia automated analyzer (PerkinElmer, Turku, Finland). Details of the assay method are described elsewhere by Browne et al (28). PAPP-A concentrations were corrected for gestational age and maternal weight and expressed as multiple of the median (MoM) using the reference equations from the Dutch national prenatal screening programme for Down syndrome based on PAPP-A measurements between 8 weeks to 13 weeks gestation of more than 10,000 pregnancies (28):

PAPP-A MoM gestational age correction; $y=12605.9606 - 552.53697*x + 7.42649*x^2 - 0.0278*x^3$, where x=gestational age at blood sampling in days

PAPP-A MoM weight correction; Exp (1.23234075 – 0.0181912*x), where x=weight in kilograms. PlGF concentrations were also corrected for gestational age and expressed as MoM (28) by using the manufacturer's (Perkin Elmer) reference equation for gestational age in days (between 9 to 13 weeks gestation) as follows :

$y=75.08 – 1.7769*x + 0.01589*x^2$, where x=gestational age at blood sampling in days.

PlGF was not corrected for maternal weight because serum PlGF concentration is not correlated with maternal weight (29).

Outcome

The outcome, gestational hypertension, was defined as a systolic BP of 140 mmHg or more and or a diastolic BP of 90 mmHg or more on at least two separate occasions, and present for the first time after 20 weeks of pregnancy (30).

Ethical considerations

Ethical approval for the study was granted by the Ethical Review Committee of the Ghana Health Service (GHS-ERC 07/09/11). All participating women gave written informed consent before they were enrolled in the study.

Statistical analysis

SPSS software (version 20.0, IBM SPSS Statistics Inc., Chicago, Illinois, USA) and R statistical software (R version 3.1.0 (2014-04-10). The R Foundation for Statistical Computing Platform: x86_64-w64-mingw32/x64 (64-bit)) were used for statistical analysis. The mean and standard deviation of continuous predictors were calculated for women who developed gestational hypertension and those who did not. Means were compared using the Student's t-test; percentages for categorical data were assessed by Chi-square test. The median with interquartile range was reported for non-normally distributed variables.

Logistic regression was used to derive the original prediction model using gestational hypertension as the outcome and the following maternal clinical characteristics as the predictors: maternal height, weight, parity, previous history of gestational hypertension, family history of hypertension and diastolic blood pressure. The maternal weight, height, diastolic blood pressure, parity, PAPP-A MoM and PlGF MoM were included in the logistic regression model as continuous variables. The principle of 10 events per variable for logistic and Cox regression analysis (31-34) was applied in model building. A history of hypertension in parents and history of gestational hypertension in a previous pregnancy were included in the logistic regression as dichotomous variables. As the variable 'previous history of gestational hypertension' was not applicable to primigravid women, a separate model was fitted for them.

PAPP-A MoM and PlGF MoM were included in the model as continuous variables so as not to lose power through categorization, and also because the appropriate cut off value of these biomarkers for the Ghanaian population is not known (28). The PAPP-A and PlGF as MoM values were included in turns and then together to the logistic regression. The predictive ability of each model (PAPP-A only, PlGF only, combined) was assessed. The models were internally validated using the bootstrapping

technique. The resulting shrinkage factor after bootstrapping was used to adjust the regression coefficients, thus correcting for model over fitting.

The performance of the models was assessed by the area under the receiver operating characteristic curve (AUC) or c-statistic. The AUC of the original model with only maternal clinical characteristics was compared to that of the models with PAPPA and maternal clinical characteristics, PlGF with maternal characteristics and both PAPP-A, PlGF and maternal characteristics.

RESULTS

Characteristics of the 373 study participants are presented in Table 1. Most of the women (81%) were multiparous. The mean age was 28.3 (SD 4.9) years and the mean gestational age at booking was 11.6 weeks (SD 1.4).

The flow chart for selection of study participants is shown in Figure 1. Of 1,010 women in the original cohort, 373 women met the inclusion criteria.

Table 2 compares characteristics of women who developed gestational hypertension to those who did not. Twenty-five women (6.7%) developed gestational hypertension. There was a difference in mean age between women who developed gestational hypertension and those who did not (30.3 (SD 5.3) years vs. 28.2 (SD 4.9) years, p=0.04). There was no difference in mean height between women with and without gestational hypertension (159.1 cm (SD 7.1) vs. 161.4 cm (SD 6.3), p=0.08). However, there was a difference in the mean weight of women with and without gestational hypertension (72.9 kg (SD 16.3) vs. 66.0 kg (SD 12.9), p=0.013). The mean diastolic blood pressure differed between women who developed gestational hypertension and those who did not (74.3 mmHg (SD 13.6) vs. 68.5 mmHg (SD 9.9), p=0.006).

Table 3 presents the median and interquartile range of MoM of PAPP-A and PlGF by gestational week. The median MoM PAPP-A (adjusted for gestational age and maternal weight) ranged between 1.68 and 4.36. The median MoM PlGF ranged between 0.90 and 1.68.

Table 4 shows the regression coefficients and the AUC of the various models for multiparous women. The AUC of the model with only maternal characteristics was 0.75 (0.64-0.86). The AUC of the model with maternal characteristics and PAPP-A was 0.78 (0.70-0.87), with maternal characteristics, and PlGF was 0.76 (0.64-0.87), and maternal characteristics with both biomarkers 0.82 (0.74-0.89). Figure 2 shows the Receiver Operating Characteristic curves for the prediction models for multiparous women.

DISCUSSION

The addition of PlGF and PAPP-A together to the model markedly improved its predictive ability, with an increase in AUC from 0.75 to 0.82 for multiparous women and 0.89 to 0.95 for primigravid women, whereas adding either one of the two had only marginal effect. These findings are in line

with other studies that reported improved prediction by the addition of biomarkers to maternal characteristics (5;18;35-37).

Several issues arise in comparing this study to other prediction studies. The first is that most prediction models predict preeclampsia rather than gestational hypertension (38). Hence there were fewer prediction models for gestational hypertension to which we could directly compare our models to. Therefore we included models for preeclampsia as well in the comparison of the model performance.

The second issue is that we derived separate models for multiparous and primigravid women. This was because the primigravid women could not respond to the question of "a previous history of gestational hypertension or preeclampsia". Being an important predictor, we maintained that variable in the model and in a sub analysis fitted a different model for primigravid women (n=71). However because of the relatively small number of primigravid women and outcome events on which these estimates are based, they should be interpreted with caution.

The third issue is that the same types of biomarkers are not used across prediction studies. Hence finding studies with the same predictors as in this study was a challenge. A number of prediction studies also added uterine artery pulsatility index to biomarkers and maternal characteristics (18;20;35) because it improves prediction. For instance, Kuc et al reported that the best detection rates for preeclampsia were obtained when maternal characteristics, biomarkers and uterine artery pulsatility index were combined (35). Akolekar et al also reported a three-fold increase in detection rates in screening for preeclampsia by the combination of maternal factors, biophysical and biomarkers compared with using only maternal factors (18).

Poon et al also reported that PAPP-A and PlGF in combination with maternal characteristics and uterine artery pulsatility index improved detection rates of preeclampsia (20). We did not include uterine artery pulsatility index in our study because uterine artery Doppler is not readily available in low resource settings.

Another issue is that most of the prediction studies have been conducted in Europe and North America. There are few studies in Sub Saharan African populations to which we could directly compare our results. Ukah et al in a prospective cohort study of pregnant women attending antenatal care in Maputo, Mozambique, measured the serum PlGF concentration in women suspected of having preeclampsia after 20 weeks of gestation. This study had as its primary outcome, the time-to-delivery after confirmation of preeclampsia (39). This study differed from ours in terms of being a diagnostic study rather than a prediction study.

The AUC is used to quantify the overall ability of a test or a logistic regression model to discriminate between two outcomes such as disease or non-disease (40-43). It generally ranges from 0.5 to 1 and represents the prediction model's ability to correctly classify a randomly selected individual as being from one of two hypothetical populations (44-46). An AUC value of 1.0 is considered perfect, 0.9-0.99 excellent, 0.8-0.89 good, 0.7-0.79 fair and 0.51-0.69 poor. An AUC of 0.5 is considered non-informative. Hence the AUC of 0.82 obtained in our study shows that the model with maternal characteristics and both PAPP-A and PlGF has good predictive ability.

Pencina et al (47) and Peters et al (36) have also indicated that increase in the AUC upon the addition of a predictor to a model shows that the predictor has improved the predictive ability of

the model. In our study, for the multiparous women, the AUC of the prediction model with only maternal clinical characteristics was 0.75 and this increased to 0.82 upon the addition of both PlGF and PAPP-A to the prediction model. For the primigravid women, the AUC of the prediction model with only maternal clinical characteristics was 0.89 and this increased to 0.95 upon the addition of both PlGF and PAPP-A to the prediction model This is an indication that the addition of both biomarkers simultaneously to the models improved the prediction performance .

The higher median MoM values of PlGF (1.28) and PAPP-A (2.29) in our study compared to the reference population of Dutch women (median MoM of 1 by default) is consistent with other studies that have shown racial and ethnic differences in the levels of these biomarkers, particularly in women of African and Asian decent (48-57). The median MoM of PAPP-A between 8 weeks gestation to 13 weeks gestation ranged between 1.68 and 4.36. That of PlGF MoM ranged from 0.90 at gestational week 9 to 1.68 at gestational week 13. Differences in the median MoM PlGF and PAPP-A levels between some ethnic groups in Ghana have also been reported in this population (28). As a result of the higher MoM values, there is the need for a correction factor for the Ghanaian population and sub populations to prevent the under estimation of risk calculations for placental disorders and aneuploidies.

Clinical and research implications

Hypertensive disorders of pregnancy, including gestational hypertension and preeclampsia, are among the leading causes of maternal morbidity in LMICs. In Ghana they rank as the third leading cause of mortality, having overtaken hemorrhage (25). The ability to predict this in women at increased risk (of the disorder) and thereby institute preventive measures to minimize their impact is a useful strategy to improving maternal and perinatal outcomes.

