Reviewer's report

Title: Trajectory of vitamin D status during pregnancy in relation to neonatal birth size and fetal survival: a prospective cohort study

Version: 0 Date: 20 Mar 2017

Reviewer: Anne Marie Zaura Jukic

Reviewer's report:

"Trajectory of vitamin D status during pregnancy in relation to neonatal birth size and fetal survival: a prospective cohort study." The authors present an analysis of a prospective pregnancy study conducted in 2013-2014 in Sweden. The women enrolled before 16 weeks of gestation and were followed for pregnancy outcomes that included pregnancy loss, preterm delivery, small-for-gestational age, and low birth weight. 25(OH)D was measured twice: before week 16 and after week 31. A small protective association was found for first trimester 25OHD and pregnancy loss. High 25OHD (>=100 nmol/l) was associated with lower odds of SGA and LBW compared with 25OHD <30 nmol/l. Women with a large increase in 25OHD from first to third trimester had the lowest odds of SGA, LBW, and preterm delivery. The results of the study are intriguing, but there are a few methodological issues that could be clarified to improve the paper.

Abstract

1) Provide units for the T1 25OHD and pregnancy loss association. The OR of 0.99 is for what amount of increase in 25OHD?

2) Consider adding gestational age range of pregnancy losses in lines 34-35.

3) Lines 38-39. For reference, it would be helpful to include the measure of 25OHD in ng/ml.

Methods

4) Please add Ns to the first paragraph.

5) Consider including a Figure to show the total enrollment in the study and how women were excluded from the analysis sample consistent with STROBE guidelines for reporting results (https://www.strobe-

7) Related to the above, why were women who terminated their pregnancies excluded from the analysis of pregnancy loss? I believe methods have also been developed to account for this competing risk. (Reprod Toxicol. 2008 Sep;26(1):31-5. doi: 10.1016/j.reprotox.2008.06.006. Statistical methods for estimating the probability of spontaneous abortion in observational studies--analyzing pregnancies exposed to coumarin derivatives. Also see: Wilcox A, Fertility and Pregnancy: An epidemiologic perspective. Oxford University Press, 2010, 157-158.)

8) Line 103, "SGA was defined as weight or length at birth <2 SD…" I think the author's mean, ">2 SD," as in a birth that was MORE than 2 SD from the mean was considered SGA?

9) It sounds like there are two different definitions of "SGA" one for weight and one for length? Is that correct, or were both short and light babies combined to make one category of "SGA"? Would the authors clarify this outcome?

10) Was it possible for SGA pregnancies to also be preterm? I am not sure that the LBW outcome adds anything to this paper and could be removed, given the inclusion of SGA and preterm delivery.

11) Line 103-109. The authors describe their outcomes before defining how gestational age was estimated, it would help to have that information here.

12) Also, how was gestational age estimated for miscarriages? The authors have medical record information which presumably includes gestational age for miscarriages?

13) Line 114. The third trimester blood sample was drawn after gestational week 31, were any preterm births delivered prior to week 31?
Would the authors explain the creation of the "season of conception" variable? It only includes two categories and appears to combine spring with winter and summer with fall? Rather than isolating summer (April to September)? (For example, see Lundqvist et al. PLoS One. 2016; 11(3), Vitamin D status during pregnancy: A longitudinal study in Swedish women from early pregnancy to seven months postpartum.)

Lines 143 to 146. Please clarify the referent groups for each outcome. For example, was SGA compared with AGA alone or AGA and LGA combined?

Line 144. Please define "change in 25OHD" is this a continuous value? Was T1 25OHD subtracted from T3 or the other way around?

Line 149-151. "Tobacco use and vitamin D supplement use were also investigated as potential confounders but did not show any confounding effect..." I do not believe that vitamin D supplements themselves are in truth confounders, but rather a surrogate for the exposure (similar to an instrumental variable), thus they should not be adjusted for. However, I am confused by this statement? Can the authors hypothesize why supplement use is not a "confounder"? Vitamin D supplement use should be a good predictor of vitamin D status, and if vitamin D is related to the birth outcomes, I would expect supplement use to also be related? (Perhaps some of the text from the Discussion could be moved here to help explain this confusing finding?) It might also help to describe what was captured as a "supplement". Were these multivitamins? Prenatal vitamins? Cod liver oil? What were women in this study using as supplements? Supplements containing multiple vitamins/minerals could be confounders, thus the need for a bit more description.

Line 152-153. The sentence "Correlation between T1..." is confusing as we are not told how change in 25OHD was defined in this analysis? Was it absolute value or did values range from a decrease over time to an increase over time? A negative correlation suggests that as T1 25OHD increased, the "change in 25OHD" decreased, but I'm not sure if that means the change in 25OHD is getting smaller, or more negative, and does negative mean a decrease over time?

Line 155. "...due to the small number of cases." Consider adding the number of women/losses here.
Results

20) Line 168. "...of which 37 were light and 56 short..." are the authors referring to SGA outcomes here? If so, it might help to use consistent language (i.e. "Of the SGA deliveries, 37 were SGA by weight and 56 were SGA by length").

21) Lines 176-178. Are these "data not shown"? Please consider including the results of sensitivity analyses in a supplemental table.

22) Lines 181-187. Please specify the comparison group for each of these results.

23) Tables. It would help to see the N's for the results tables. This could be done by including a column before each outcome with the Ns. Alternatively Table 1 could include columns for 25OHD. For example, in Table 3 it is unclear how many births were both SGA AND deficient in 25OHD? Also, be sure to clarify how many pregnancies were excluded from the multivariable model due to missing covariate information.

Discussion

24) Lines 263-264. Was physical activity related to 25OHD status in the women with both measures?

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

No

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.

Unable to assess
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.

I am able to assess the statistics

Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable

Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests.

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments
which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal