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

**Authors:**

Kerstin Uvnäs Moberg (k_uvnas_moberg@hotmail.com)

Marie Berg (marie.berg@fhs.gu.se)

Anette Ekström (anette.ekstrom@his.se)

Sarah Buckley (drsarahjbuckley@gmail.com)

Soo Downe (SDowne@uclan.ac.uk)

Eleni Hadjigeorgiou (eleni.hadjigeorgiou@cut.ac.cy)

Bogumila Kielbratowska (bogumila.kielbratowska@gumed.edu.pl)

Alicja Kotlowska (kotlowska@gumed.edu.pl)

Luise Lengler (luise.lengler@t-online.de)

Fatima Leon-Larios (fatimaleon@us.es)

Bengt Lindström (bengtblind@hotmail.com)

Claudia Meier Magistretti (claudia.meiermagistretti@hslu.ch)

Zada Pajalic (zada.pajalic@hioa.no)

Anna Dencker (anna.dencker@gu.se)

**Version:** 3  **Date:** 12 Jan 2019

**Author’s response to reviews:**

To BMC Pregnancy and Childbirth: Dear Editor,

PRCH-D-18-00653R1

Maternal plasma levels of oxytocin during physiological childbirth - a systematic review with implications for uterine contractions and central actions of oxytocin study.
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

Corresponding author: Anette Ekstrom, RN, RM, Professor in Nursing and Midwifery

On behalf of the authors responding to revisions

Kerstin Uvnas Moberg MD, PhD, Full professor of physiology

Sarah Buckley MB, ChB; PhD candidate

Marie Berg, RN, RM, Professor in Nursing and Midwifery
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. However, a few concerns that need to be addressed by the authors to further improve the quality of this article.

The authors found and reassessed the profiles of oxytocin and maternal physically and psychologically changings.

(Comments)

1. On page 5, line 99, I couldn't understand the terms of "mammalian young". Does it mean "offspring"? The sentence "mammalian young" should be corrected to "mammalian offspring".

We have changed in line with your suggestion.

2. The authors indicated that the variation of serum oxytocin levels due to several assay. Please note that which is appropriate to measure the serum oxytocin levels during labor by RIA or ELISA.

Yes, we agree, therefore we changed the text to clarify this question in the “Methodological considerations” section, as follow:

Enzyme-linked immunosorbent assay (ELISA, EIA) is another type of immunological method used to measure oxytocin levels. Studies using ELISA have obtained very high oxytocin levels, along with different effect patterns, compared to studies using RIA [34]. For example, some studies that used ELISA have found no rise of oxytocin levels during pregnancy [35]. In addition, the validity and reliability of ELISA as a measure for oxytocin levels have been seriously questioned [36]. We therefore decided to only include studies in which oxytocin levels were measured by RIA as this technique is the most valid one.

3. On page 24, line 565, please correct the word from "text" to "text" or "texts".

We have changed this as suggested.
4. On page 30, from line 708 to 713, the authors indicated that oxytocin link to maternal behavior, and inhibition of neurological system such as epidural anaesthesia resulted in blocking maternal behavior and attachment due to blocking of central oxytocin release by nervous system. On the contrary, on page 32, from line 760 to 764, the author indicated that oxytocin gives pain relief via brain opioid system. Which is more dominant among these evidences when pregnant woman receives epidural anaesthesia for pain relief during labor?

We have extensively revised the sections regarding central effects of oxytocin in the brain during labour and birth, including the impact of epidurals. The titles of the new sections are now:

Central actions of oxytocin during labour and birth
Examples of central oxytocin effects during labour and birth

5. On page 35, line 836, please correct from "…oxytocinase," to "…oxytocinase."

We have changed this as you suggest.

6. On page 36, the author described that pulsate administration may help to decrease the total dosage of synthetic oxytocin, and recommended interval of 30-40 minutes administration. If you know the evidences that too high and frequent exposures of oxytocin may occur the down regulation of the sensitivity of oxytocin receptor on uterine myometrium, please add the information of these evidences.

We have clarified this in following sections. The titles of the new sections are now:

Levels and effects after infusion of synthetic oxytocin
Implications for clinical use of synthetic oxytocin in labour and birth

The evidence you asked for is included in references 49 and 62.