Biomarkers have shown some promise in improving the prediction of gestational hypertension and other hypertensive disorders in pregnancy, although a lot more research is still needed. Future studies using larger sample sizes should be conducted to confirm the findings of this study. When confirmed, one factor to be considered in the use of biomarkers in prediction models in the clinical setting would be the cost of carrying biomarker tests, especially in LMIC settings. A feasible approach in this regard would be the use of dried blood spot samples (DBS) instead of serum which requires refrigeration during storage and transport. DBS have been widely used in newborn screening for sickle cell disease (58;59), human immunodeficiency virus screening in newborns and for other disorders (60-69). It is cheaper than conventional serum assay and logistically simpler to implement in screening programmes because samples can be obtained and transported from remote locations where the laboratory infrastructure is limited. The technique for sample taking is also simpler and requires less training compared to venepuncture. In using DBS however, an issue to be considered is how well the concentration of the biomarkers in whole blood correlates with that of DBS. Pennings et al (70) and Browne et al (71) have shown that the correlation coefficient between serum and DBS concentrations for PAPP-A and β-hCG were both greater than 0.94. Cowans et al also reported that β-hCG stability is improved in DBS as compared to serum storage. This makes the collection, storage, transport and assay of biomarkers using DBS feasible in low resource settings.

It is recommended that this study should be replicated locally and externally in similar settings using larger sample sizes to validate the findings of this study before possible translation to clinical practice.

The feasibility and sustainability of any planned introduction and eventual scale-up in the use of biomarkers to improve prediction of hypertensive disorders has to be assessed using a cost benefit analysis.

Conclusion

The addition of PAPP-A and PlGF to a prediction models based on maternal clinical characteristics (diastolic blood pressure, family history of hypertension in parents, history of gestational hypertension in a previous pregnancy, parity, height and weight) markedly improved prediction of gestational hypertension. This study should be replicated using a larger sample size.

LIST OF ABBREVIATIONS

PAPP-A	Pregnancy Associated Plasma Protein-A
PlGF	Placental Growth Factor
MoM	Multiple of the Median
ROC	Receiver Operating Characteristic Curve
AUC	Area under the Receiver Operating Characteristic Curve
LMIC	Low and Middle Income Country
DBS	Dried Blood Spot Sample
HDPS	Hypertensive Disorder of Pregnancy
GH	Gestational Hypertension
PE	Preeclampsia
RIVM	Dutch Institute for Public Health and Environment
BP	Blood Pressure
SD	Standard Deviation
IQR	Inter Quartile Range

Authors' contributions

EA designed the study, collected data, carried out statistical analysis and wrote the initial draft of the manuscript. KK-G assisted with data analysis. JLB, PCS, KAK, IAA and DEG provided scientific guidance and were also actively involved in the preparation and review of the manuscript. All the authors read and approved the final manuscript.

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APPENDIX | TABLES & FIGURES

Table 1 | Baseline characteristics of the study population (n=373).

Variable	Mean (SD) or N (%)
Age (years)	28.3 (4.9)
Height (cm)	161.2 (6.3)
Weight (kg)	66.5 (13.3)
Systolic blood pressure (mmHg)	110.5 (12.9)
Diastolic blood pressure (mmHg)	68.9 (10.3)
Gestational age at booking (weeks)	11.6 (1.4)
PlGF MoM corrected for gestational age	Median 1.28, IQR (0.96-1.88)
PAPP-A MoM corrected for gestational age	Median 2.29, IQR (1.15-3.86)
PAPP-A MoM corrected for gestational age and maternal weight	Median 2.34, IQR (1.19-3.82)
Parity:	
Primigravid women	71 (19.0%)
2-3 pregnancies	116 (31.1%)
>4 pregnancies	186 (49.9%)

Table 2 | Baseline characteristics of the study population by the outcome, gestational hypertension.

Variable (Mean (SD))	Gestational hypertension (No) N=348	Gestational hypertension (Yes) N=25	P-value
Age (years)	28.2 (4.9)	30.3 (5.3)	0.04
Height(cm)	161.4 (6.3)	159.1 (7.1)	0.08
Weight (kg)	66.0 (12.9)	72.9 (16.3)	0.013
Systolic blood pressure (mmHg)	110.1 (12.7)	116.4 (14.2)	0.018
Diastolic blood pressure (mmHg)	68.5 (9.9)	74.3 (13.6)	0.006
Gestational age at booking (weeks)	11.6 (1.4)	11.3 (1.5)	0.38

Table 3 | Median and interquartile range of MoM of PAPP-A and PlGF by gestational week (n = 373).

