Author’s response to reviews

Title: Improved prediction of gestational hypertension by inclusion of Placental Growth Factor and Pregnancy Associated Plasma Protein-A in a sample of Ghanaian women

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RESPONSES TO REVIEWERS- REPH-D-17-00388

We would like to thank the reviewers for their valuable comments and hope to have addressed the point-by-point critique satisfactorily below.

Reviewer #1.

1. Comment

Introduction: line 95 on aims of the study have to be shifted to the end of the introduction.

Response:

We agree with this comment. Therefore we have made the following changes in the text of the manuscript. On page 4 under “introduction” line 95 has been shifted to lines 99 to 103.
2. Study design and study population:
   a. Was there any power for sample size estimation?

Response:

   a. This study was nested in a larger cohort study and we did not undertake a sample size calculation. Instead we used Harrell’s principle of 10 outcome events per variable for logistic and Cox regression analysis (1-4) to obtain a sample size that had adequate number of outcome events to undertake the analysis. Using an incidence of gestational hypertension of between 5% to 10% in the Ghanaian population and 8 predictors in the prediction model, the sample size of 393 was arrived at. The text has been changed on page 5 (line 118 to line 122).

   b. Comment

The sample of 1,010 women does not statistically represent all Ghanaian pregnant women.

Response:

Although the women in the study cut across the socio-economic and ethnic strata in Ghana, the sampling was not random. We have therefore changed the title on page 1 (line 1 to line 3) to “improved prediction of gestational hypertension by inclusion of Placental Growth Factor and Pregnancy Associated Plasma Protein-A in a sample of Ghanaian pregnant women”.

3. Comment
   a. Gestational age in weeks or days.

Response:

Gestational age has been changed from days to weeks throughout the manuscript.

   b. Comment

Why did you exclude the primigravid women?

Response:

The primigravid women were excluded because one of the variables, “previous history of gestational hypertension or preeclampsia”, was not applicable to them. Not having been pregnant before, the primigravid women could not answer that question. We could not assign a “no”
answer to the primigravid women nor impute for that variable because doing that was not valid. As a result the logistic regression analysis involved only the multiparous women. However we have attached the report of the analysis for primigravid women as a supplementary file. Because of the relatively small number of women and events on which these estimates are based, we urge caution in the interpretation of the estimates, considering the rule of 10 events per variable for logistic and Cox regression analysis (1-4). A future study using a larger sample size with adequate number of primigravid women is recommended.

c. Comment

Why take BP readings 5 minutes apart instead of 4 hours apart?

Response:

For routine measurement of blood pressure in a clinic setting, Pickering et al (5) recommended that “a minimum of two blood pressure readings should be taken at intervals of at least one minute apart, and the average of those readings should be used to represent the patient’s blood pressure”. For practical reasons at the antenatal clinic setting we considered a minimum of 5 minutes interval between repeated blood pressure measurements for women with normal blood pressure readings. However where the high blood pressure was identified initially it was measured again four hours later (10). So no changes have been made in the text of the manuscript.

4. Comment

Flow chart: First correct the word days please , 373 women were included in the article having gestational hypertension , were there any cases whom the gestational hypertension progressed to preeclampsia and you have exclude them ????

Responses:

a. We agree with your comment. Therefore “gestational days” has been changed to “gestational weeks” and the corrections have been effected in the flow chart (attached as a supplementary file).

b. All the 373 pregnant women included in the study did not have gestational hypertension at the time of their enrollment into the study. They were all normotensive. As we followed them
through pregnancy, 25 out of 373 women developed gestational hypertension after 20 weeks of pregnancy. None of the women in the cohort who developed gestational hypertension progressed to preeclampsia. We have addressed the reviewers point by adding text to this effect on page 5 (line 126 to line 127).

5. Comment

Table 1: Nulliparous means woman who have never had a delivery more than 24 weeks gestation. primiparous means a woman who have only one delivery more than 24 weeks gestation. Please change the word to primigravid women.

Response:

We agree with your comment and have accordingly changed “nulliparous” to “primigravid” throughout the manuscript.

B. Reviewer #2: Comment on submitted paper for Reproductive Health

General appraisal

1. Comment

This paper contains interesting data, and contributes to the corpus of data regarding biochemical screening for preeclampsia / pregnancy induced hypertension risk. In particular there are at present only few data from LMICs and in particular from Sub-Saharan Africa. It requires in my view a change of position in the discussion and conclusion part, as formal recommendation of routine 1st trimester biochemical screening is still very much a subject of controversy for HICs, let alone where resources are limited (1).

