Reviewer’s report

Title: Safety classification of herbal medicines used among pregnant women in Asian Countries: A Systematic Review

Version: 0 Date: 09 Jun 2017

Reviewer: Angela Lupattelli

Reviewer's report:

Thank you for giving me the opportunity to review this paper. The authors reviewed the literature to identify the most commonly used herbs in Asian countries, and assessed their safety in pregnancy used three references sources. The topic is interesting, however there are several concerns that should be addressed by the authors.

One general comment is about the title of the paper, formulation of the aims and methods section. In the title please consider rephrasing the word "concerns" since there is little evidence about the negative effect of herbal remedies in pregnancy, and the findings of the authors are very much dependent on the reference sources used to assess the safety. By reading the Aims, the reader gets the impression that the literature review has been done on prospective cohort or case-control studies that assessed pregnancy outcomes following in utero exposure to herbal remedies. However, later on in the paper, it becomes evident that the paper had two distinct aims: first, to systematically review the literature to obtain information about the most commonly used herbs in pregnancy in the Asian countries; second, to assess the safety of these common herbs using three references sources. Please consider structuring the Aims and the Methods section accordingly to enhance clarity.

Abstract:

Please rephrase the aim according to my previous comment, since this paper was not a systematic review of the literature on prospective and/or case-control studies assessing the safety of herbal remedies.

In the conclusions the authors state that none of the reviewed studies assessed adverse effects of herbal remedies in pregnancy; I feel this is not surprising since the authors only reviewed cross-sectional studies, which cannot assess any measure of negative effect of herbs on maternal-fetal health.

Background: Line 64-67: would it possible to indicate what herbal remedy/remedies were found to increase the risk for SGA and miscarriage?
Methods:

I feel the Methods section should be better organized in light of my first general comment.

Please consider removing or shortening the text from line 85 to 90 since this goes beyond the scope of the investigation. The authors should consider to describe in a better way why and for what purpose they chose to restrict the review to cross-sectional studies.

The author also assessed the quality of the cross-sectional studies included, however there is no information on how these studies defined a herbal modality. Was the definition comparable across studies? How did the authors ensure that all these studies used same definition of herbal remedy?

Line 94: please indicate whether two or more independent persons did the literature search.

The section on the Safety Documentation of Identified Herbs should be more systematically described. First, the authors should describe why and how these three references sources were chosen to assess the safety of herbal remedies. These sources may be out of date given their publication dates (2004 and 2007). In a previous study (Kennedy et al., 2016) classifying the safety of herbal remedies in pregnancy in a European, American and Australian population the following sources were used: the textbooks "The Essential Guide to Herbal Safety", "Herbal Medicines in Pregnancy & Lactation", "Botanical Safety Handbook", and "Botanical Medicine for Women's Health", with addition of the Natural Medicines database. If a particular herbal medicine was not listed in the above mentioned reference sources, additional sources were used; Handbook of Medicinal Herbs and PDR for Herbal Medicines. Could any of these sources be relevant for the current study?

Please consider using PubMed/EMBASE to search for safety studies on herbs rather than Google Scholar. The way these search were conducted should also be described in a more appropriate way.

What was the level of agreement across these sources with respect to risk in pregnancy? The authors should consider stating what criteria were applied when discordant information was given in the sources on the same herb. Was any of the reference sources used as primary?

The authors should also consider describing what it is defined by the letter classification A, B, etc. in the Methods (and not only as footnote in the Tables). If this letter system is derived from the FDA risk categorization, this should be clearly stated. However the FDA has since 2016 a
new classification system for medication exposures in pregnancy, since the letter system was obsolete and not informative.

It is unclear to the reader on what ground the final "potentially harmful" classification was based; did it consist of any letter category other than A? If this is the case, I feel it will produce misleading results, particularly in relation to category B. Beyond, as stated above, the letter risk categorization is not so informative in terms of what is known on the safety of medication exposures in pregnancy.

Results:

It would be relevant to provide information on the plant part, type of extract, dose form, dosage etc. if that was available from the reviewed studies. This information should also be considered in terms of safety assessment of herbs. Same comment applies to the timing of use of the assessed herbs in pregnancy. The risk for congenital anomaly, for instance, may not be relevant when the herb is taken in the third trimester.

The authors classified 18 out of 31 herbs as potentially harmful. I find this proportion quite high. I feel this is a consequence of the reference sources used. For instance, in the study by Kennedy et al. (2016), "peppermint" and "chamomile" were classified as safe herbs in pregnancy when the reference sources listed earlier were used. Could the author expand their safety assessment using more reference sources, such as text books specifically on herbal exposures in pregnancy?

The authors should also clarify why in Table 4 herbs could have multiple classifications. If this is a consequence of discordant information between sources, it should clearly stated how this issue was solved. For instance, chamomile was classified as B and D, but the authors considered it as potentially harmful herb in pregnancy. In this instance, I feel there is some lack of reflection about the dose of chamomille use.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable

Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?
If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal