Prediction of perinatal death and maternal outcomes in women with hypertensive disorders in pregnancy remote from term: a validation study from a longitudinal cohort in Ghana- Study Protocol

Background

Maternal and perinatal deaths remain high in low- and middle-income countries, despite global efforts to reduce these[1]. They continue to be a priority in the Sustainable Development Goals (SDG 3.1, 3.2) as well an important objective of the Ghana National Health Research Agenda[2]. The global and local efforts to improve maternal and perinatal health have resulted in marked improvements in access to care with increased antenatal care coverage and facility-based deliveries. Whilst these are essential in order to ensure skilled care is provided, this has disclosed a new bottleneck that hampers further gains: quality of care.[1,3,4] The quality of care that facilities are able to deliver is too often restricted in low and middle-income countries (LMICs) because of persistent resource shortages, including the number of health professionals available.[3] Increasingly, risk-based medicine is employed to address the resource problem and improve outcomes as reflected by a rapidly growing field of prediction research, facilitated by technological developments in information sciences and substantial increased availability of (big) data.[5–8] In this approach, an individual's predicted risk of an (adverse) outcome, allows to triage patients in low-, moderate or high risk, with corresponding options for intervention to prevent or treat disease. Thus, risk prediction models can guide the organization and provision of quality health care to the right person at the right moment - crucial especially in resource-constrained settings.

Hypertensive Disorders of Pregnancy (HDP) in Ghana

In Ghana, HDP are one of the leading causes of maternal and perinatal deaths.[1,9] HDPs include various diseases, ranging from gestational hypertension (GH) to the more severe expressions on the disorder

spectrum: pre-eclampsia, eclampsia and hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome. Ten to fifteen percent of maternal mortality is related to HDP, with nearly all deaths occurring in low- and middle income countries (LMICs).[10] The previously conducted reproductive age mortality survey (RAMOS) in the Great Accra Region, Ghana, identified that 14.6% of maternal mortality cases are caused by (pre-)eclampsia. [11] Pre-eclampsia can also affect the fetus - especially at early onset, as it may cause restricted growth and can lead to prematurity as a result of either the spontaneous onset of preterm labor or (iatrogenic) early delivery to protect mother and fetus; both potentially leading to perinatal mortality.[10,12] There is universal agreement that all patients with severe pre-eclampsia should be delivered if the disease develops after 34 weeks of gestation or if there is evidence of maternal or fetal distress.[13] Severe early-onset pre-eclampsia before 26 weeks is associated with high maternal morbidity and very poor perinatal outcome, even in developed countries[14]. This leaves the gestational age between 26 and 34 weeks as the key grey zones needing to be elucidated.

Substantial disagreement exists considering the optimal management for severe pre-eclampsia remote from term (26 weeks or more but less than 34 weeks), as it results in a conflict between maternal and perinatal health. Options include an interventionist approach of immediate delivery as definitive therapy for all cases, regardless of gestational age. Yet, this results in excessive numbers of (iatrogenic) prematurity, which is associated with high perinatal mortality. On the contrary, one could opt for a conservative approach to prolong the pregnancy until either development of fetal lung maturity fetal or maternal distress, or gestational age of 36 weeks is achieved. However, expectant management can lead to complications for both mother and baby, particularly in LMICs where monitoring opportunities are limited.[15]

Most studies about the optimal management for women with severe pre-eclampsia before 34 weeks of gestation[16–18] are conducted in high resource country settings, concluded that expectant management under certain conditions is associated with greater pregnancy prolongation and

improved perinatal outcomes. However, trial results and guidelines from these contexts must not be readily translated to LMIC settings. For example, the recent MEXPRE randomized multicenter trial in LMIC settings in South-America[19] did not demonstrate the benefit of expectant management of severe pre-eclampsia from 28 to 34 weeks and showed an increase in adverse outcomes of placental abruption and small for gestational age.

The key bottleneck to resolve the existing controversy is the lack of reliable predictors of adverse maternal and perinatal outcomes. This is especially relevant for LMIC settings, where pregnancy monitoring systems may be lacking, response times are longer and neonatal intensive care unit facilities are possibly unavailable. With reliable predictors, patients can be appropriately triaged between interventionist management and expectant management.

