Author's response to reviews

Title: Risk of Infection and adverse outcomes among pregnant working women in selected occupational groups: A study in the Danish National Birth Cohort

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Author's response to reviews: see over
We are thankful for comprehensive comments. We acknowledge the critical remarks regarding methods and discussion and inaccurate citations. The discussion has been completely rewritten and the list of references has been updated and now includes several of the suggested references from the DNBC as well as a number of other new references. Other references have been omitted so the updated reference list is shorter than the first version and hopefully more focused. We here provide a point-by-point list of the reviewer’s comments and our response.

REVIEWER I

Major Compulsory Revisions

Methods

1) Methods are a little unsatisfactory. The authors link the infection (or some morbidities) with adverse pregnancy outcomes through the selection of specific occupational groups, where the risk of infection is high. But in these sectors the adverse pregnancy outcomes may be due also to other types of exposure (chemical agents, etc.).

We agree with the reviewer in this comment. Thank you very much. To solve this lack we have compared, in each working group, risks of adverse pregnancy outcomes in women who suffered from infections with the risks in women who did not suffer any infection during pregnancy and we have constructed a new table 4 with the results. From this new analysis, as reviewer thought, we observed that there was no association between suffering from infections during pregnancy and the risk of miscarriages, male infant, preterm and very preterm birth, small for gestational age and APGAR <7 at 5 minutes in any of the occupational groups studies. Only in women who work with animals, the prevalence of CAs was higher among children of women who
suffered from infections during pregnancy. We comment extensively these results in the discussion section.

2) References n. 16 and n. 17. We think that for the detailed description of the DNBC study it is better to cite the following article: “Olsen J et al. The Danish National Birth Cohort – its background, structure and aim. Scand J Public Health 2001 29:300-307”. References n. 16 and n. 17 are subsequent studies, and may be cited after (e.g., as a reference for variables related to the adverse pregnancy outcomes).

Thank you very much for this helpful suggestion. These references should be arranged according.

3) Reference n. 19 refers to CATS technique. In the text, the authors say that they use CATI technology. This reference seems to be misplaced. Please, verify the correctness of the reference and clarify this point.

This was an error and we thank the reviewer for his/her thoroughness. We used CATI technology and not CATS technique. It has been corrected in the text.

4) I think that statistical analysis on the risk of infection may be implemented. For example, the number of episodes (for some interview questions) can be analyzed.

We have followed this helpful suggestion. We have implemented the analysis accordingly. We have included a few variables in table 2: the number of episodes of absenteeism due to illness for more than three days, the number of episodes of fever, and the number of episodes of diarrhoea during pregnancy.

5) In the statistical analysis, authors bring together in one group (group E) “all other workers” with “unemployed women”. This could imply a potential bias and a detailed comment on this argument is essential. Did the results change, when excluding the “unemployed women” from the analysis?
The reviewer is right on having commented that the unemployed have different characteristics. Because that, we have eliminated the unemployed women from the group of reference and have re-done the analysis. We observe that the results change very lightly, but we think that methodologically it is more correct.

6) The numbers on population in study are presented in a confusing way: how many women were in the study? In the text (page 7) it is said that 87,708 is “the final study population” but in table 3 it results 83,448 (64,379+8,699+9,151+932+287). The difference is births without adverse outcomes? The same for table 2, the sum is 87,633 (67,894+9,394+9,126+932+287). Moreover, it is said that 90,301 pregnancies (about 90% of total pregnancies enrolled in the study) participated in the first interview. How many of them were cancelled for no contact? It is said that the excluded pregnancies were: 2,425+93+42+24+3+1=2,588. But 90,301-2,588=87,713 which is different from 87,708! If I am correct, clarify these points.

Thank you for helping us with finding this writing errors. We have now reported the right numbers on the study population in the methods section, and we have added an explanatory figure (figure 1).

7) The analysis on adverse pregnancy outcomes is only mentioned in the methods. It seems to be added as a supplementary analysis, secondary to the aim of the study (in contrast of what said in the Background section). I think that this analysis needs to be described in detail in the methods. Moreover, the title of the study does not properly convey what has been found and should be changed in something like: “Risk of infection and adverse outcomes among pregnant working women in selected occupational groups”.

