Author’s response to reviews

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

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Author’s response to reviews:

Dear editor,

We have addressed the comments of the reviewer below (our current response is "Response 2"). We left the original reviewer comments and our original response (response 1), for clarification.

In addition, two smaller errors have been detected and changed, marked in green in the manuscript (abstract, line 37 and table 3, line 4).

We hope that you are satisfied with our response and these changes.
Reviewer reports:

Anne Marie Zaura Jukic, PhD (Reviewer 2): I appreciate the authors' responses and I have only a couple of residual questions. I've included my original comment and the authors' response for clarity.

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?

Response 1: This has been clarified by adding the word continuous to the sentence (page 2, line 37).

I don't think this answers the question? The OR is comparing one level of 25(OH)D to another, even when fit continuously, thus the comparison might be for a 1 ng/ml or 1 nmol/l increase in 25(OH)D. Can the authors clarify that the OR is for a 1 nmol/l increase in 25(OH)D?

Response 2: We have added the unit. The sentence now reads “T1 25OHD was negatively associated with pregnancy loss, and 1 nmol/l increase in 25OHD was associated with 1% lower odds of pregnancy loss (OR 0.99, p=0.046).”

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

Response 1: We would like to accommodate this suggestion, but this information is unfortunately not available. Pregnancy loss is not determined by antenatal care but by the emergency gynecology ward and these medical records were not included in the ethical approval
for the study. Data on pregnancy loss was based on self-report information by the women and gestational duration at fetal demise was not always provided. We have tried to clarify this in the paper.

I'm sorry, I'm confused - in a later comment the authors state that they have the LMP date for the losses (see comment 6 of the review response)?

Response 2: As stated in the initial reviewer response, we have date of last menstrual period but not the week of pregnancy loss/fetal demise for early losses (which most of the miscarriages were). Due to the organization of Swedish healthcare, early miscarriages are treated/diagnosed by the emergency gynecology ward and we do not have access to those medical records, where the gestational age at fetal demise would be clarified. This means that we can only say with certainty if pregnancy loss presented before or after gestational week 14. The exact week of fetal demise is only known for pregnancy loss after gestational week 14. As stated in the response to the previous concerns about left truncation, we used the date of LMP and the date of enrollment to the study but not the date of fetal demise.

13) Line 114. The third trimester blood sample was drawn after gestational week 31, were any preterm births delivered prior to week 31?

Response 1: Yes, there were a few (N=10) who delivered before the second blood sample could be drawn. This has been added to the results section (page 9, lines 181-182).

It would be interesting to mention of these 10 pregnancies also had low 25(OH)D at T1.

Response 2: We have added this information (1 of 10 was deficient) to the results section, page 10 lines 181-182.

14) 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.)

Response 1: Season was defined by the months that UVB-exposure is sufficient for endogenous 25OHD production in Sweden. This definition is also based on previous data from the current latitude in Sweden (Brembeck P. Determinants of vitamin D status in pregnant fair-skinned women in Sweden. Br J Nutr. 2013;110(5):856-64). This definition of season previously captured almost 30% of the variation in 25OHD concentration, among pregnant women on the current latitude (57-58°N) in Sweden. The study by Lundqvist et al was conducted on a higher latitude (64°N) which might warrant a different definition.

Would the authors add this information and the reference to the paper?

Response 2: This information and the reference have been added, page 7-8 lines 134-136.

15) 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?

Response 1: This has been clarified (page 7, lines 150-152).

I'm sorry, I asked this because I believe there may be evidence of higher risk of LGA for deficient mothers. (For example, see Morales et al. Deficit of vitamin D in pregnancy and growth and overweight in the offspring. International Journal of Obesity (2015) 39, 61-68; doi:10.1038/ijo.2014.165). Do the authors think this is possible, and have they looked at this in their data?

Response 2: It is possible that vitamin D status could be associated with LGA. However, since we have a few cases of LGA (N=47) in the relatively large data set, we have no concerns that the LGA cases would dilute the results for the non SGA group (LGA+AGA).
We do not see any tendencies toward an association between poor vitamin D status and LGA. If anything, vitamin D deficiency might be associated with lower risk of LGA (4% deficiency among LGA pregnancies, compared to 10% among the other women) but this has not been investigated in detail. As LGA is associated more with gestational diabetes rather than placental transport (like the outcomes included in this paper), we do not wish to include LGA as an outcome in this paper.