Author's response to reviews

Title: Serum screening in first trimester to predict pre-eclampsia, small for gestational age and preterm delivery: Systematic review and meta-analysis

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Author's response to reviews: see over
To reviewer Rebecca Allen
1. Grammatical errors in the 1st sentence of the abstract. Change earlier to early and have to has.
Response: Thanks for your kind advice. We have reviewed the sentence and corrected the error.
2. In the methods section of the abstract please add "and" contact with experts
Response: Thank you for the notification. We have reviewed the section and added the word.
3. There appears to be a discrepancy between documentation in the abstract results section that states PlGF to be the best predictor of preeclampsia and the results section under PP13 which states that PP13 is the most accurate predictor of early preeclampsia. This needs clarifying
Response: Thanks for your suggestion. We have carefully analysed the discrepancy and changed "most" to "more" in the result section.
4. 1st paragraph of background please delete the s after two to eightfold
Response: Thanks for your notification. We have reviewed the paragraph and deleted the s.
5. More detail is needed in the methods section regarding the search terms used so this could be replicated by a reader if wanted
Response: Thanks for your kind advice. We have reviewed the section and added more details on search terms.
6. It needs to be stated over what time frame the studies were looked at
Response: Thanks for your suggestion. We have reviewed the method section and added the time frame.
7. Within the results section you should include how many women were in the studies identified. I.E total number of women in 103 studies and then within the sections examining the different biomarkers and outcomes you should again describe how many women were included in the data set
Response: Thanks for your kind suggestion. We have reviewed the section and added necessary numbers.
8. Throughout the manuscript 1th needs to be changed to 1st
Response: Thank you for the notification. We have reviewed the manuscript and corrected the error.
9. On the figures there's headings where it says "continuous" what does this mean? Please clarify
Response: The meaning of "continuous" has been explained in the legend: continuous: Likelihood ratio calculated from receiver operating curve analysis.
10. In the last paragraph of the results section on betaHCG it states that the best predictor for preterm delivery was hCG <0.5MoM and the best predictor for preterm delivery <34 weeks is a hCG>95th centile. This seems odd and is probably due to the heterogeneity an d small number of studies but further discussion of this should be made in the discussion section
Response: Thanks for your kind suggestion. We have carefully reviewed the odd result and discussed it in the discussion section.
11. Following on from the above comment there should be more discussion in the discussion section regarding the strengths and limitations of the study
Response: Thanks for your advice. We have added discussion of strengths and limitations in the discussion section.
12. There needs to be a PRISMA checklist
Response: Thanks for your suggestion. We have added the PRISMA checklist and attached it as appendix.

To reviewer Francesco D’Antonio
1) Systematic review of diagnostic accuracy require specific tools to assess study quality. I would advise using QUADAS-2 to ascertain the quality of the included studies.
Response: Thanks for your suggestion. We have added QUADAS-2 and attached it as appendix.
2) In this review, the authors opted to express the diagnostic accuracy of the different serum biomarkers as likelihood ratios. Being a review of diagnostic accuracy, results should be expressed as sensitivity, specificity, positive and negative likelihood ratios and diagnostic odd ratio. In order do this, either bivariate meta-analysis or a hierarchical summary receiver operating characteristics (HSROC) model should be used.
Response: Thanks for your advice. We have applied the method you suggested and added sensitivity, specificity to the diagnostic accuracy.
3) The overall diagnostic performance of a test is strictly related to the occurrence of a given outcome in the population analysed. The figures for predictive accuracy reported in the different studies are likely to be affected by the type of population analysed (low vs high risk). I would advise performing a sub analysis according to the population analysed.
Response: Thanks for your kind suggestion. All of the studies we selected are population of low risk so we are unable to perform a sub analysis. We didn’t choose the population of high risk since there are few studies on it. However, it is a good suggestion and we would look at it in our future study. We have added it as limitation into the discussion section.