Prediction models for HDP

A number of such risk prediction models have been developed for both maternal and perinatal outcomes of women with HDP. For predicting maternal outcomes, the most established model is the full PIERS (Pre-eclampsia Integrated Estimate of RiSk) model.[20] This model combines maternal clinical symptoms and laboratory findings and showed a moderate to good prediction of adverse maternal outcomes (AUC ROC 0.77, 95%CI 0.72-0.82) in an external validation study performed in LMIC settings.[21] Because the fullPIERS model required laboratory tests that were not always available in LMICs settings, the miniPIERS model was adapted from the fullPIERS model. The miniPIERS model is developed in the miniPIERS cohort and is based on clinical characteristics to identify pregnant women at primary health facilities in LMICs at increased risk of severe adverse outcomes.[22] The miniPIERS model has an area under the receiver operating characteristic curve (AUC ROC) of 0.768 (95% CI 0.735–0.801) which means a good discriminative ability of the model. The AUC ROC of this model in external validation (the fullPIERS cohort) was 0.713 (95% CI 0.658–0.768). For the prediction of perinatal outcomes with HDP affected women, so far only one model has been developed to predict perinatal outcomes of women with HDP in low and middle income-settings. In

their study, Payne et al. developed a perinatal death model to assess the risk of perinatal mortality for pregnant women with HDP based on the miniPIERS cohort.[23] Predictors included in this model were maternal age, a count of symptoms, and dipstick protein urea. With an Area Under the Receiving Operating Characteristic Curve (AUC ROC) of 0.75 (95% CI 0.71-0.80), the model's discriminative performance good. Furthermore it showed good calibration (Hosmer–Lemeshow goodness of fit test statistic of 2.14 (p = 0.98)) with a well fitted calibration curve. This model has not been externally validated yet, a necessary step to show that the model can perform well in other populations too.[24] Both perinatal and maternal models have not been validated in Ghana, or implemented in facility settings in LMICs to assess the effectiveness, barriers and opportunities.

Objectives

This research will address the general aim to externally validate prediction models to predict adverse maternal and perinatal health outcomes for women with HDP remote from term in Ghana.

Methods

Study design and population validation cohort (SPOT-cohort)

This clinical epidemiology research project is embedded in the Severe Pregnancy Outcome Triage-studies (SPOT-studies). The SPOT cohort is a multicentre prospective cohort that has been conducted in different referral hospitals in the Greater Accra Region and Eastern Region of Ghana. The SPOT studies started in November 2017.

The participating referral hospitals are the Greater Accra Regional Hospital, Tema General Hospital, La General Hospital, Lekma General Hospital, Eastern Regional Hospital and Korle-Bu Teaching Hospital. Four of these hospitals are within the Greater Accra Region, and Eastern Regional Hospital is in the Eastern Region of Ghana. All of these hospitals have a referral function within their region. These hospitals were selected because of their referral function, the availability of a Neonatal Intensive Care Unit (NICU), their large volume of patients/ workload and sufficient infrastructure to

conduct this study. The hospitals have an estimated annual number of deliveries of >30,000. The estimated incidence of HDPs within these facilities is about 8%.

Girls and women of at least 16 years old admitted to a hospital with HDP (for classification please refer to Table 1) between the gestational ages of 26 weeks and 34 weeks pregnancy have been found eligible for inclusion. Exclusion criteria are spontaneous active labour during admission and/or the presence of any of the severe maternal outcomes before inclusion or before collecting the independent variables. These outcomes are: maternal mortality or one or more serious other morbidities related to the central nervous system, cardiorespiratory renal, hepatic, hematologic or other morbidities (for a detailed description please refer to Appendix 1: Definitions maternal outcomes).

During admission, all women have been receiving standard management of their condition according to their hospital's guidelines.

Outcomes

Outcomes of this study include both adverse maternal and perinatal outcomes, and are aligned to the miniPIERS, fullPIERS and perinatal adverse outcome models.

For the external validation of the miniPIERS and fullPIERS models, the primary maternal outcome in this study will be a composite outcome of maternal death and severe maternal morbitidy as described in box 1 below. Maternal death in this study will be defined as "death of a women while pregnant or within 42 days of the end of pregnancy, irrespective of the duration and the site of the pregnancy, from any cause related to or aggrevated by the pregnancy or its management, but not from accidental or incidental causes"[25].

The primary perinatal outcome in this study will be a composite outcome of stillbirth and early neonatal death (up to discharge from the hospital) from any cause. Stillbirth is defined using the existing World Health Organization (WHO) definition: any baby who dies after the gestational age of 28 weeks but before/during birth (WHO)[26]. Given the purpose of this research project (to predict adverse outcomes after admission), we will only consider cases eligible where stillbirth occurred after admission to the hospital. Early neonatal death includes only those occurring during hospital admission. This approach follows the outcome definition of the development cohort and was originally chosen as follow up post-discharge was not available in the development cohort.

To identify outcomes, clinical files (during admission) and hospital discharge data are being used. While outcome collection is not being blinded to predictors, we consider the risk of bias minimal given the fixed nature of the outcome.

