Author’s response to reviews

Title: Progesterone in women with arrested premature labor. A report of a randomised clinical trial and updated meta-analysis.

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Author’s response to reviews:

Reviewer reports:

Reviewer #1: Wood et al. have investigated impact of vaginal progesterone (200mg) for prevention of preterm birth in women with arrested premature labor. The study initially targeted 60 patients to include in their study, but only 41 women were enrolled in the trial due to several reasons explain the results section of the manuscript. One of the reasons is that the provider changed its progesterone product. It is important to know why the product is changed? Was the progesterone product used in the study was not effective or is the new progesterone product was an alternative formulation, or same chemical structure but new lot? Even if the new progesterone product is alternative progesterone formulation it should not be a reason to terminate the study as this study also included meta-analyses of studies used 17-hydroxyprogesterone caporate. These should be clarified in the text to better explain the termination reason.

We feel that we have adequately and transparently explained why the trial was terminated. We have added more information lines 117-120

Below, I also suggest some minor changes.

In the abstract section:

- Include patient number analyzed in the clinical trial part of this study.

Already included line 29 of abstract
- Spell out "RCTs" in Selection Criteria. Change as requested

Introduction Section:

- Introduction section is very short. It may include a paragraph describing pathogenic mechanisms of premature birth and/or progesterone levels during pregnancy and term and premature labor etc. We feel the brevity of our introduction is appropriate. There is really no clear proposed mechanism for how progesterone (in humans) is involved in term or preterm labor.

Results Section:

- Meta-analysis: Ultimately, 18 trials (including ours) were identified and 14 were included in the meta-analysis. 4 trials were excluded from meta-analysis (exclusion reasons are given for 3 ), It not clear why the 4th one was excluded.

thank you for noting this should have been 15 as per figure 1. Corrected line 138.

Reviewer reports:

Reviewer 2: PRCH-D-16-00308

Progesterone in women with arrested premature labor. A report of a randomised clinical trial and updated meta-analysis

This study describes the results of an RCT that compared the effectiveness of vaginal progesterone vs. placebo in women with arrested premature labor. The trial was terminated and the results were combined with other studies to perform an updated meta-analysis. Both the trial and the meta-analysis of high-quality trials showed no benefit of vaginal progesterone which is why the authors concluded that progesterone is not effective for preventing preterm birth following arrested preterm labor.

In general, I really like the approach of combining the RCT data to data from other RCTs within the trial manuscript and also their caution against basing conclusions on all available evidence, but to rather focus on the more high quality studies. Additionally, the authors should be commended for their willingness to share their study data in the Open Science Framework.

I do have some, mostly minor, comments, many of which are related to the reporting of the study and meta-analysis.

Major comments

Abstract

1. Main results. Add that the trial was terminated early and indicate what the aimed sample size was, e.g. "after recruiting 41/X women, the trial was terminated prematurely". Changed line 29 abstract
Introduction

2. The authors indicate that they performed an updated meta-analysis, but they do not refer to a meta-analysis that was previously performed. Can the authors either refer to an existing meta-analysis that they plan to update, or simply state that they performed a meta-analysis? Clarified we performed a meta-analysis line 53

Methods

3. RCT. The RCT had two primary outcomes: gestational age at delivery and latency to delivery. Since these were prespecified in the protocol I won't suggest to change this, but it is somewhat uncommon to use two primary outcomes, unless the outcomes are completely different and independent. We wanted to use both as the first gives a sense of clinical significance but the second, even if the first was null, gives an indication of biologic effect. This was pre-specified in the protocol.

Discussion

4. The discussion could be more extensive, e.g. by elaborating on how their results (of the RCT and meta-analysis) compare to previous studies and meta-analyses (e.g. Suhag et al AJOG 20151), what future research should focus on, etc.

