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: Helle Andersen

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ENHE-D-18-00411

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

The study is based on 381 pregnant women (< GW 17) living in a floricultural area in Mexico where pesticides, inclusive organophosphates (OPs), are routinely used. Associations between hypothyroxinemia and PON1 genotype and para-occupational pesticide exposure were investigated. The MS is mostly well written, but the aims and hypothesis of the study are less clear. I have some concerns mainly related to the exposure classification and the statistical analyses as listed below:

Pesticide exposure classification

The women were classified as para-occupationally exposed if their partner was occupation ally exposed to pesticides but since they all live in a floricultural area and probably have a higher "background exposure level" it is not oblivious that a classification based on the partners "take-home exposure" is meaningful. Biomonitoring data would have strengthened the study but since such data are not available more information on the exposure situation are warranted to evaluate the risk of exposure misclassification: a) residential exposure - did all the women live in close proximity to pesticide floricultural areas? b) partner’s exposure - work function, which pesticides, were OPs used by all the partners? c) was the exposure different between summer and winter? d) did the families report residential use of pesticides/OPs?

Statistics and results

A high fraction, 54%, of the women in this study had hypothyroxinemia. Iodine deficiency (even mild) is a risk factor for hypothyroxinemia and accordingly "consumption of iodine supplements from the 3 months before pregnancy to the date of the interview” was included as a binary covariate (Yes or No). However, it is not explained how iodine supplements for a shorter period was handled, i.e., if a woman took supplement from 1 month before pregnancy - was she then categorized as No? Please clarify.
Compared to winter sampling, a higher percentage of those who gave samples in summer had hypothyroxinemia (Table 2). Did use of pesticide deviate between summer and winter and how? If season is related to pesticide exposure level, "season" would be an obvious potential confounder, but this variable was apparently not included in the data analysis, why?

At page 11 the authors states that "None of the three studied polymorphisms was found to be in Hardy Weinberg equilibrium;"

How did the authors take this result into consideration in the further data-analysis?

The authors further state that: "no linkage disequilibrium was observed among the three polymorphisms".

Other studies report significant linkage disequilibrium between PON1 192 and PON1 55. Therefore, some data illustrating the inter-individual distribution of the polymorphism would be relevant to illustrate the lack of linkage disequilibrium.

In Table 3, the associations between para-occupational pesticide exposure and hypothyroxinemia were adjusted for maternal PON1 genotype and associations between PON1 genotype and hypothyroxinemia were adjusted for para-occupational exposure (according to the Table footnote). Please explain the rationale for these adjustments and whether the ORs were affected by these adjustments.

The crude results (unadjusted ORs) should be included in Table 3 and 4 to provide information on the robustness of the associations.

Discussion

Some discussion of the high percentage of women with hypothyroxinemia in relation to the general population would be relevant. Is this fraction (54%) higher than in other areas in Mexico or representative for Mexico? What is known about the iodine intake in Mexico or the specific region compared to the levels recommended for pregnant women by the World Health Organization (250 mcg daily).

According to the last section (before the conclusion), the authors adjusted for both season and iodine supplementation but conclude that these variables did not confound the associations. Does this statement mean that the crude associations were changed less than 10% for each of these variables? Please explain.

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