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, \( \chi^2 \) 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 probability.

Setting: Primary care antenatal clinics in Ghana.

Participants: 2529 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 (0.60 to 0.77) in the validation cohort. Calibration was good in both cohorts. The negative predictive value of women in the development cohort at high risk of GH was 92.0% compared to 94.0% in the validation cohort.

Conclusions: 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.

INTRODUCTION
Hypertensive disorders of pregnancy (HDP), which include gestational hypertension (GH), preeclampsia, eclampsia and the haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome are the third leading cause of maternal deaths globally, with most of these deaths occurring in low income and middle income countries (LMICs). The International Society for the Study of Hypertension in Pregnancy (ISSHP) classifies HDPs as chronic hypertension, gestational hypertension, preeclampsia-de novo or superimposed on chronic hypertension and white coat hypertension. HDPs 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%). In Ghana, 14% of all female deaths are pregnancy related with HDPs being the third leading cause of maternal deaths (9%) after haemorrhage (22%) and induced abortion (11%).

The underlying causes of HDPs are not fully known, however accurate prediction of women at increased risk of HDP 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. They combine two or more items of patient data to predict clinical outcome and prior to application in clinical practice should be externally validated. The main approaches to predicting the occurrence of GH include the use of maternal clinical characteristics, uterine artery Doppler and biomarkers. Although a number of prediction models for HDP,
mainly preeclampsia and eclampsia have been developed in high-income countries, they may not be suitable for LMICs because of differences in the availability and the cost of diagnostic tools.\textsuperscript{16}

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

METHODS
Study design and population
Development cohort
The prediction model was developed in a prospective cohort of 2529 pregnant women attending ANC 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 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 number GHS-ERC 02/1/10).

The sample size estimation was based on the incidence of HDPs in the Ghanaian population and on the principle of 10 outcome events per variable.\textsuperscript{17} The Ghana Maternal Health Survey of 2007\textsuperscript{4} had estimated that 9\% of all maternal deaths were due to HDP. 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 2529.

Data was obtained from the women’s medical records as measured by midwives during routine ANC. The midwives had been given standardised training in data collection. Candidate predictors were selected based on a review of the literature on variables available for both cohorts.

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 used. These hospitals provide primary ANC similar to that received by the women in the derivation study. The inclusion criteria were women <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 sociodemographic characteristics and obstetric history. Weight, height, BP and urine protein at the initial and subsequent ANC visits was obtained from the maternal health record books. Pregnancy outcomes were obtained from the hospital’s maternity register. Data were 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 140 mm Hg or more and/or diastolic BP of 90 mm Hg or more on at least two separate occasions, and present for the first time after 20 weeks of pregnancy.\textsuperscript{23} In both cohorts BP 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, 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.\textsuperscript{24} Two readings were taken at an interval of 5 min and the average was used to represent the woman’s BP. 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 SD 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 $\chi^2$ test. Missing data were imputed by multiple imputation using ‘Multivariate Imputation by Chained Equations (MICE)’ function in R.\textsuperscript{25} Missing values were imputed 10 times and Rubin’s rule\textsuperscript{26} was applied to pool results over the 10 imputed data sets. Predictors that were related to GH by a predetermined 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 forced in the model while systolic blood pressure dropped out of the model because of collinearity with diastolic blood.
pressure. 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). 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 <1, between 2 and 6 and ≥7 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. Statistical data analysis was performed by use of SPSS software (V.20.0, IBM SPSS Statistics, Chicago, Illinois, USA) and R statistical software (V.3.1.0 (2014–04–10)).

RESULTS
Table 1 describes the baseline characteristics of the development and validation cohort 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 BP also differed between women who developed GH and those who did not (71.9 mm Hg (SD 11.6) vs 66.2 mm Hg (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
The 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

Table 1 Characteristics of the development and validation cohort at first antenatal visit stratified by GH

| Variable | Development cohort | Validation cohort |
|----------|--------------------|-------------------|
| Age (years) | 28.9 (6.7) | 29.8 (5.7) |
| Height (cm) | 159.9 (6.7) | 160.6 (6.7) |
| Weight (kg) | 73.3 (19.0) | 66.2 (13.2) |
| Systolic BP (mmHg) | 116.0 (15.2) | 108.7 (10.8) |
| Diastolic BP (mmHg) | 71.9 (11.6) | 66.2 (9.1) |
| Gestational age (weeks) | 21.9 (6.1) | 20.5 (6.9) |
| Educational level | | |
| None | 30 (11.8%) | 230 (10.4%) |
| Primary | 55 (21.7%) | 424 (19.1%) |
| Junior High School | 101 (39.9%) | 999 (44.9%) |
| Senior High School | 42 (16.6%) | 410 (18.4%) |
| Tertiary | 25 (9.9%) | 160 (7.2%) |
| Family history of hypertension | 30 (11.8%) | 230 (10.4%) |
| Previous history of GH | 40 (15.3%) | 23 (10.0%) |
65.9 kg (SD 7.5), p<0.001). The mean diastolic BP differed between women who developed GH and those who did not (75.2 mm Hg (SD 12.6) vs 69.1 mm Hg (SD 10.5), p<0.001), as did mean systolic BP (115.6 mm Hg (SD 14.5) vs 111.6 mm Hg (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 ORs of predictors of GH in the development cohort.

These are maternal height, weight, diastolic BP, history of hypertension in the parents, previous history of GH in the mother and parity. The c-statistic of the model was 0.70 (95% CI 0.67 to 0.74).

