Author's response to reviews

Title: Prediction of uncomplicated pregnancies in obese women: a prospective multicentre study.

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Author’s response to reviews:

Dear Editor,

Thank you for the opportunity for a revised submission of our manuscript entitled “Prediction of uncomplicated pregnancies in obese women: a prospective study”. We have carefully considered each of reviewer’s comments and amended the paper accordingly.

Please find below our response in italics for each of the comments raised. We are including in this re-submission a revised version of the manuscript (with tracked changes) and the Additional files 5 and 6. The figures and the Additional files 1-4 have not been changed (they are included in their original format in this revised submission).

Please do not hesitate to contact us should you require further information.
Sincerely,

Dharmintra Pasupathy

Response to reviewer’s comments (responses in bullet points under each comment):

Reviewer reports:

Reviewer #1: This is a well written paper, using data from the UPBEAT trial to attempt to identify a lower-risk group amongst pregnant women of high BMI, the concept being that these lower risk women might need less surveillance/less intensive model of care than women of high BMI with a less favourable risk profile.

My main comments are around making revisions to (a) put this research more explicitly in context/give more detail compared with similar studies, to enable the reader to better judge how clinically useful the modelling in this study might be (b) be a little more cautious in interpretations of findings/conclusions.

• Thank you for your comments and for the suggestions for improving our manuscript.

Abstract comments: Suggest change first sentence of conclusion to "Clinical factors and biomarkers can be used to help stratify pregnancy and delivery risk amongst obese pregnant women". Use of "help" better conveys that clinical factors and biomarkers can be an aid, without giving the impression that these factors are all that is needed (which for a model with AUROC of 0.72, and 0.69 for clinical factors, is clearly not the case).

• We have changed the first sentence of the conclusion (Abstract, page 4, line 29).

I would also suggest that (a) the AUROC when using clinical factors only goes into the results section of the abstract (b) the sensitivity/specificity/PPV/NPV using the clinical factors is inserted into the abstract, as the clinical factors model best reflects information that would be universally and easily available to clinicians (and able to be applied tomorrow in the real world, for units who think the model is helpful).

• We have included the AUROC and test performance for the clinical model (Abstract, page 3-4, lines 26-28) as advised. In keeping with the word count and to ensure that the results on prediction are clearly presented, we have removed effect sizes for all factors associated with uncomplicated pregnancy and birth.

Results:
Table 4 shows the proportions of women with complications by 5ths of the overall model: please also in this table give the outcomes using the 5ths of the clinical factors only, as this is what is most likely to be used in practice.

- We have included another table (table 5) with the complications by 5ths of the clinical model (Results section, page 13, lines 219-220 and page 13, line 231). Of note, the sentences previously on lines 212-215 (page 12) were now moved to the next paragraph (page 13, line 220-224).

It would also be good to have in the results what the AUROC and confidence interval (and also the upper 5th results, where it seems the model would most likely find clinical use if it is going to) using clinical factors plus HbA1C, but not adiponectin. As it would conceivably be reasonable to have an HbA1C on women with high BMI, but adiponectin levels are unlikely to be available outside of research setting without compelling evidence of benefit, it would be of interest to know how much difference there is between the clinical, full model, and HbA1C (but not adiponectin) plus clinical model.

- We have included information in the text and an Additional file which describe performance of this alternative model using clinical factors and HbA1c (Results section, page 13, lines 224-229 and Additional file 5)

Line 207 results - negative likelihood ratio not ration Line 211 results - ratio not ration

- Thank you for pointing out these errors. We have now corrected them (results section, page 12, line 211 and page 13, line 223).

Discussion:

1) Previous study of predicting uncomplicated pregnancy and birth in nulliparous women of any BMI is mentioned - would be good to mention some more of those findings for comparison (e.g. that over 60% of that cohort has no complications versus a third in this one). It would also be good to more explicitly discuss expected levels of complications in pregnancy generally/in other "high risk" and unselected groups that are referenced but not further discussed (e.g. expand on "Women with the highest prediction of uncomplicated pregnancy and birth (those in the upper fifth) had similar levels of risk of most complications to those seen in an unselected obstetric population [12, 20-22]"). This would help place the high BMI risk group and your data relating to this in context for the reader.

- We have added more information regarding the previous study in nulliparous women (Discussion section, page 14-15, lines 264-270). We have also provided more information of the risk of complications in unselected or other populations (discussion section, page 15, lines 283-287).

2) More acknowledgment of the limitations of the models e.g. an AUROC of 0.72, and modest PPV/NPV, is warranted (especially when that is with adiponectin and HbA1C, neither of which
are routinely performed in pregnancy, particularly adiponectin which is essentially a research measurement). As the authors focus on, the model is most likely to be of use in (roughly) predicting the proportion (upper 5th) of women who are least likely to have complications, who may be suitable to have less intensive surveillance. Again, the clinical model and its upper 5th prediction and sens/spec/PPV/NPV should be discussed, not just the full model, if the authors are seriously proposing use of their model to triage care of pregnant women of high BMI.

- We share the reviewer’s view and acknowledge that this predictive model has limitations. In the original manuscript, we discussed that a higher AUROC might be desirable as our model would suggest lower risk of adverse outcomes in a group of obese women which would otherwise be considered ‘high risk’ by definition (Discussion section, page 15, lines 289-290) and the options one might seek to further improve performance (Discussion section, page 15, lines 293-295). We have now added a sentence emphasising that we recommend assessing alternative care pathways based on these prediction models in research settings prior to implementation in clinical practice (Discussion section, page 15, lines 291-293 and Conclusion section, page 18, lines 348-350). We have also discussed the performance of the clinical model where relevant in the discussion (Discussion section, page 15, lines 290-291 and page 16, lines 308-309).

Reviewer #3: Congratulations on your work. The paper is well written and concerns an interesting subject. There are 2 issues you should comment on in your paper:

1. Please comment on your result that OR of previous history of GDM or PE is 0.58. What is your hypothesis on that?

- Thank you for your comments. The OR for a previous history of GDM or PE of 0.58 reflects a reduction in the odds of an uncomplicated pregnancy and birth outcome. As it has been suggested that pregnancy is a stress test to a woman’s cardiovascular system (Poli-de-Figueiredo et al. BMJ 2003;326 DOI:10.1136/bmj.326.7394.845), we suggest that failure of the physiological cardiovascular adaptation to the first pregnancy highlights the risk for future events, including recurrence in subsequent pregnancies. The focus of the manuscript is risk stratification of women with obesity and therefore we would rather not discuss the mechanisms of individual risk factors either in the original submission or in this revised version.

2. Could you describe what were the interventions performed in your study group. Obesity is a known risk factor of thrombo-embolism - were there any antithrombotic prophylaxis administered? Was low dose aspirin administered in obese women to prevent preeclampsia?

- The intervention in the UPBEAT trial was confined to diet and physical activity; other than this routine antenatal care was provided to all women. The trial intervention did not include any aspirin or thromboprophylaxis recommendations. According to UK guidelines, antithrombotic prophylaxis is administered based on risk assessment where obesity is one risk factor, but obesity alone does not determine the need for treatment (RCOG Green-top Guideline No. 37a). Aspirin is recommended for women at high risk for preeclampsia based on risk
assessment; BMI>35 kg/m2 is a moderate risk factor but alone it does not determine the need for aspirin (NICE Clinical Guidance 107). We did not assess compliance to the use of aspirin and thromboprophylaxis. We have now added a sentence stating that routine antenatal practice according to UK and local practice was provided to all women in the study (Methods section, page 6, lines 76-78).