Gestational week	Number of women (%)	MoM PAPP-A, median (IQR), adjusted for gestational age and maternal weight	MoM PAPP-A, median (IQR), adjusted for maternal weight	MoM PlGF, median (IQR), adjusted for gestational age
8	17 (4.5)	4.36 (1.06-8.47)	4.46 (1.19-6.42)	1.17 (0.85-1.51)
9	40 (10.7)	1.68 (1.04-4.64)	2.04 (0.86-4.25)	0.90 (0.73-1.36)
10	86 (23.1)	2.39 (1.45-3.83)	2.33 (1.44-4.12)	1.15 (0.97-1.66)
11	71 (19.3)	1.76 (0.85-3.05)	1.96 (0.88-3.01)	1.21 (0.95-1.49)
12	66 (17.6)	2.21 (1.06-3.65)	2.26 (1.20-3.34)	1.29 (1.03-1.91)
13	93 (24.8)	2.63 (1.49-4.51)	2.55 (1.57-4.05)	1.68 (1.34-2.94)
Total	373	2.29 (1.15-3.86)	2.34 (1.19–3.82)	1.28 (0.96-1.88)

IQR= Interquartile range, MoM=multiple of the median.

The median MoM value of the reference population by default is 1. The gestational age and weight adjusted PAPP-A median MoM was 2.29. The weight adjusted PAPP-A median MoM was 2.34 and the median PlGF MoM was 1.28.

Table 4 | Regression coefficients and AUC of prediction models for multiparous women (n=302).

Variable	Model with only maternal characteristics	Model with addition of PlGF MoM	Model with addition of PAPP-A MoM	Model with addition of PlGF MoM and PAPP-A MoM
Intercept	9.68	10.0	10.46	12.18
History of hypertension in parents	-1.52	-1.50	-1.60	-1.65
Previous history of hypertension in pregnancy	0.47	0.55	0.42	0.72
Weight	0.026	0.025	0.024	0.023
Height	-0.097	-0.099	-0.102	-0.112
Parity	0.29	0.29	0.33	0.34
Diastolic BP	0.036	0.036	0.037	0.042
PlGF MoM	–	-0.15	–	-0.713
PAPP-A MoM	–		0.033	0.098
AUC	0.75 (0.64-0.86)	0.76 (0.64-0.87)	0.78 (0.70-0.87)	0.82 (0.74-0.89)

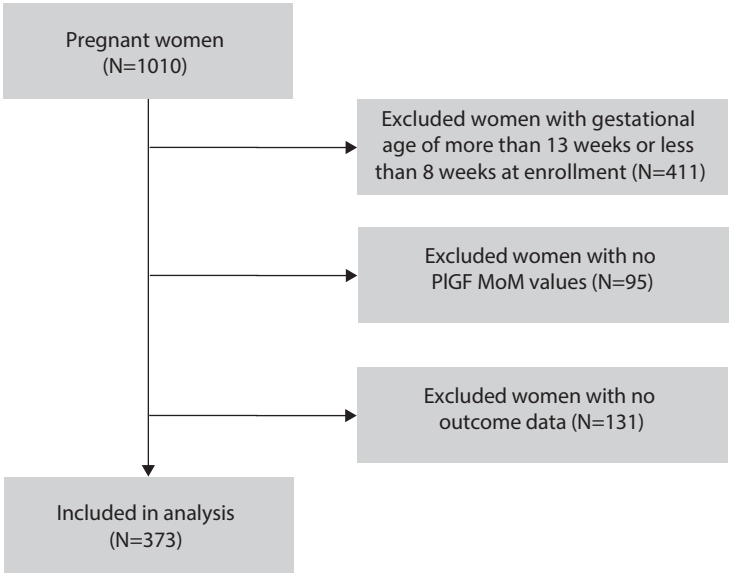

Figure 1 | Flow chart illustrating participant selection.

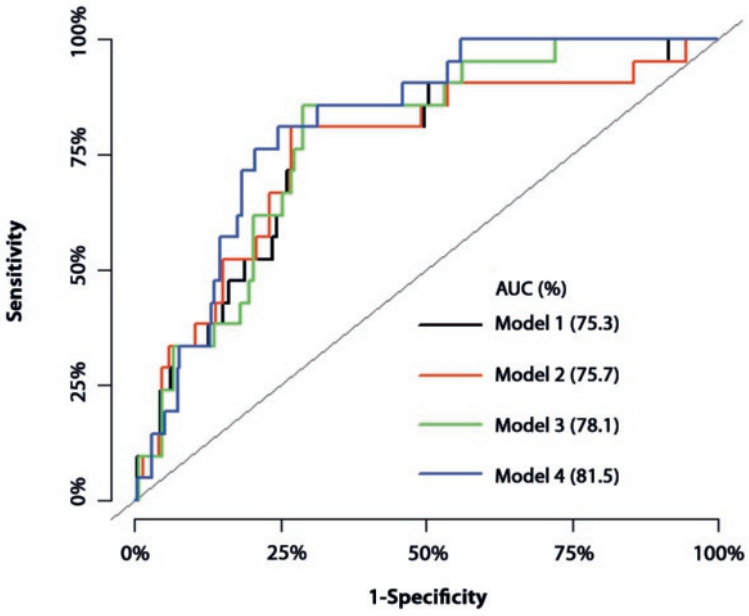

Figure 2 | Receiver operating characteristic (ROC) curves for the multiparous prediction model.

