**Author’s response to reviews**

**Title:** Intra-amniotic inflammation and child neurodevelopment: a systematic review protocol

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**Author’s response to reviews:**

Dear Dr Moher,

We thank you for the opportunity to review our manuscript.

We also want to thank the reviewers for their thorough review. You will find our answers to their comments below. Changes to the manuscript are highlighted. All authors agreed with the final version of the manuscript.

Best regards,

Amélie Boutin PhD

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**Reviewer reports:**

Editor:

- Is the standardized form already developed? Will this be piloted?
Authors: We had planned to pilot the data extraction form on 3 articles. We added this information in the methods section.

- Will you also perform forward citation screening (papers that cited the included papers) in addition to backwards citation screening (papers that are cited in the included papers)?

Authors: We had not planned on using a forward citation, but we thank the editor for this suggestion. We added this screening process to the methods.

- Will authors assess publication bias?

Authors: We planned on assessing the risk of publication bias through visual examination of funnel plots (added to the text).

- How will the primary outcome, child neurodevelopment, be analyzed? As authors acknowledge there are different methods of neurodevelopment assessment, however the intention is still to pool data. How will this work?

Authors: We detailed our planned analyses:

Characteristics of included studies will be detailed, and relative risks and/or adjusted relative risks between intra-amniotic inflammation and neurodevelopmental outcomes will be reported with their 95% confidence intervals. The various dimensions of neurological development will be pooled separately. We will stratify analyses according to scales used to measure the neurodevelopmental outcomes. Relative risks will be pooled using Mantel-Haenszel method and DerSimonian and Laird random effects, and presented in a forest plot. When adjusted measures of association are reported, adjusted relative risks will be pooled with an inverse variance method and DerSimonian and Laird random effects. If available, means and standard deviations of neurodevelopment scores will be used to compute mean differences between groups and pooled using inverse variance with random effect models. Additionally, if concentrations of intra-amniotic inflammatory markers are available for groups of patients with favourable and unfavourable outcomes, mean differences of inflammatory markers will be pooled similarly.

- Could you specify what you mean with studies with a high risk of bias (for sensitivity analysis). Is this a high risk of bias on one of the areas of the RoB tool, or on more than one e.g.?
Authors: We specified that a study will considered at high risk of bias based on the presence of at least one domain at high risk of bias.

Reviewer #1:

1. Why is the search restricted only to these three databases?

Authors: We think that these three databases offer a large coverage of the scientific literature related to the field and topic. Considering the comment of Reviewer #2, we added CINAHL.

2. There is no gray literature search, which could generate publication bias in the review

Authors: We added that we will search for potentially eligible studies by screening abstracts from conference proceedings published in the Journal of Obstetrics and Gynaecology of Canada, the American Journal of Obstetrics and Gynecology, Obstetrics & Gynecology, and the International Journal of Gynecology & Obstetrics, the American Journal of Perinatology, the Journal of Perinatal Medicine, the Journal of Maternal-Fetal and Neonatal Medicine, the British Journal of Obstetrics and Gynaecology, Pediatrics, Paediatrics & Child Health over the last 5 years.

Reviewer #2:

The purpose of this protocol was to summarize evidence on the association between amniotic inflammation/infection and child neurodevelopment. Authors provided succinct background information detailing the need for a systematic review.

I have a few comments on the BACKGROUND: lines 59-61. I encourage the authors to expand on this paragraph to make it easier for the reader to better understand the intended meaning.

For example:

a. Line 59: Yoon et al. observed that elevated amniotic interlukin-6 or interlukin-1 beta, INDICATORS OF INTRA-AMNIOTIC INFLAMMATION, in women with PTL….

Authors: We thank the reviewer for this comment and clarified the paragraph.
b. Line 60: Increased risk of white matter lesion in whom? Mother or child?
Authors: We clarified that the white matter lesions were observed in children.

I invite the authors to consider the following points in the METHODS section:

a. In lines 65-67, authors mentioned that there were few cohort studies measuring the association between intra-amniotic inflammation and child neurodevelopment. Later on in lines 85-86, they mentioned that they will review of literature on randomized trials and cohort studies. I wonder, however, if there are sufficient randomized trials on this topic among maternal and child populations to conduct a review.

Authors: We do expect to find very few (if any) randomized trials eligible to the review, but we did not want to exclude this study type. We think that if randomized trials are available, their findings should be part of this review, at least in qualitative analyses if quantitative analyses are not possible.

b. In lines 147-151, authors listed subgroup analyses for five indicators. Do they anticipate enough studies and samples to conduct all five sub-group analyses?

Authors: We do not expect there will be enough studies for subgroup analyses, but if enough studies are eligible, we will conduct the analyses. We decided to plan such subgroup and sensitivity analyses beforehand, even though there might not be enough studies to conduct them.

c. The primary outcome is child neurodevelopment. Can authors specify the type of child neurodevelopment they anticipate, i.e. cerebral palsy, autism spectrum disorder, learning disability, or attention deficit hyperactivity disorder?

Authors: We specified the various neurodevelopment measurements anticipated.

Neurodevelopment outcomes may include measurements of behavioral development, intelligence quotient, diagnosis of cerebral palsy, learning disabilities, etc. As studies related to this specific topic are uncommon, accepting different methods of neurodevelopment assessment (e.g., Bayley III scale, Stanford Binet Intelligence Scale, Rapid Neurodevelopmental Assessment, Ages and Stages Questionnaire, Brief Infant-Toddler Social and Emotional Assessment)
d. Information source: authors can consider adding CINAHL to their list of databases for peer-reviewed literature.

Authors: We added the database to the list.

e. Eligibility criteria: what is the time reference on searches conducted in this review? Will authors consider all peer-reviewed literature from inception to date? Or will they limit the search to a particular date?

Authors: We considered the literature available from the inception of the databases up to November 2017.

f. Eligibility criteria: Do authors anticipate studies published in other language than English? How will they deal with articles published in a different language?

Authors: We specified that no language restriction will be applied and a translation will be obtained for articles written in languages other than English, French or Spanish.