Author’s response to reviews

Title: Maternal plasma levels of oxytocin during physiological childbirth – a systematic review with implications for uterine contractions and central actions of oxytocin

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Response to BMC

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To BMC Pregnancy and Childbirth: Dear Editor,
Dear Kedra Wallace,

Thank you for the opportunity to resubmit and improve our manuscript. We are very grateful for the reviewers’ comments and have taken them seriously into consideration.

Below we will respond to each of the comments and questions raised by the reviewers. We have also edited the manuscript with one of the authors who is a native English speaker.

We hope that our responses will be sufficient to allow publication of our revised manuscript in BMC Pregnancy and Childbirth.

Best regards

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On behalf of the authors responding to revisions

Reviewer reports:

Keiichi Kumasawa (Reviewer 1): In this investigation, the authors reviewed and integrated the extracted 20 articles that investigated the profiles of oxytocin levels, the relationship between uterine contraction and oxytocin levels, the central action of oxytocin, and the effect of synthetic oxytocin.
This study is very important in finding and recognizing the historical and high-quality studies and integrating these evidences about oxytocin.

And in the revised manuscript, the authors responded to my comments.

Thank you for your valuable comments during the review process.

Kedra Wallace (Reviewer 3): Methods:

- Please define what is meant by physiological labour.

  Spontaneous vaginal birth without any medical interventions.

  Answer: Women having a spontaneous labour and birth at term, without complications and without medical interventions. This has been added to the manuscript.

- How were 710 duplicates removed? If all of the publications in CINAHL (n=561) and PsycINFO (n=102) were also repeated in Pubmed that only equals 663. Perhaps the search terms used should be added to the text, and if the authors mean that 4,749 publications yielded from the search terms and among those there were 710 duplicates then that should be clarified. I think that is what is meant, but it is not clear.

  Answer: Thank you, we have revised the flowchart in the method section and in Figure 1, in line with your suggestions.

- Please remove the word an from line 10 on page 7

  Answer: thank you, this is done.

- The statement about RIA being included since it was the most reliable technique is inappropriate since this is a review of manuscripts. The authors did not choose what technique was used to assess oxytocin, rather they are reporting on what other authors used. Likewise the following lines, about the reliability of oxytocin measurements in saliva and other fluids are also in appropriate as this again is a systematic review. They should be definition of a systematic review be included, especially in light of more recent work using saliva and other bodily fluids to assess oxytocin. If the authors care to make a suggestion about the validity or the ease of using these other fluids then that should be done in the discussion.
Answer: No studies in which ELISA was used was identified in the search. We have changed the text in the article in line with this. In addition, RIA is the technique of choice for measurement of oxytocin levels. ELISA has been severely criticized as being unspecific.

As indicated in the title, in the present article we review only oxytocin levels in plasma. Therefore, any paper in which oxytocin measured in saliva and urine was not included.

The reasons for this decision are very specific. Oxytocin in plasma to a major extend reflects oxytocin of hypothalamic origin released into the circulation from the pituitary. We were interested in circulating oxytocin and its relationship to uterine contractions and also because oxytocin is released in parallel into the circulation and the brain from the supraoptic and paraventricular nuclei during labor and birth. Therefore circulating oxytocin levels in part reflect the release and effects of oxytocin in the brain during birth. There are no data that show that oxytocin released in saliva and urine represent oxytocin of hypothalamic origin. Due to its chemical properties’ oxytocin is not likely to pass from blood to saliva in any significant amount. Furthermore, oxytocin like other peptides are degraded to fragments in the kidney. In addition oxytocin is produced in many different organs and cell types in the body and therefore oxytocin measured in saliva and urine may have a local origin.

- Maybe I missed it but were there ZERO papers that met the inclusion/exclusion published after 2001? If so then how does the results from this systematic review relate to what we practice/teach/theorize in 2019?

Answer: Yes, it is the fact, and therefore it is so important to bring this paper performed to professionals around childbirth. The results are of high quality from a technical and methodological point of view and would in fact be hard to reproduce today until completely new types of measurements are available.

Results:

- The comments made after each review of a manuscript make this systematic review appear to be a review of oxytocin assay. Is that the goal of the authors? If so this needs to be clarified. If not these comments need to be removed, as they are unnecessary.

Answer: thank you for useful comment. The comments about the methods have been moved from the results text section to table 3.
Discussion:

- Again it's not clear what the authors want the readers to understand from this review. Is it the central actions of oxytocin (as the title would imply) or the utility of RIA vs other bioassays. Either way, the manuscript needs to pick just one of these topics and be condensed greatly to reflect this topic.

Answer: The role of oxytocin for uterine contractions and for possible central effects of oxytocin is discussed, not part of the results.