Model 1(black line): Maternal characteristics only (75.3)
Model 2 (red line): Maternal characteristics and PlGF MoM
Model 3 (green line): Maternal characteristics and PAPP-A MoM
Model 4 (blue line): Maternal characteristics with PlGF MoM and PAPP-A MoM

CHAPTER 6

General discussion

This thesis set out to explore the extent and variations in hypertensive disorders of pregnancy as a major cause of maternal mortality in Ghana, a low resource setting, and to provide options for a simple predictive model for women at high risk which can support efforts in reducing morbidity and mortality due to gestational hypertension in Ghana. The preceding chapters have provided the international evidence on the state of prediction models for hypertensive disorders of pregnancy, the variation in the incidence of hypertensive disorders of pregnancy in Ghana, how routine healthcare data can be used to derive and validate a prediction model for hypertensive disorders of pregnancy and the added prediction ability of the model by the inclusion of serum biomarkers as predictors.

We found sub-national variations in the incidence of gestational hypertension between some regions and districts in Ghana (1). The rural areas had a lower incidence compared to the urban areas. We further examined some factors accounting for the variation. Obesity was found to be correlated with a higher incidence of hypertensive disorders of pregnancy (2). We infer that urbanization and its attendant changes in dietary and other life style patterns could be partly responsible for the observed variations (3-5). O'Brien et al (6) in a systematic review of 13 cohort studies and Barton et al (7) have shown a consistent and linear rise in the risk of preeclampsia with increasing pre-pregnancy BMI.

Studies have also shown an increasing trend in the incidence of HDPs which may partly be attributed to increasing rates of overweight and obesity among women in the reproductive age group (8,9). The Ghana Demographic and Health Surveys of 2003, 2008, and 2014 reported an increasing trend of overweight and obesity among the population. Overweight and obesity in women of reproductive age (15-49 years) increased from 25% in 2003 to 30% in 2008 and up to 40% in 2014 (10-12). The rising global trend in obesity (9,13-15) is a call to action to governments, communities and individuals to take measures to reverse the trend. Opportunities to control obesity through health education and promotion of healthy diets and regular physical activity could result in reduction of hypertensive disorders of pregnancy and other non-communicable diseases (16). The recently launched WHO Global Action Plan on Physical Activity 2018-2030 (17) provides guidance for member states to promote more physical activity in response to the increasing trends in non-communicable diseases. The four policy action areas of active societies, active environments, active peoples and active systems involves governments, communities and individuals working to create opportunity for people to safely engage in physical activity. Member states should effectively adopt and implement this policy to reduce the incidence of obesity which is a known risk factor for the hypertensive disorder of pregnancy.

There are opportunities to measure and track changes in the incidence of the hypertensive disorders of pregnancy using routine health management information system (HMIS) data (18,19). However issues with the quality of the data should first be addressed. For example, in our study, we observed incomplete HMIS data such as blood pressure, gestational age, weight and urine protein in the antenatal and delivery registers. Some of these gaps were due to incomplete entry of data in the HMIS system. Other gaps in the HMIS data could be attributed to the design of the antenatal and delivery registers, which had not made provision for these variables to be captured. Some health workers, realizing the need for such data, improvised by creating additional space for recording of these variables. Unfortunately, this was not standardized as different clinics recorded different

additional variables thereby limiting the comparability of patient data. Another reason for data incompleteness was because some basic tests such as urine protein and urine glucose were not being performed and so no data for those variables was being recorded. Although staff was aware of existing protocol requirements, routine dipstick test for urine protein for instance was often not done for pregnant women because of stock out and non-availability of test kits. Also, the urine protein results were not recorded in the antenatal register, again because it was not one of the variables in the register. These shortcomings have recently been addressed in the revised antenatal registers. Improving the quality of routine HMIS would be an effective approach to producing the evidence base related to local area variations in HDPs incidence. The use of routine HMIS data for such tracking of maternal health services is relatively simple, inexpensive and likely to be more cost effective than the use of special surveys. Interventions such as expanding the range of variables that are captured in the antenatal and delivery registers would make a major difference in the quality of the evidence available to inform decision making and track progress towards achieving the Sustainable Development Goal 3 of improved maternal health. Addressing stock out and non-availability of urine protein testing strips and other logistics is also a step that can make a difference not only to data quality but also to the health and outcome of pregnant women and newborns. Health policies and programmes should pay more attention to collecting evidence on local variations in maternal health conditions and take account of these local variations in the planning and delivery of health services.

Using a retrospective record review, the study was limited by the information obtained and recorded in the antenatal clinic and delivery registers. Hence detailed risk factor information such as family history of hypertensive disorders in pregnancy, chronic hypertension, diabetes, twin pregnancies, and personal lifestyle conditions such as smoking, dietary habits and physical activity could not be ascertained (1).