Changes made to discussion lines 169-72

Minor comments

Abstract

1. Background. Add "be" after "may". done

2. Search strategy. Add last search date.

3. Main results. Add that the effect of "-0.95 days" relates to a mean difference. Done line 128, 129.

Methods

4. Were the RCT and meta-analysis reported according to reporting guidelines? If so, please add (e.g. CONSORT and PRISMA), and if not, please do so. Added statements line 89 and 115.

5. RCT. Please describe who approached the women to participate in the study. Line 61

6. The secondary outcomes listed in the manuscript are summarized. Consider to write these out in full detail as they are presented on clinicaltrials.gov NCT01286246. Added line 79-81
7. According to Kernan et al. JCE 1999 it is advised to adjust for covariates that is stratified for in the randomization. This means regression analyses should be performed instead of the Mann-Whitney U-test, student's t-test, and Fisher's exact test. To our knowledge this is not universally applied in clinical trials. Additionally, we feel that more complex analysis makes it far more difficult for the average clinician to understand and therefore trust the results. Ultimately, we performed the analysis that we decided on apriori and to change this after the fact would not be appropriate. We appreciate the advice for future trials.

8. Meta-analysis. Was there a protocol of the review/meta-analysis? Was it registered on PROSPERO? Please add this info. The trial was registered but not the meta-analysis as it was only planned on completion of the trial.

9. Please present the specific search strategy in an appendix.

10. Risk of bias was assessed "using standard criteria", but items, e.g. reporting of outcomes, seem to be missing from the criteria. A better risk of bias tool may be the one developed by the Cochrane Collaboration. We prefer a simplified system which has been described in the literature and we have used in a previous meta-analysis2. It is not manifestly different from the Cochrane “risk of bias” tool. It is worth noting that the risk of bias assessment is largely ignored in Cochrane reviews as to our knowledge among the obstetric reviews there are none with subgroup analysis by study quality.

11. The authors indicate that the included trials were graded as "high or low quality". Consider replacing "quality" by "risk of bias". See above.

12. The authors indicate that they will use both fixed and random effects models, but from the methods it is unclear what criteria are used for the choice on the type of model, e.g. based on the level of statistical heterogeneity above a certain threshold. Using fixed effects if no heterogeneity is standard and we do not think requires explanation.

13. Please define "trial quality". As per lines 105-8 as per Juni et al see ref below.

Results

14. RCT. Please refer to appendix figure 1 for the flow diagram of the RCT. Corrected line 125.

15. Line 120. A "+" is missing in "02".

16. Meta-analysis. According to the text 4 studies were excluded (18-14), but Figure 1 indicates there were 3 exclusions. Which one is correct? If there was a fourth exclusion, what was the reason of exclusion? Please make clear why studies were excluded. Noted by other reviewer and corrected line 138,So for the first two exclusions you could say that they focused on acute tocolysis rather than maintenance tocolysis, and for the last on that they focused on women with a previous premature delivery rather than a more genaral group. Additional information line 139
17. Lines 133-136. What were the comparator treatments? How many women were randomized to each of these treatments? This information is supplied as indicated in the manuscript in Table 1.

18. Line 137. Additional information was requested from authors. Can the authors elaborate on the information that was requested? Information provided line 145-6


20. Line 140-141. Was there statistical heterogeneity between the strata of the subgroups? This information should be added to the text. Information is provided in the figures 2-7. We feel this would be very redundant to add to text.

21. Line 142-143. Consider rewriting this sentence as: The proportion of births before 34 weeks gestation was not statistically significant reduced with treatment (OR 0.80, 95% CI 0.60, 1.08; Figure 3). Frankly we prefer the original text

22. Line 153-155. The authors indicate that progesterone was associated with a reduction in risk, but of what risk? Risk of perinatal death? Yes added to line 163

Discussion

23. Line 164. Remove "adequate". Word is not found in line 164

24. Line 173. Low power is obviously an issue of the RCT, but indeed not of the meta-analysis. This is a matter of opinion. Not sure what change the reviewer is suggesting.

25. Lines 177-178. Is there any info on ongoing trials on this subject (dosage)? Additional information added line 194.
