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11th August 2015

Re: Manuscript Number 20213; Title: Preeclampsia – What is to blame? The Placenta, Maternal Cardiovascular system or both?

Dear Editor-in-Chief

We would like to thank the reviewers (Nos 611279 and 2445078) who took the time to read our manuscript and provide us with invaluable feedback. All of the points have been duly noted and considered, and where applicable, revisions to the manuscript have been made. We address the specifics of the feedback below.

Reviewer 611279

Thank you for your constructive feedback. This was not a systematic review article, instead it was a mini-review of the available evidence and literature to support a new hypothesis for the aetiology of PE as outlined in our manuscript. We therefore do not feel it is necessary to outline the search strategy used in this case, as this does not lend itself to a systematic review. The majority of the cardiovascular evidence has been taken from work published by our group in the past. As per your comments, we have included a new figure to illustrate and summarise the aetiological pathways we have described within the manuscript. Whilst we acknowledge your comments about other aetiologies (such as raised intra-abdominal pressure) and the pathophysiology being likened to abdominal compartment syndrome, the purposes of our mini-review was not to carry out a review of all of the possible aetiologies of PE or to discuss the pathophysiology of the disease process - instead it was to provide the evidence of a dual aetiology which we believe to be the cause of PE. We have however revised the manuscript to include the potential role of raised intra-abdominal pressure in PE.

Reviewer 2445078

Thank you for your comprehensive and constructive feedback. We have addressed your major comment of including the role of heme-oxygenase 1 (HO-1) in PE and have revised the manuscript accordingly. We have noted the comments about consistent use of abbreviations and the manuscript has been revised accordingly. The various other language points have been revised and will of course be re-checked by the journal editors prior to publication.

Yours Sincerely,

D Vinayagam