A systematic review of prediction models we undertook showed that although prediction models abound and are widely used in high income countries (20), this is not the case in LMIC. Models developed in high income countries may not currently be applicable in LMIC because predictors such as serum biomarkers and uterine artery pulsatility index are not routinely measured in these countries. At the moment, this leaves us with the option of using routine easy-to-collect maternal clinical characteristics as predictors. However, prediction models using only maternal clinical characteristics at best perform modestly with an area under the curve in the range of 0.6 to 0.8 (21-23). To effectively use prediction models in the LMIC context, the barrier of high cost of assays for serum biomarkers can be surmounted through the application of dried blood spot (DBS) analysis. DBS improves access to blood samples in situations where standard blood collection is constrained by unavailability of laboratory infrastructure and storage. Compared to traditional venepuncture techniques, DBS is relatively easy to perform and a minimal amount of blood is required. The DBS samples can be shipped by regular mail to centres where blood analysis can be carried out (24). DBS have been used for monitoring HIV viral load (25) and newborn screening for sickle cell disease (26,27). DBS allows a significant reduction in the cost of assays. Martial et al (28) carried out a cost evaluation of DBS home sampling as compared to conventional sampling for therapeutic drug monitoring in children. They computed total costs from a societal perspective by adding up

healthcare costs, patient related costs and costs related to loss of productivity of the caregiver. Switching to DBS sampling was associated with cost reduction of 43% for hematology-oncology patients and 61% for nephrology patients. The relative ease of blood collection and transportation as well as reduced overall costs of DBS sampling makes it a feasible option for pregnant women in LMIC to have access to biomarker assays, thereby benefiting from the application of prediction models for early detection of hypertensive disorders of pregnancy. Uterine artery Doppler measurements are also not routinely done in LMIC. As has been done with the development of low-cost, portable and robust equipment for ultrasonography, uterine artery Doppler imaging equipment could also be developed to make the service more accessible and affordable.

A prediction model using routinely collected maternal clinical data was developed and validated in our studies (23). The prediction model's ability to discriminate between women at high and low risk of the disorder was improved by the inclusion of serum biomarkers as predictors in the model (29). Evidence abounds of improved prediction through the inclusion of serum biomarkers as against using only clinical maternal characteristics. Although measuring these biomarkers in LMIC is challenging at present, prioritizing the control of hypertensive disorders of pregnancy by policy and decision makers could make this possible.

There is adequate evidence to enable identification of women at-risk hypertensive disorders of pregnancy using prediction models. Pregnant women at risk of HPD identified in the first trimester of pregnancy could benefit from aspirin, which is proven to reduce the severity of hypertensive disorders of pregnancy. Routine health management information system data can be used to measure and track the incidence of hypertensive disorders of pregnancy in populations. These tools have worked in other parts of the world to reduce morbidity and mortality due to hypertensive disorders of pregnancy and the same can be applied in LMIC to improve maternal health. However, the challenges of poor data quality have to be addressed so the potential of using routine data to track maternal health indices can be achieved. Efforts by governments and stakeholders in LMIC in researching into affordable assays for serum biomarkers should be a priority. In particular there should be increased investment in the development of assays for the use of DBS. Priority should be given to further development of low cost devices applicable in low resource settings. Such efforts would enable LMIC which have a disproportionately high burden of HDPs and maternal mortality to benefit from the use of prediction models available for early identification of at-risk pregnant women.

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Summary

Hypertensive disorders of pregnancy are important causes of maternal morbidity and mortality. Coordinated effort is required to reduce maternal morbidity and deaths due to these disorders and thereby attain the SDG-3 goal. This thesis describes the nature of hypertensive disorders of pregnancy in Ghana, a low middle income country and provides evidence on the use of prediction models for early identification of pregnant women at risk of the hypertensive disorders of pregnancy. **Chapter 1** provides an overview of the hypertensive disorders of pregnancy and their effects on maternal health as well as an outline of the thesis.

Chapter 2 describes the estimation of the incidence of pregnancy induced hypertension (PIH) across ten districts in the highly urbanized Greater Accra region and the predominantly rural Upper West region of Ghana, using routine hospital data. The quality of the health management information system (HMIS) data was assessed. Key variables for routine assessment of PIH such as blood pressure (BP) at antenatal visits, weight and height were observed to be 95% to 100% complete. However gestational age and BP at delivery were not consistently reported. The incidence of PIH differed significantly between Greater Accra region (6.1%) and Upper West region (3.2%). Prevalence of obesity among pregnant women in Greater Accra region (13.9%) was significantly higher than that of women in Upper West region (2.2%).

Instead of relying on surveys to track maternal health indicators, we recommend an improvement in the quality of routine data. Surveys are more time intensive and also more expensive to conduct. Measures should be taken to control the rising trend of obesity which correlates with higher incidence of pregnancy induced hypertension.

In **Chapter 3**, a systematic review of prediction models for gestational hypertension and preeclampsia was conducted with the aim of assessing the methodological quality of the prediction modeling studies and to find prediction models that can be applied in low-and middle-income countries.

Seventy percent of the prediction models reviewed combined biomarkers with maternal clinical characteristics. Of the thirty-two prediction models reviewed, only three had been developed in a low- and middle-income country (LMIC).

