Reviewer's report

Title: THE CYTOKINE PROFILE OF WOMEN WITH SEVERE ANXIETY AND DEPRESSION DURING PREGNANCY

Version: 0 Date: 20 Sep 2018

Reviewer: Linnea Karlsson

Reviewer's report:

This study aims at investigating the associations between circulating cytokines and major depression (MDD) and/or anxiety among pregnant women. Overall, the topic is relevant, reports from pregnant populations are scarce, the sample size at larger end of the range of the studies in the field, and the manuscript is coherently written by using acceptable English language. The methods for assessing depressive and anxiety symptoms as well as cytokines are standardised and valid, although only a single blood sample (women at different phases of gestation) was used for the cytokine assessments.

I have several major concerns concerning several aspects of the paper, the most crucial ones being related to the group constructions and the availability of confounders (#1-3):

1. One of major issues is the selection on the phenotype/study groups, if I understood the text correctly. It is very difficult to believe that women without depression would all present with so low levels of each of the selected cytokine that this would be the reason for excluding this comparison group (page 5, lines 33-36). The inclusion on non-depressed, non-anxious comparison group would have been especially important in this group of pregnant women where pregnancy and its phase themselves produce variation in the circulating cytokine concentrations. This statement in page 5 also questions the validity of the cytokine assessment method as it really is hard to figure out how it could be the way it is currently written.

2. Related to the above: please, explain, why no group with SD only was included? And what problems does this limitation import to the interpretation of the results? And what is the rationale for the selection of the phenotypes of SA and SA + SD? Why compare these two groups? The rationale is not clear after reading the introduction, which emphasises depression (which is not independently studied here)?

3. The other major issue is the lack of controlling for the use of psychotropic medication, cigarette smoking, and BMI in these groups of patients. For example, SSRI medication, which might easily be more prevalent in the SD + SA group than SA only, is reportedly related to cytokine concentrations (Latendresse et al, 2013). Further, one would expect that if the SA+ SD is more impaired and more ill than SA only, the prevalence of cigarette
smoking would also be higher in that group? What was the proportion of overweight women in each group (and again, here a group free from other SA + SD would have been important).

4. What was the reason for running separate (correlation) analyses in the two groups instead of using a single model with the cytokine concentration as the independent variable and the grouping, Hamilton scores and covariates as the dependent variables? It should be noted that also in the SA group most significant correlations come from the HDRS, not from HARS. Potentially interactions, between the grouping and the Hamilton scores, adjusted by gestational age (at least) would reveal whether it is actually the depression score that drives these effects regardless of the phenotype grouping (which is not on a very strong grounds, re: earlier comments).

5. I may have missed something, but could not find the results were the analyses on cytokine concentrations and psychiatric symptoms were adjusted for the gestational week? It was stated that gwk affected the cytokines (as it should) but no numbers of the adjusted analyses were presented? Or were the parameters of the ANOVA analyses (page 8) those figures - then it should be more clearly stated how the adjustment affected the initial correlation between the cytokines and SA/SA+ SD? This would also limit the number of statistical analyses, albeit multiple comparison was corrected here for.

6. I miss having clear hypotheses at the end of the introduction. Why these cytokines were selected? Why these comparison groups? What was expected?

7. The latter half of the conclusions extends too much beyond the findings of this study. No relations between the cytokine profile and pregnancy outcomes are assessed here, so we really do not know, what the clinical implications, especially regarding screening and treatment are as there are no references for an optimal cytokine profile in pregnancy. Please revise this and retain to the results of your study. This also applies to the conclusions in the abstract.

8. The abstract would improve from adding the rationale for the study and clarifying the setting (the comparison groups) in the methods.

9. There are also issues in the discussion, but as the points related to the methods and presentation of the results are likely to lead to subsequent changes in the discussion, it is difficult to comment the current version in greater detail.
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.

No

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

No

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

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