Author's response to reviews

Title: The Role of Vitamin D in Pre-Eclampsia: A Systematic Review

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REVIEWER #1

Thank you for your valuable comments and helpful feedback – we really appreciate it. This is a structured literature review. A PRISMA flowchart was, however, still included within the figures section of the first submission and we have now updated the flowchart to describe our process for excluding studies from the review. Please refer to Figure 1 of the submission to further review the checklist and our process for screening articles. The methods section has been updated to provide more detail about the search strategy.

REVIEWER #2

1. Thank you for your time in reviewing this manuscript and important suggestions for its improvement. We have ensured that a uniform set of acronyms were used for vitamin D, PIGF, and VEGF and that all acronyms are reported correctly.

Thank you for this observation. We have ensured that the correct unit is used consistently within all instances referring to dosage in supplementation (IU) and all instances referring to plasma/serum concentration (nmol/L).

2. Thank you for this suggestion. The reference in the first paragraph of the introduction has been updated to reflect more recent WHO data (updated November 2015).
Thank you for your feedback. Since one of the case control studies reviewed in this article (Robinson et al, 2010) investigated cases of early onset severe PE, we do believe it was necessary to define early versus late-onset disease in the introduction. Early vs. late onset disease carry different clinical characteristics, features, associated biomarkers and risk for maternal mortality as described in a review by Raymond et al (now cited in the discussion). EOSPE carries a higher risk for maternal mortality and adverse pregnancy outcomes. Findings from Robinson et al, 2010 suggest that there may be a potential threshold effect of vitamin D deficiency upon EOSPE. The distinction between EOSPE and PE may guide clinical/supplementation recommendations. This has been elaborated on further in the discussion section.

Thank you for bringing this to our attention. We agree and have updated the definition of eclampsia in the introduction to clarify that it is the occurrence of unexplained seizures during pregnancy.

3. Thank you for your comments and helpful feedback. This is a structured literature review. We have included a PRISMA flowchart to describe our process for excluding studies from the review. The methods section has been updated to provide more detail about the search strategy. We have included search terms and search criteria. We have now described who screened titles, abstracts and full papers. We have described the inclusion and exclusion criteria and the data extraction process. This includes how data was cross-checked for agreement between reviewers and which elements were extracted. We described how any data discrepancies were resolved.

Thank you. In our discussion, there is a brief mention of the challenge in establishing a dosage recommendation of vitamin D during pregnancy. This is due to the limited data on the most efficacious dose of vitamin D to prevent pre-eclampsia while avoiding toxicities such as hypercalcemia and hypercalciuria. We have now also referenced the reported findings from the Cochrane review of possible increased incidence of preterm birth with vitamin D and calcium supplementation in this section.

4. Thank you for this suggestion – the discussion section discusses the limitations of the RCTs reviewed. We mention that the major weakness of the reviewed RCTs were that investigators were unable to study vitamin D supplementation independently of calcium, other multivitamin/micronutrient supplementation or fish oil. Thus, these studies are unable to tease out the effects of vitamin D on PE in isolation from other micronutrients.

5. Thank you for this comment. Meta-analysis was considered; however, given the limited number of studies investigating the relationship between vitamin D and PE, and the variability in study design, the authors decided that it would not have been appropriate to apply a single appraisal tool to all studies.

Thank you for this useful suggestion. We have included a table of the observational studies and another table of RCTs reviewed in this paper. The table of observational studies is organized by study design (cross-sectional, case control, retrospective cohort and prospective cohort). The table of RCTs reviewed now presents a clearer description of the interventions used and the key findings. To answer your question, the Olsen trial supplemented from 20 weeks onward.
6. Thank you for this important comment. We have built upon our discussion to include this limitation.

7. Thank you for this suggestion. We have added OR/RR results cited for studies showing no association, as well. However, not every study reviewed measured an OR and RR (some compared median or mean vitamin levels across groups).

8. Thank you for bringing this to our attention. We have removed this section from the paragraph on vitamin D and birth outcomes. We have removed the discussion of IGF-1 throughout the paper.