Most of the prediction studies fell short to report according to the criteria for developing or validating a prediction model as outlined in the CHARMS (check list for critical appraisal and data extraction for systematic reviews of prediction modeling studies) statement. The use of biomarkers, though enhancing performance of prediction models, may limit the applicability of prediction models in most low- and middle-income countries because these biomarkers are currently not routinely measured in these settings. Research to develop affordable, easy-to-use uterine artery Doppler imaging equipment and diagnostic assays for serum biomarkers is recommended so the prediction models can be used in LMIC to improve maternal health.

In **Chapter 4**, a prediction model for gestational hypertension using maternal clinical characteristics obtained at the antenatal clinic visit was developed and validated. The c-statistic, which is an index of the discrimination ability of the model, was 0.70 and 0.68 for the development

and validation cohorts respectively. The prediction model had moderate ability to differentiate women at high risk of developing gestational hypertension after 20 weeks gestation.

Chapter 5 assessed whether adding the biomarkers Pregnancy Associated Plasma Protein-A (PAPP-A) and Placental Growth Factor (PlGF) to maternal clinical characteristics improved the prediction of a previously developed model for gestational hypertension in a cohort of Ghanaian pregnant women.

Pregnant women who were normotensive, at gestational age at recruitment of between 8 weeks and 13 weeks and provided a blood sample for biomarker analysis were eligible for inclusion. Serum biomarkers PAPP-A and PlGF concentrations were measured by the AutoDELFIA immunoassay method and multiple of the median (MoM) values corrected for gestational age (PAPP-A and PlGF) and maternal weight (PAPP-A) were calculated. The Area Under the Receiver Operating Characteristic Curve (AUC) was used to assess the predictive ability of the models.

The area under the curve (AUC) of the model with only maternal clinical characteristics was 0.75 and 0.89 for multiparous and primigravid women respectively. The AUCs after inclusion of both PAPP-A and PlGF were 0.82 and 0.95 for multiparous and primigravid women respectively.

We concluded that adding the biomarkers PAPP-A and PlGF to maternal characteristics in a prediction model for gestational hypertension improved predictive ability. Further research using larger sample sizes in similar settings to validate these findings is recommended.

Finally **Chapter 6** discusses the application of the findings of this thesis to improving maternal health in low and middle income countries. Research and development of low cost assays for biomarkers are recommended to be prioritized to enable the use of prediction models to identify women at risk of hypertensive disorders of pregnancy early and institute appropriate measures for care.

Samenvatting

Hypertensive aandoeningen in de zwangerschap: Bevindingen en implementatie in lage- en middeninkomenslanden

Hypertensieve aandoeningen in de zwangerschap zijn belangrijke oorzaken van maternale morbiditeit en mortaliteit. Een gecoördineerde aanpak is nodig om maternale morbiditeit en het aan deze aandoeningen gerelateerd overlijden terug te brengen, en hiermee doel drie van de *sustainable development goals* te bereiken. Dit proefschrift beschrijft de kenmerken van hypertensieve aandoeningen in de zwangerschap in Ghana – een land met een laag-middeninkomen – en bespreekt de wetenschappelijke bewijsvoering voor het gebruik van predictiemodellen voor de vroege identificatie van zwangere vrouwen met een risico op hypertensieve aandoeningen in de zwangerschap. **Hoofdstuk 1** geeft een beschouwing over hypertensieve aandoeningen in de zwangerschap en de effecten op maternale gezondheid. Tevens geeft het een introductie tot dit proefschrift.

Hoofdstuk 2 beschrijft een schatting van de incidentie van zwangerschap-geïnduceerde hypertensie (PIH) in tien districten in de sterk verstedelijkte *Greater Accra*-regio alsmede in de voornamelijk rurale *Upper West*-regio, waarbij gebruik werd gemaakt van routinematig verkregen ziekenhuisdata. De kwaliteit van data uit het gezondheidsmanagement informatiesysteem (HMIS) werd beoordeeld. Voor belangrijke variabelen in de routinematige beoordeling van PIH, zoals bloeddruk (BP) bij antenatale controles, gewicht en lengte, werd gevonden dat deze in 95% tot 100% compleet waren. Echter, zwangerschapsduur en BP ten tijde van de bevalling werden niet consequent gerapporteerd. De incidentie van PIH verschilde significant tussen de *Greater Accra*-regio (6,1%) en de *Upper West*-regio (3,2%). De prevalentie van obesitas bij zwangere vrouwen in de *Greater Accra*-regio (13,9%) was significant hoger dan bij vrouwen in de *Upper West*-regio (2,2%).

Het wordt geadviseerd om graadmeters van maternale gezondheid te volgen en de kwaliteit van de routinematige data te verbeteren, in plaats van te vertrouwen op enquêtes – welke zowel kostbaarder en meer tijdsintensief zijn om uit te voeren.

Er dienen maatregelen te worden getroffen om de stijgende trend van obesitas onder controle te krijgen, gezien obesitas correleert met een hogere incidentie van zwangerschap-geïnduceerde hypertensie.

