Reviewer’s report

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

Version: 0 Date: 31 May 2016

Reviewer: Beth Payne

Reviewer’s report:

Thank you for the opportunity to review this excellent structured review of Vitamin D supplementation and pre-eclampsia incidence. The manuscript was comprehensive and well written overall. I have the following suggestions for your consideration prior to publication:

1. There is inconsistency in acronyms and names used for Vitamin D, PlGF and VEGF throughout the manuscript. It would be easier to follow if the authors chose a consistent set of names and ensured all acronyms used are reported correctly. Similarly, all dosages reported should be converted to a consistent format for easier interpretation. Some are reported as IU and others ng/mL.

2. In the introduction the references used for pre-eclampsia impact are quite old. Authors may consider referencing more recent work by the WHO or Global Burden of Disease groups. I am also not sure the differentiation of risk between early onset vs late onset disease adds to the paper. If word count is an issue the intro could be shortened. Finally, the definition of eclampsia as characterized by severe hypertension and proteinuria is inaccurate. There is a growing body of evidence that suggests eclamptic seizures often occur in the absence of markers of severe PE such as described here.

3. In methods, the search strategy and review process is not well described. What terms were used exactly, who reviewed titles, abstracts, full papers and how were disagreements resolved should all be reported. In a systematic review on this topic published in the Annals of Nutrition and Metabolism by Hypponen et al. their review ending in March 2013 on a more narrowly focused question (not considering angiogenic factors) retrieved 407 manuscripts of which 15 were finally included. Authors may wish to double check their results against this previous review and discuss any differences in papers included. There is also a Cochrane review of vitamin D supplementation in pregnancy that is relevant to discuss and was not included here. How does this review add to the information presented in these previous papers? The Cochrane review found possible increased incidence of preterm birth with Vitamin D and calcium supplementation combined - did the authors encounter any other potential negative consequences to Vitamin D supplementation?

4. In the discussion there is an excellent description of some of the limitations of the epidemiological studies reviewed overall. This is variably done within the results as well for individual studies and was missing in some areas. It would be useful to discuss the quality of the RCTs reviewed.
5. Did the authors consider meta-analysis of the evidence for or against the role of Vitamin D in PE? There is a wealth of information presented in this paper but it is hard to digest in purely text format. If meta-analysis is not used a graphical or tabular presentation of results for easier comparison would be helpful to the reader. The only table included has basic info about the trials reviewed but was unclear as to the interventions used. For example, did the Olsen trial supplement from 20 weeks onward or just once at 20 weeks?

6. It does not appear like a consistent method of defining PE was utilized across studies reviewed. More detail on this topic and how it may have impacted results is required.

7. Authors should add in OR or RR results cited for all studies discussed whether statistically significant or not. It is hard to interpret the impact and quality of some of the studies discussed without information on actual results.

8. The final paragraph in the section on Evidence of role of Vitamin D in relation to birth outcomes does not appear to fit under this subheading as no birth outcomes are discussed. Can you explain the link between PE, IGF-1 and vitamin D further or consider removing this. It is also briefly discussed later in the manuscript but without a clear indication how they are all related.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Unable to assess

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

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Please indicate the quality of language in the manuscript:

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