7. On this article, please replace from "+-" to "±" using special character of "Symbol" style.

We have changed this as you suggest.
Aviva Lee-Parritz (Reviewer 2): This manuscript attempts to distill information about oxytocin function and effects during labor form a wide variety of smaller studies, via a systematic review.

1. This is not really research, more of a very long and overly written review of the literature, not a meta-analysis. The studies reviewed span a long time frame, with a variety of techniques and outcomes. Is it not clear to me why the authors would comment on old, sub-optimal studies?

We do not agree with the reviewer that this paper is a literature review. In fact, we have rigorously conducted this study as a systematic review according to PRISMA guidelines.

In addition, we do not agree that the data is outdated or suboptimal, as it refers to basic biological findings that remain constant, irrespective of the time of data collection.

We believe that it is very relevant for contemporary maternity care providers, as clarified in the Background section:

Previous studies that measured oxytocin levels during birth were mainly published in the 1970s to 90s. Most of these older studies are of high quality and provide an accurate assessment of oxytocin levels, and would be difficult to perform today because of technical, practical and ethical reasons. It is of importance to bring back this forgotten but highly relevant knowledge to healthcare professionals of today involved in labour and birth. In addition, there are many misunderstandings regarding the effects of endogenous oxytocin and exogenous synthetic oxytocin during childbirth that could be resolved by access to this knowledge, with benefits for clinical care.

2. Page 2 line 45-46: Why look at both of these, and why only if reported?

We are not totally clear what this reviewer means, but we assume it is in relation to including data about oxytocin levels with infusion of synthetic oxytocin.

This is clarified in the “Background” section as follows:

In addition, data from the reviewed studies on plasma levels of oxytocin after infusions of synthetic oxytocin will be included. This will allow comparison between oxytocin levels observed during physiological birth and in birth induced or augmented with synthetic oxytocin.

And also in “Levels and effects after infusion of synthetic oxytocin”

While the use of synthetic oxytocin was not initially the subject of this review, some of the included studies measured oxytocin levels when synthetic oxytocin was infused. In view of the widespread use of synthetic oxytocin for induction and augmentation of labour, we decided to include this information.
In addition, it is advantageous to compare levels of oxytocin in physiological labour and after infusions of synthetic oxytocin that are obtained in the same study, because it allows a more accurate comparison of oxytocin levels under these two conditions.

We believe that it is of critical importance that clinicians administering this drug have an accurate knowledge of synthetic oxytocin dosage, oxytocin levels and differences in effect patterns compared to physiological labour and birth.

3. The writing is laborious, tedious and redundant.

We appreciate this feedback and have now extensively edited the introduction and discussion to improve clarity and brevity and reduce any repetition and redundancy.

4. There is nothing really new here, nor is there anything that a clinician or scientist would use to for clinical care or research plan.

We do not agree with this feedback, as indicated in response to question 1.

In addition, we have extensively discussed the positive effects of oxytocin exerted in the maternal brain in physiological labour and birth in the sections “Central actions of oxytocin during labour and birth” and “Examples of central oxytocin effects during labour and birth”

We have also specifically addressed the question “How can the administration of synthetic oxytocin in labour and birth imitate physiological patterns and effects, as far as possible?” in the sections ”Levels and effects after infusion of synthetic oxytocin” and ”Implications for clinical use of synthetic oxytocin in labour and birth”

5. There was not much difference between the introduction and the conclusions, except that the authors made conjectures about how things might be understood or how administration of oxytocin might be modified for more physiological results, none of which are really supported by the data or by experimentation.

We have edited the introduction and discussion to reduce any repetition and improve brevity, as indicated in answer 3.

We do not agree that our discussion is conjectural as we include many scientific studies to support our findings and discussions. In particular, we address how administration of oxytocin might be modified for more physiological results in the section “Implications for clinical use of synthetic oxytocin in labour and birth.”
6. Page 9 line 195-199. The authors state the studies diverge on almost all aspects and therefore, decided to embark on a narrative description. They do not state why this would be needed or helpful.

We agree that our studies differed and could not be combined easily. We therefore made extensive narrative descriptions of each paper, which allowed us to categorise the data and to summarise and make conclusions, which we present in the figures and tables.

We address why we think this scientific knowledge is needed and helpful in question 1.