Reviewer’s report

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

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Reviewer: Ewoud Schuit

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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".

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?

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.

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 2015), what future research should focus on, etc.

Minor comments

Abstract

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

2. Search strategy. Add last search date.

3. Main results. Add that the effect of "-0.95 days" relates to a mean difference.

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.

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

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.

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.

8. Meta-analysis. Was there a protocol of the review/meta-analysis? Was it registered on PROSPERO? Please add this info.

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.

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

13. Please define "trial quality".

Results

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

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. So for the first two exclusions you could say that they focused on acute tocolysis rather than maintenance tocolysis, and for the last one that they focused on women with a previous premature delivery rather than a more general group.

17. Lines 133-136. What were the comparator treatments? How many women were randomized to each of these treatments?

18. Line 137. Additional information was requested from authors. Can the authors elaborate on the information that was requested?

19. Line 140. What was the comparator treatment? Placebo? Please add.

20. Line 140-141. Was there statistical heterogeneity between the strata of the subgroups? This information should be added to the 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).

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

Discussion

23. Line 164. Remove "adequate".

24. Line 173. Low power is obviously an issue of the RCT, but indeed not of the meta-analysis.

25. Lines 177-178. Is there any info on ongoing trials on this subject (dosage)?
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

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.

Yes

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.

I am able to assess the statistics

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

Acceptable

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