Reviewer’s report

Title: Para-occupational exposure to pesticides, PON1 polymorphisms and hypothyroxinemia during the first half of pregnancy in women living in a Mexican floricultural area.

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Reviewer: Julie Herbstman

Reviewer’s report:

In this report by Torres Sanchez et al., the authors evaluate the association between para-occupational exposure (defined as living with a partner who is involved in pesticide application) during pregnancy and hypothyroxinemia; and whether this association is modified by PON1 polymorphisms. The authors do not find an association between exposure and hypothyroxinemia but do observe significant associations between PON1 polymorphisms and hypothyroxinemia. It is difficult to know how to interpret the significance of this finding independent of pesticide exposure.

Major Concerns:

1. Exposure classification is based on self-reported occupation of partners of pregnant women and was dichotomized as "para exposed" vs. not. There is a lot of potential for exposure misclassification, particularly among pregnant women who live in an area where the primary industry is floriculture. This authors discuss this limitation but in my opinion, underestimate its importance as a possibility for the lack of observed association between exposure and thyroid function, which was the primary goal of this study. This is a major limitation.

2. I am not sure how to interpret the association between PON1 polymorphisms and hypothyroxinemia independent of exposure. The authors do a lot of speculation about why this is important but if the primary role of this gene is to detoxify OP exposure, it is not clear why genotype is important if not to modify the effect of exposure, which it does not appear to do in this population.

3. It is not clear why the authors did not consider thyroid hormone parameters as continuous measures. This would give them more statistical power to observe associations with exposure (and interactions with PON1 polymorphisms).

Minor Concerns:

1. There were ~100 women who were eligible and agreed to participate but were not included in this report due to missing information. While there were no observed demographic differences between those who were and were not included, the authors could employ techniques (e.g., inverse probability weighting) to evaluate the potential bias that this selection might introduce.
2. Lines Page 7, 14-18. It is not clear to me what intra-assay and inter-assay variation refers to. Were control samples analyzed in each batch? It is not clear to me how these ranges were calculated.

3. It is somewhat surprising that over half the study participants were classified as hypothyroid. While it is a common condition, a rate of 54% seems rather high. A relatively small proportion of participants took iodine supplements yet iodine supplementation status was not associated with hypothyroxinemia (Table 2). Are these results consistent with previous reports in this population?

4. What are the implications of the fact that none of the three polymorphisms studied were in Hardy Weinberg equilibrium (Page 11, line 39). Is this unexpected?

5. Page 11, Line 50-52: I would not reword this. Given the 95% CI, I would not consider the observed results to be an increase in hypothyroxinemia.

6. Page 16, Line 37: It is difficult to understand how the authors conclude that there could be a potential interaction between PON1-108CT and OP para exposure when they did not observe such an interaction. If the authors think that this is a real possibility, they should discuss why they did not observe it. If the authors believe that their study was underpowered to detect this interaction, they should provide a power calculation to demonstrate how many women they would potentially need to observe this association.

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