8) The authors do not specify how the adverse pregnancy outcomes were retrieved. Please provide some details in the methods and add some references (e.g., reference n. 16). The adverse outcomes analyzed may be linked to the infections but also to
other risk factors (e.g., exposure to organic solvents?). This point needs a comment in the discussion.

Thank you very much for these helpful suggestions. We have included a new section in which we describe the variables and the analysis with respect to adverse pregnancy outcomes. Furthermore, we have changed the title accordingly. We have included a point in the discussion section regarding other risk factors that may be linked to the pregnancy outcomes, as the reviewer suggests.

Results

9) The fields of table 3 should be further detailed in methods. For example: What are the “Major anomalies”? This is mentioned only in the footnote of table 3 (that they refer to the EUROCAT classification) without any further specification in the text and bibliographic references. Just as the term APGAR<7 that is assumed known without explanation in full.

Thank you very much. All these aspects have been explained in a new section of the methods.

Discussion and Conclusions

10) The results should be interpreted more extensively. For example the statement: “the prevalence of male infants were higher among women who worked with animals” needs to be further commented and, if possible, supported by other evidence. May this finding be due to chance? Further investigations are necessary.

The discussion has been completely rewritten accordingly.

11) For some groups of workers (e.g., laboratory worker, hairdresser, hospital workers) the adverse pregnancy outcomes were already analyzed in other studies for the same cohort (DNBC). This should be commented and discussed.
The list of references has been updated and now includes several of the suggested references from the DNBC as well as a number of other new references.

12) The discussion merely addresses the content of paragraphs of the results section. Limits and strength points are only mentioned. I think that some implications that could derive from these limitations (or strengths) should be examined. The discussion has been revised accordingly.

13) A comment on the interview-related bias and on the selection of occupational groups should be added (more extensively).

14) The comment on the self reported bias should be deepened. How can this affect the results? Same for the non-use of a JEM. A more accurate discussion and proper references are required.

15) The fact that “only about 60% of those invited chose to participate” (page 5) needs a comment (may represent a limit). See reference n. 18.

16) The mean gestational age at time of interviews (16 and 30 weeks) may influence the results? Add a comment. Following these suggestions in point 13 to 16, a paragraph commenting the weaknesses of the study has been included at the end of the discussion section.

17) A comment about major preventive measures currently in force on health protection of workers (especially during pregnancy) from exposure to infections in Denmark might be added. A comment has been included.

18) The conclusions are too brief. Add some sentences on the relevance of the study. Thank you very much. We have extended the conclusions, including some references to the relevance and the originality of the study.
Minor essential revisions

1) Abbreviations should be defined when first used, if not provided in the list of abbreviations (e.g., CATI, APGAR). Please, spell out these terms.

2) Add the page number in the manuscript.

Abstract

3) Page 3, 4 lines to the end: the CI needs a digit after the dot (CI:1.0-1.???).

4) The sections of the abstract are not well balanced. Shorten the section of results.

Background

5) Page 4: References 2 and 3 are inverted?

Methods

6) Page 6, line 12: Please insert interquartile range!

7) Page 6: The list of interview questions in the text is wrong: there are 8 questions and not 7 (a number is missing “if she had had cold score or genital herpes (yes/no)”

8) Page 6, line 19: “cold score”: Did you mean “cold sore”?

9) Page 8, line 6: “20.”? Please, insert a digit (“0”) or delete the dot.

Results

10) Page 9, line 3: the word “groups” is repeated.

11) Page 9, line 6: delete a dot.

12) Page 9, 2 lines to the end: CI needs a digit after the dot (CI:1.0-1.???).

13) Tables are difficult to read (numbers are sometimes divided into two lines). Format the tables to display each entry in a single row.

Discussion

14) Page 12, line 3, sentence: “We did not see these associations in this study”. What kind of associations was not observed in this study? I think that the authors have not analyzed the association between cystitis and adverse pregnancy outcomes. Clarify this assertion.
15) Page 12, line 12, sentence: “Our results suggest that .... , women in specific occupations may still be at increased risk of infections during pregnancy”. I think that it must be specified that the increased risk of infections (during pregnancy) was observed between workers in specific occupational groups (highly at risk of infections) and the “other workers”.