Text Box 1: Maternal Morbidity Outcomes

- Central Nervous system
  - Eclampsia (≥1 fits)
  - Glasgow coma score <13
  - Stroke of reversible ischemic neurological deficit
  - Transient ischemic attack
  - Cortical blindness or retinal detachment
  - Posterior reversible encephalopathy
- Hematological
  - Transfusion of any blood product
  - Platelet count <50x109 per L, with no transfusion
- Hepatic
  - Dysfunction, INR >1.2 in the absence of DIC or treatment of Warfarin. DIC is defined as: having both: abnormal bleeding and consumptive coagulopathy (i.e., low platelets, abnormal peripheral blood film, or one or more of the following: increased INR, increased PTT, low fibrinogen, of increased fibrin degradation products that are outside normal non-pregnancy ranges)
  - Hematoma or rupture
- Renal
  - Acute renal insufficiency (creatinine >150 µmol/L; no pre-existing renal disease)
  - Acute renal failure (creatinine >200 µmol/L; pre-existing renal disease)
- Cardiorespiratory
  - Positive inotropic support
  - Infusion of a third parenteral antihypertensive drug
  - Myocardial ischemia or infarction
  - SpO2 <90%
  - ≥50% $FiO2^{1}$ >1 h
  - Intubation (other than for cesarean section)
  - Pulmonary edema
- Obstetric
  - Admission-to-delivery interval [1]
  - Postpartum hemorrhage requiring transfusion or hysterectomy

Predictors

This external validation study will use the predictors from the fullPIERS model, miniPIERS model and Payne's perinatal death model (Table 2). In case we need to update the models to improve its performance by including additional predictors, the candidate predictors will be selected based on: (1) those that have been demonstrated to increase the risk of maternal outcomes, stillbirth or neonatal death in previous studies published in literature and (2) those available within our dataset. We will use only predictors collected at the moment of admission.

In the SPOT cohort, investigators have not been blinded in collecting predictor variables. However, given the prospective nature of this research, where the outcome status is still unknown during admission, we anticipate limited bias here.

Sample Size

There is no consensus on the recommended sample size for prediction modelling studies.[27] For validation studies, It has been desired to have at least 100,[28] but preferably 250 or more events.[29] Based on our interim ananylsis we estimated perinatal deaths/neonatal deaths percentages to be around 13-18 percent. Therefore, we expect a sample size of 600 women with HDP in our cohort to be reasonable to externally validate the perinatal model. Drawing from the miniPIERS cohort consisting of comparable women from LMICs experiencing hypertensive disorders of pregnancy (HDP), we anticipated that approximately 20 percent of women would experience a composite outcome. Thus, we estimated that a sample size of 600 women would be sufficient for model validation too. In case we need to update the model and add potential new predictors, we will calculate the

amount of candidate predictors based on a widely used rule of thumb of having at least 10 outcomes per parameter estimated.[30,31]

Study procedures and data quality

In this study, data has been collected with paper questionnaires. Regular data quality checks have been performed by the local study coordinators. To optimize the quality of data, the paper questionnaires subsequently have been entered double in a digital database. Further details of our study procedures are provided in the to-be published version of our study protocol.[32]

Missing Data

Due to the setting of our study, where women are recruited when hospitalized and stay enrolled during admission mostly until the end of the pregnancy, we expect limited loss to follow up. In case of missing data, we will first analyse the nature of missing data: Missing Completely At Random (MCAR), Missing At Random (MAR) or Missing Not at Random (MNR). The analysis will be chosen accordingly, and will furthermore depend on the type of variables (outcome versus predictors) that are missing. We will consider complete case analysis or multiple imputation techniques to deal with the missing data.

Statistical Analysis

We will determine baseline characteristics of participants in our validation cohort using descriptive statistics. We will present these characteristics as mean and standard deviation for continuous variables, or as frequencies with percentages for categorical and dichotomous variables. We will perform univariate comparisons of patient characteristics

between women who experienced a composite outcome, and those who did not. We will consider a p-value of <0.05 as statistically significant. In the event a model extension is needed, we may transform continuous predictors if needed depending on their distribution.

Model performance

The equation of the perinatal death model[23] is the following:

> Logit (logarithm of the odds) (pi) = -4.75 + 0.024 (maternal age) + 0.389 (indicator for presence of one symptom) + 1.338 (indicator for presence of two or more symptoms) + 1.119 (indicator for dipstick proteinuria of 2+ or 3+) + 1.457 (indicator for dipstick proteinuria of 4+)

The equation of the miniPIERS[33] and fullPIERS[34] models are the following:

> MiniPIERS Logit (maternal composite outcome) = -5,77 + [-0.298 x indicator for multiparity] + [- 1.07 x log gestational age at admission] + [1.34 x log systolic blood pressure]+ [-0.218 x dipstick proteinuria 2+]+ [0.424 x dipstick proteinuria 3+] + [0.512 x dipstick proteinuria 4+] + [1.18 x indicator for occurrence of vaginal bleeding with abdominal pain] + [0.422 x indicator for headache and/or visual changes] + [0.847 x indicator for chest pain and/or dyspnoea]

