Reviewer's report

Title: Effect of prenatal anxiety on lower respiratory tract infections modified by ROS-related genes

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Reviewer: Elodie Merlot

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This is an interesting prospective study, well written, investigating the influence of maternal trait of anxiety on the occurrence of respiratory diseases during the first year of life, in relation with polymorphisme of a few genes related to immunity (CD14) and anti-oxidant control (glutathione-S-transferases). This study deserves to be published. However, several points should be improved.

Major compulsory revisions:

1. My first main remark is that authors argue that they are looking at the effects of prenatal stress on respiratory tract infections (RTIs). However, as explained in the Methods section, they used the state trait anxiety inventory (STAI) score that assesses a personal characteristic of the mothers, which is expected to be the same during pregnancy and after delivery, even if the questionnaire was filled during late pregnancy. Thus babies from anxious mothers were exposed to the stress of having a stressed mother during fetal development, but also during the first year of life: this is not prenatal but perinatal stress. At the very end of the discussion, authors assert that they adjusted the results for the exposure to maternal post-natal anxiety. It is hard to understand this could be done, since the STAI was measured only once at 36 weeks of pregnancy, and since no other indicator of post-delivery maternal anxiety was included in the statistical analysis presented in the statistical section. Please clarify this point by either being more accurate in the method section and post-natal indicators of anxiety, or removing the last assertion of the discussion. If the second option is chosen, this means that authors investigated the effects of a peri-natal (pre- + post-natal) stressor but not a prenatal stressor only. The title, abstract and text of the article (especially introduction) must be corrected in that direction.

2. A second major criticism is that the final number of mother/child pairs included in the study is not clear at all from the method section. Furthermore, the criteria of inclusion and exclusion from the study are described in another published article, but not in the present article. This is severely missing.

Minor Essential Revisions

Abstract:

3. The abstract should specify that the respiratory diseases were recorded during the first year of life.
Background:

4. The common pathway of oxidative stress to prenatal stress and RTIs is asserted in the introduction without any reference from the literature. This idea requires to be developed more and supported by appropriate references, maybe by shifting some parts from discussion to the introduction.

5. Similarly, the role of glutathione and glutathione S transferases (GST) in antioxidant and stress responses must be described (even briefly) to help a naïve reader regarding oxidative stress. The nature of the polymorphism of the different GST must be described (that some have a one or two nucleotide variations, some have copy number variations) and the relationship of this polymorphism with anti-oxidant capacities of the individuals must be shortly but accurately described. Same remark for CD14 polymorphism.

Method section:

6. Please give more information on the women and infants enrolled in the study. The description of the cohort is an important element that should not be given in another article but present in this one also.

7. Are the descriptive variables of Table 1 the only descriptive variables collected from the study population? Important data when regarding maternal prenatal influence, infant development and the occurrence of respiratory diseases during the first year could be: maternal body mass index, if the mother had a professional activity (during and after pregnancy), presence of older siblings at home (parity of the mother), birth weight and growth during the first year of life, if children were spending some time at the day care in contact with other children or raised at home.

8. As said above, the criteria of inclusion and exclusion from the study must be described. Furthermore, the way of exclusion of mothers: 809 women minus 39+6+31 makes 733 and not 631. What were the reasons of exclusion of the remaining 102 women? Among the 631 women, 440 completed the questionnaire. It is not explained then why only 394 children where finally genotyped.

9. The assessment of 1 year outcome variables section omitted to say that children were blood sampled for genotyping (or was it a birth?).

Statistical analysis

10. Authors omitted to explain for which descriptive variables the logistic regression was adjusted except parental history of allergic diseases. How was made the choice of including or not the possible confounding variables? Where the other variables tested and removed from the model in a second step? The result of the statistical test leading to the excluding of these confounding factors from the logixtic regression could be added in a column in table 1.

Results:

11. In Table 1 and all over the results section, it is unclear whether the Lower
respiratory tract infection variable (and associates frequencies and odds ratios) included or not bronchiolitis. It should be specified everywhere: “Lower respiratory tract infection (including bronchiolitis)” or “Lower respiratory tract infection (excluding bronchiolitis”).

12. Table 2: The adjusted and unadjusted results for lower RTI are exactly the same. Is there a mistake? Same question for bronchiolitis.

13. The number of patients used for building the tables 3 and 4 is different (207 vs 205 low STAI score mothers, 187 vs 186 high STAI score mothers); Obviously, some biological samples were lost for estimation of copy number variation of GSTT1 (table 4). This should be clearly stated in the genotyping or the statistical section of the method section.

Discussion:
14. The discussion contains some assertions without bibliographic references (lines 278, 279, 293).

15. Line 314-15: why the more severe characteristics of LRTIs may account for their increased risk?? Develop and argue this hypothesis.

16. Line 319: why using a birth prospective cohort was a limitation of the study?

17. Line 325-328: this is indeed an important question; see my comment at the top of this report.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests: I have no competing interest, I am not working in the medical biology field.