References

16) References should be cited in the order they appear in the text and arranged in numeric order in the reference list. Instead, in the text, it is cited first the number 1, then number 4 and 12 and so on (they are not in numerical order).

17) The reference list should show only the references cited. Instead, the range of references [20-23] and [25-28] do not seem to be cited in the text.

18) If there are more than one reference to support an argument, it is advised to cite only the more recent (e.g., 34, 35; or 38, 39 and 40).

19) Check the formatting of some references (e.g., n. 7).

We have now corrected the Minor essential revisions and we thank the reviewer for his/her thoroughness.

Discretionary revisions

1) A supplementary analysis separating “unemployed women” from “other workers” might be performed.

As the reviewer suggests, these new analysis has been done, and the results commented.

REVIEWER II

1. In the article about possible infections and risk of pregnancy outcomes the main finding is that there are some (small) increased risks at the epidemiologic level in this large sample. I assume that the pregnancy outcome variables have a higher
validity than the exposure variables. I would therefore advise the authors to modify the ms. somewhat accordingly.

Thank you very much. We have followed this helpful suggestion and have revised the ms accordingly.

2. Abstract: Re write the background. You have NOT looked at infections, but at risk of exposure to potentially infective agents. There is not a high risk, but an elevated risk. The overall population risk is relatively small.

The reviewer is right. We have re-wrote the background of the abstract accordingly.

3. Background: In the Nordic countries, pregnant women are often employed, but also often on sick leave certificate. The level of exposure is related to type of work, but also to presence in the work place. This dilemma is not addressed in this paper.

Also: working in pregnancy is also a balance between risk to the fetus and risk to the mother, and discomfort and problems for the mother as well. The reviewer is right. We have included a comment in the discussion section: A high level of sick leave during pregnancy has been reported (ref Kaerlev et al). During sick leave the women were not exposed to infections at work, and this may have underestimated our associations. Viral infections may be more complicated than bacterial. In this paper, this is not addressed. Also, differentiate between exposure to infective agents, subclinical infections and manifest infectious disease with symptoms. The risk factor here is elevated potential exposure to infective agents.

4. Population: Between March and November ......pregnant women in Denmark in early stages of pregnancy were invited (it is not the GP who is early pregnant....).

This was an error and we thank the reviewer for his/her thoroughness. It was corrected in the text.
5. Infection Variables The variables are self reported. Absence is only noted for infections, and does not capture lesser exposure, nor problems with subclinical infections. One possible bias that is not adequately addressed, is that health workers may be more prone to detect infections (urinary tract infections by access to urine stix, for example) and therefore either over-report or more adequately repost levels of infections, while other workers may under-repost.

The reviewer is right. We have included a paragraph commenting this weakness of the study has been included at the end of the discussion section. Also, we have extended the analysis and have compared, in each working group, risks of adverse pregnancy outcomes in women who had suffered a real infection with the risks in women who did not suffer any infection during pregnancy and we have constructed a new table 3 with the results.

6. I am also curious to hear how condylomata can be associated with workplace exposures, as it is supposed to be a sexually transmitted infection.

The reviewer is right and we have eliminated this variable from the analysis.

7. Other variables: you state that: "low" category included unskilled workers.......I would rephrase, as most workers have skills, even if they are not formal skills. I would call them workers with no formal skilled training.

The text has been corrected accordingly.

8. Results: I assume the tables and statistics are adequate.

10. Discussion: My above comment on bias may apply here. The study would have been stronger if the infections were observed or diagnosed, but they are not. Thus, the validity of these variables are somewhat questionnable and potential biases should be debated. The increased risk, both absolute and relative (odds) is not very high. The job
descriptions in this study is also broad and not very specific. Thus, a variety in job tasks can drive results in both directions.

In the discussion section we have commented the new results (table 4).

9. The statement on: "exposure to infections during pregnancy ....may be reduced by changing work tasks" is very unspecific. It may be taken out or replaced with a different statement: "Where there is known infection exposure risk, a change in work exposure may have to be achieved to job task rotation or sick leave absence....." OR SIMILAR.

10. The text has been corrected accordingly.

11. The conclusion is wrong. The main finding here is not about exposure to infections, but on outcome of potentially exposed people. Infections have NOT been diagnosed nor verified.

The conclusion was corrected accordingly.