> FullPIERS: Logit (maternal composite outcome) = 2.68 + [- -0.0541 x gestational age at eligibility] + [1.23 x chest pain or dyspnoea] + [-0.0271 x creatinine]+ [0.207 x platelets]+ [0.00004 x platelets^2)] + [0.0101 x aspartate transaminase] + [-0.00000305 x aspartate transaminase^2] + [0.00025 x (creatinine x platelets)] + [-0.00256 x (platelets x SpO2)]

We will start by assessing the model performance by determining the two key components that characterize the performance: discrimination and calibration[35] in our cohort. Calibration is the alignment among the predicted and the observed outcomes. This determines the predictive accuracy of the model. It will be presented with a calibration plot, a calibration plot and intercept and we will calculate the O:E ratio. Discrimination is the capacity of the model to differentiate between women with the adverse perinatal outcome event and those without. We will present this using the AUC.

Afterwards, in case we need to further update the model in the scenario the predictive accuracy is lower than in the development cohort, we will use the different steps as described in the article of Moons et al. (2012).[8] They describe 6 different steps:

1) Adjustment of the intercept (we expect to have a higher baseline risk in the validation cohort)
2) Method 1+ adjustment of all predictor regression coefficients by one overall adjustment factor
3) Method 2+ extra adjustment of regression coefficients for predictors with different strength as compared to the predictors in the development cohort
4) Method 2+ stepwise selection of additional predictors
5) Re-estimation of all regression coefficients based on validation data
6) Method 5+ stepwise selection of additional predictors

Subgroup analysis

In addition, for the perinatal validation study, because of the discrepancies in gestational age between the validation cohort and the development cohort, we will assess whether we

have sufficient power to stratify different risk groups based on gestational age (domain validation). Furthermore, we will evaluate whether we have enough power to stratify women according to their HDP diagnoses (pre-eclampsia versus other diagnoses).

All statistical analysis will be performed in R studio version 4.0.3.

Project Management and Time-schedule

Since this project uses existing data only, we will perform the following activities: data cleaning, data analysis, writing the report and other dissemination activities. We will start with the perinatal validation study in 2021. After this, we will continue by validating the maternal models.

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Table 1. Classification of Hypertensive disorders of Pregnancy (HDPs)	
Pre-eclampsia	Blood pressure ≥140/90 mm Hg (at least one component, twice, ≥4 h apart, ≥20+0 weeks) and either: • Proteinuria (of ≥2+ by dipstick, ≥0.3 g per day by 24-h collection, or ≥30 g/mol by urinary protein: creatinine ratio), or • Hyperuricemia (greater than local upper limit of local non-pregnancy normal range)
Superimposed pre-eclampsia	Rapidly increasing requirements for antihypertensive drugs, systolic blood pressure >170 mm Hg or diastolic blood pressure >120 mm Hg, new proteinuria, or new hyperuricemia[22]
Severe pre-eclampsia	• Elevated blood pressure, systolic ≥ 160 mmHg or diastolic ≥ 110 mmHh, at least one component, twice, ≥4 h apart, ≥20+0 weeks; and proteinuria (of ≥2+ by dipstick, ≥0.3 g per day by 24-h collection, or ≥30 g/mol by urinary protein: creatinine ratio) • HELLP syndrome: homolysis, elevated liver enzymes, and low platelets; even in the absence of hypertension or proteinuria[36]

	• Pre-eclampsia with severe symptoms (headache, blurred vision, right upper quadrant pain, etc.).
Gestational Hypertension	Blood pressure ≥140/90 mmHg (at least one component, twice, ≥4 hours apart, ≥20+0 weeks) without significant proteinuria
Chronic Hypertension	blood pressure ≥140/90 mmHg before 20+0 weeks of gestation
Partial HELLP	Homolysis and low platelets OR low platelets and elevated liver enzymes)[22]
Eclampsia	The presence of pre-eclampsia and convulsions

Table 2. Predictors from fullPIERS, miniPIERS and perinatal death model	
predictors	**Data format**
Perinatal death model	
Maternal age	Years (Continuous)
Count of symptoms	0, 1, ≥ 2 (Categorical)
Dipstick proteinuria	Negative, 1+, 2+, 3+, 4+ (Categorical)
miniPIERS model	
Multiparity	0,1 (binary)
Gestational Age at admission	Weeks (continuous)
Systolic Blood Pressure	MmHg (continuous)
Symptoms	0,1 (binary)
Dipstick proteinuria	Negative, 1+, 2+, 3+, 4+ (Categorical)
FullPIERS model	
Gestational Age at admission	Weeks (continuous)
Serum Creatinine	Umol/L (continuous)
Aspartate transaminase (AST)	U/L (continuous)
Platelet count	$\times 10^9$ per L (continuous)
Oxygen (SpO2)	% (continuous)
Symptoms	0,1 (binary)