The final prediction model was:

\[
\text{Final model: Logit (GH)} = -1.53 - 0.031 \times \text{Height} + 0.38 \times \text{Hypertension in parents} + 2.26 \times \text{Previous GH} + 0.024 \times \text{Weight} + 0.041 \times \text{Diastolic BP} - 0.10 \times \text{Parity}.
\]

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

Figure 1 shows the calibration plot for the development cohort.

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

The calibration plot shows a reasonable 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. Again 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 categorisation 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 positive likelihood ratio was 1.22 for low risk and 3.24 for moderate risk while the negative likelihood ratio was 0.32 for low risk and 0.76 for moderate risk.

Table 5 presents information on the categorisation 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 positive likelihood ratio was 1.15 for low risk and 7.31 for moderate risk while the negative likelihood ratio 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.

**Table 2** Adjusted OR of predictors of GH at the first antenatal care visit in a cohort of 2529 pregnant women

| Predictor                  | Adjusted OR (95% CI) | p Value |
|----------------------------|----------------------|---------|
| GH in a previous pregnancy | 9.55 (5.42 to 16.84) | <0.001  |
| Hypertension in parents    | 1.46 (1.06 to 2.02)  | 0.022   |
| Diastolic BP (mmHg)        | 1.04 (1.03 to 1.06)  | <0.001  |
| Height (cm)                | 0.97 (0.95 to 0.99)  | 0.002   |
| Weight (kg)                | 1.02 (1.01 to 1.03)  | <0.001  |
| Parity                     | 0.90 (0.66 to 1.23)  | 0.51    |

BP, blood pressure; GH, gestational hypertension.

![Figure 1](image1.png) Calibration plot in development cohort.

![Figure 2](image2.png) Calibration plot in validation cohort.
studies.10 28

external validation, consistent with
the original cohort (0.70 (95% CI 0.67 to 0.74)) was
managed to prevent progression to severer forms, a
favourable pregnancy outcomes. Given that GH can be
which are severer forms of the disorder. However,
generally not available in many low-resource settings.
and the equipment for analysing these biomarkers is
the Ghanaian setting. Both approaches are expensive
of the non-routine use of these parameters in ANC in
artery Doppler in our prediction model. This is because
model,16 have focused on preeclampsia and eclampsia
who developed hypertension before 36 weeks of gesta-
tion using systolic BP , diastolic BP and weight. The AUC
reduced to 0.75 (95% CI 0.68 to 0.81) after external val-

The small decrease in c-statistic in our study
reduction in c-statistic in our study implies that the model predicts well based on data rou-
tinely collected as part of ANC and can be applied to
the pregnant women in the study setting.

Most prediction models for HDPs, such as the SCOPE
model,13 have focused on preeclampsia 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 a recent systematic review for first
trimester prediction of preeclampsia showed that a com-
bination of uterine artery Doppler, maternal character-
istics and two or more biomarkers yielded detection
rates of 38–100%.14 The best rates were reported for the
combination of Inhibin A, PLGF, PAPP-A, uterine artery
Doppler and maternal characteristics.14 The difficulty of
predicting GH using only maternal clinical character-
istics 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 fre-
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 HDPs 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 assess-
ment information for future decision-making. In the
interim however, despite the fact that the modest PPV in
the development and validation cohorts show the limita-
tion and difficulty of predicting GH using only demo-
graphic 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 con-
verted into a simple user friendly clinical decision-
making support tool for use in ANC clinics in low-
resource settings that enables frontline providers of
maternal health services to use a score chart to quickly
categorise women into different risk levels. The strength
of this model is the use of a few maternal clinical

### Table 3

| Predictor                        | Score |
|---------------------------------|-------|
| History of hypertension in parents | No=0  |
|                                 | Yes=4 |
| GH in a previous pregnancy      | No=0  |
|                                 | Yes=24|
| Diastolic blood pressure (mm Hg)| ≤60=0 |
|                                 | 61–70=1|
|                                 | 71–80=2|
|                                 | 81–90=3|
|                                 | ≥91=4 |
| Height(cm)                      | ≥161=0|
|                                 | 156–160=1|
|                                 | 151–155=2|
|                                 | ≤150=3|
|                                 | ≤70=0 |
|                                 | 71–80=1|
|                                 | 81–90=2|
|                                 | ≥91=3 |
| Weight (kg)                     | ≥1=0  |
| Parity                          | 0=1   |

GH, gestational hypertension.
variables already routinely obtained by caregivers 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 lifesaving. Obtaining the information does not involve expensive procedures such as uterine artery Doppler. 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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**Table 4** Categorisation 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=1641) Score (2–6) | 158 (9.1%) | 1483 (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%) | 12.6% | 99.7% | 85.0% | 39.7% | 4.05 | 0.93 |

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

**Table 5** Categorisation 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 (66.7%) | 27.2% | 72.8% | 80.0% | 28.6% | 7.26 | 0.93 |

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

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

| 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 (mm Hg) | 66.8 (11.6) | 66.8 (11.6) | 69.5 (10.7) | 69.5 (10.7) |
| Systolic BP (mm Hg) | 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%) |

BP, blood pressure.
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Contributors EA designed the study, collected data, carried out data analysis and wrote the initial draft of the manuscript. RHGG assisted with data analysis. DEG, RHGG, IA, KAHKK-GLJLJL 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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Development and validation of a prediction model for gestational hypertension in a Ghanaian cohort

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