In **Hoofdstuk 3** werd een systematische review van predictiemodellen voor zwangerschaps-hypertensie en pre-eclampsie uitgevoerd, met als doel het beoordelen van de methodologische kwaliteit van de predictiemodelleringstudies en het vinden van predictiemodellen die kunnen worden toegepast in landen met een laag-middeninkomen.

Zeventig procent van de beoordeelde predictiemodellen combineerde biomarkers met maternale klinische kenmerken. Van de 32 beoordeelde predictiemodellen waren er slechts drie ontwikkeld in een land met een laag-middeninkomen (LMIC).

De meeste predictiestudies schoten te kort in het rapporteren volgens de criteria voor het ontwikkelen danwel valideren van een predictiemodel, zoals beschreven in de CHARMS

(checklist voor kritische beoordeling en data-extractie voor systematische reviews van predictiemodelleringstudies) verklaring. Hoewel het gebruik van biomarkers de prestatie van predictiemodellen verbetert, kunnen zij de toepasbaarheid van predictiemodellen in landen met een laag-middeninkomen tevens beperken, gezien deze biomarkers momenteel niet routinematig worden gemeten in deze settings. Het werd geadviseerd om middels onderzoek betaalbare en makkelijk te gebruiken apparatuur voor arteria uterina Doppler-echografie en diagnostische assays voor serum biomarkers te ontwikkelen, zodat de predictiemodellen kunnen worden toegepast in LMIC en hiermee maternale gezondheid verbeteren.

In **Hoofdstuk 4** werd een predictiemodel voor zwangerschapshypertensie op basis van maternale klinische kenmerken, welke werden verkregen bij bezoek aan de antenatale kliniek, ontwikkeld en gevalideerd. De c-statistiek, een index voor het onderscheidend vermogen van een model, was 0,70 en 0,68 voor respectievelijk de ontwikkeling- en validatiecohorten. Het predictiemodel had een matig vermogen om vrouwen met een hoog risico op het ontwikkelen van zwangerschapshypertensie na 20 weken zwangerschap te kunnen onderscheiden.

Hoofdstuk 5 onderzocht of het toevoegen van de biomarkers zwangerschap geassocieerd plasma proteïne A (*Pregnancy Associated Plasma Protein-A*; PAPP-A) en placentaire groeifactor (*Placental Growth Factor*; PlGF) aan de maternale klinische kenmerken de predictie van een eerder ontwikkeld model voor zwangerschapshypertensie in een cohort van Ghanese zwangere vrouwen zou verbeteren.

Zwangere, normotensieve vrouwen, met een zwangerschapsduur tussen de 8 en 13 weken, welke een bloedmonster voor biomarkeranalyse verstrekten, kwamen in aanmerking voor inclusie. Concentraties van serum biomarkers PAPP-A en P1GF werden bepaald met behulp van de AutoDELFIA immunoassay methode en MoM (*multiple of the median*) -waardes, gecorrigeerd voor zwangerschapsduur (PAPP-A en P1GF) en maternaal gewicht (PAPP-A), werden berekend. De oppervlakte onder de *Receiver Operating Characteristic* (ROC) -curve (*area under the curve;* AUC) werd gebruikt om het voorspellend vermogen van de modellen te beoordelen.

De AUC van het model met alleen de maternale klinische kenmerken was 0,75 en 0,89 voor respectievelijk multiparae en primigravidae. Wij concludeerden dat het toevoegen van de biomarkers PAPP-A en P1GF aan maternale kenmerken in een predictiemodel voor zwangerschapshypertensie leidt tot een verbeterd predictievermogen. Om deze bevindingen te valideren wordt het aanbevolen om nader onderzoek te verrichten, waarbij gebruik wordt gemaakt van grotere steekproefgrootten in vergelijkbare omstandigheden.

Tot slot bespreekt **Hoofdstuk 6** de toepassing van de bevindingen van dit proefschrift op het verbeteren van maternale gezondheid in landen met een laag-middeninkomen. Het wordt geadviseerd om onderzoek naar en ontwikkeling van betaalbare assays voor biomarkers te prioriteren, zodat predictiemodellen in gebruik kunnen worden genomen en op die manier vrouwen met een risico op hypertensieve aandoeningen in de zwangerschap vroeg kunnen worden geïdentificeerd en passende maatregelen kunnen worden getroffen voor de zorg.

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Curriculum vitae

Edward Antwi was born on 23rd December, 1966 at Atibie-Kwahu in the Eastern Region of Ghana. He had his secondary education at the St. Peters Senior High School, Nkwatia, from 1978 to 1985. He holds a Bachelors degree in Medicine and Surgery (MBChB) and a Master of Public Health degree from the University of Ghana. In 2011, he obtained the MSC Epidemiology degree from the University of Utrecht, the Netherlands and continued with his PhD studies at the same university. His PhD work has been on hypertensive disorders of pregnancy with a focus on prediction models for early detection of the disorders.

Edward has worked at various levels of the Ghana Health Service as a clinician and a public health Specialist since 1995.

List of publications

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