As an example of this, Cheng et al did not find markers to be useful for detecting early or late onset preeclampsia in China (2).
Response:

We accept your recommendation to revise the discussion and conclusion parts of the manuscript taking into account challenges of first trimester biochemical screening especially in low and middle income countries. Although biomarker screening is a challenge in low resource settings, Poon and Nicoliades (6) showed that first trimester biochemical screening is of benefit as first trimester screening using a combination of maternal factors, mean arterial pressure, uterine artery Doppler, maternal serum PAPP-A and PIGF identified about 95% of early onset preeclampsia for a false positive rate of 10%. However they acknowledge that first trimester screening for late onset preeclampsia has not been as effective. Cohen et al (7) and Akolekar et al (8,9) also found that biomarkers along with other maternal clinical characteristics are able to predict preeclampsia in the first trimester of pregnancy.

2. Comment

For the present study, one option would be to replicate the study on a larger population in particular to have results for preeclampsia (early or late onset). Recommendation for local trials has been made in the discussion of the Cheng study which is probably the best option.

Response

We agree with your recommendation to replicate this study on a larger population locally and elsewhere. In future, the study design should make provision for obtaining results for early and late onset preeclampsia.

3. Comment

Another issue is that of the additional benefit of each separate marker to the prediction model, as each requires additional economic resources. This topic is well discussed by Prefumo and Farina (3).

Response

Thank you for your comment. We have reported the additional benefit of each biomarker and in combination with other predictors to the prediction model on page 11 (table 4), on page 13 (line 292 to line 297) and in a supplementary file (table 5).
4. Comment

Finally I looked up the UK screening portal, and other guidelines and Cochrane type evidence and could find NONE introducing population based 1st trimester preeclampsia screening.

Response:

Thank you for your comment. Our study explored the possibility of using biomarkers that are assessed during the first trimester for screening of fetal aneuploides to also predict gestational hypertension.

5. Comment

Conclusion

The data are useful, and come from an African population for which there are not many studies, and therefore should be available to scientists in this area, which means they should be published.

The M&M section and the results section are up to standards. The fact that the main outcome is PIH and not preeclampsia is not a major issue because these diseases are linked and the aim is to add to the corpus of knowledge.

On the other hand the introduction and in particular the discussion lack both distance and reference to doubt regarding the appropriateness of introducing such screening.

Response:

Thank you for your comment, which we have considered. We agree that at this time it may not be possible to introduce biomarkers in the screening of hypertensive disorders of pregnancy into routine antenatal care.
6. Comment

If the authors can access more information about the limited level of evidence and transform their viewpoint and rewrite the introduction and section, I think this paper is of interest.

Response

Following your comment, the methods section has been amended and the changes highlighted on pages 4 and 5.

Reviewer #3:

1. Comment

ABSTRACT: There are few grammatical errors that need to be corrected e.g page 2 lines 32-33 should be obtaining antenatal care or attending antenatal clinic. Similarly lines 32-34 should be recasted.

Response:

Thank you for your comment. The grammatical errors have been corrected. Line 33 to 34 of page 2 now reads “attending antenatal clinic”. Page 2 line 33 to 34 has been rephrased to read as “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” on page 2 ( line 34 to line 37 of the manuscript).

2. Comment

INTRODUCTION: Hypertensive disorders of pregnancy is not a single condition yet the authors refer to them as the condition eg lines 85 and 86 page 4.
Response:

Thank you for your comment. Lines 85 and 86 on page 4 have been revised on page 4 (line 81 to 85) to read as “Hypertensive disorders of pregnancy (HDP) 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”.

b. Comment

The statement in lines 103-104 should be referenced.

Response:

The statement has been referenced as follows:

Page 4, line 92 to 93:


Page 4 line 94 to 98:

3. Comment

METHODS: What informed the choice of the two hospitals used in the study? for the purposes of clarification the authors should define gestational hypertension in the context of their study.

Responses:

a. The two hospitals are government hospitals which are accessible to all members of the public. Persons attending these hospitals cut across the socio-economic and ethnic strata of the city. The 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. This has been stated to the text of the manuscript (page 5, line 110 to line 113).

b. Thank you for your comment. Gestational hypertension in the context of this study has been defined on page 7 (lines 166 to 168) of the manuscript as “as a systolic blood pressure of 140 mmHg or more and or a diastolic blood pressure of 90 mmHg or more on at least two separate occasions, and present for the first time after 20 weeks of pregnancy (3)”.

REFERENCES


6. First trimester maternal factors and biomarker screening for preeclampsia. Leona C. Poon and Kyros H. Nicolaides. Prenatal Diagnosis 2014; 34:618-627 ,


