Reviewer's report

Title: Birth after preeclamptic pregnancies: association with allergic sensitization and allergic rhinoconjunctivitis in adolescence. A historically matched cohort study.

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Reviewer: Franca Rusconi

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In this paper the authors looked for an association between maternal preeclampsia and allergic disorders, sensitisation, asthma and lung function in adolescence.

They found an association between severe preeclampsia and allergic rhinoconjunctivitis and elevated IGE levels in offspring, while no association was found with asthma and lung function.

The topic is an important one, as there is a growing interest in early-life exposures and outcomes such as allergy and asthma.

As the authors point out there are no data so far on an association between preeclampsia and allergy in offspring. However, biological plausibility, as the authors also agree, is not so clear, so we need to be cautious before considering such an association as a causal one. I am particularly worried about the fact that the authors possibly selected adolescents with allergic symptoms (mothers/adolescents who are atopic could be more willing to participate) and that in the analysis they do not correct for maternal atopy.

I have some major points to raise (major compulsory revisions)

1. In the Introduction the authors should better discuss the topic of the relationship between preeclampsia, BPD, and childhood wheezing, not as an inflammatory problem. I would suggest to delete the phrase starting with “Both wheezing and asthma...inflammation”; this could be substituted with “Preeclampsia has been also associated to an increased risk of RDS and BPD in preterm infants and to recurrent wheezing in a general population of pre-school children”. I would further discuss how the pathophysiology of these conditions could be due either to an increased soluble antiangiogenic factor (this has been demonstrated for BPD, as correctly stated by the authors) or by a congenital reduction in airways calibre/compliance in particular in IUGR/SGA infants.

Possible additional references for these observations: Gagliardi et al, Pregnancy disorders leading to very preterm birth influence neonatal outcomes: Results of the population-based action cohort study. Pediatr Res 2013;73:794-801.

Finally, I would delete also phrases on the short/long term effect of BPD which are not important for the topic at hand, starting from “These are also inflammatory conditions..” to “….irrespective to neonatal disease”.

2. Do the authors know if among mothers who had preeclampsia and who decided not to participate/or whose offspring decided not to, there was a lower prevalence of asthma or atopic diseases in comparison with those who participated? If the authors do not have these data I think: a) they should tell us the reason for not participation; b) they should discuss this point as a possible limitation.

3. The analyses should have been adjusted for maternal atopy, but I suspect that the authors do not have this information. If they have it I would suggest to use a combined variable as a confounder (maternal asthma or atopy); if they do not have data on maternal atopy this is to be acknowledge as a limitation in the discussion.

4. The authors adjust for some variables (birth weight z-score for gestational age, gestational age, caesarean section, and respiratory distress syndrome) which are in fact intermediate between maternal preeclampsia and outcome. For instance, maternal preeclampsia reduces birthweight (increases small for gestational age infants and reduces birthweight z-scores); if smaller infants have a greater likelihood of developing asthma, adjusting for birthweight z-score will “overadjust” and will reduce/eliminate the contribution of preeclampsia to asthma. It is generally believed that one should not adjust for intermediate variables in analysis (e.g. Robins JM, Greenland S. Identifiability and exchangeability for direct and indirect effects. Epidemiology 1992;3:143-155). I would suggest to perform multivariable analyses without these variables.

In addition in the final analysis I would keep important potential confounders such as: maternal asthma/atopy, gender, maternal smoking in pregnancy.

5. Another limitation the authors need to discuss is the very low number of subjects in the analyses; this could be a problem in particular for ever and current asthma, for which the authors did not find an association with preeclampsia. This need to be acknowledge in the discussion.

For ever asthma another point is that the authors did not investigate wheezing disorders in the first few years of life. As they state correctly, these have been related to preeclampsia in previous works; the present study therefore does not contradict previous results, and this should be stressed in the discussion.

Discretionary revisions

1. It is not clear to me if the LR-p the authors report refers to the whole model (exposure + covariates), or if it refers to the exposure only (i.e., if the LR-P tests the joint hypothesis “mild preeclampsia OR=1 AND severe preeclampsia OR=1”); the test relevant for the reader is this last one.
Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
'I declare that I have no competing interests'