Author's response to reviews

Title: Arabin Cervical Pessary for Prevention of Preterm Birth in Cases of Twin-to-twin Transfusion Syndrome Treated by Fetoscopic LASER Coagulation: The PECEP LASER Randomised Controlled Trial

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Version: 2 Date: 12 Mar 2017

Author’s response to reviews:

Reviewers comments:

Reviewer #1:

1) Abstract: methods section of abstract, final sentence currently begins "352 women will be included in order to decrease the rate of preterm delivery from 40% to 26%" - should read "352 women will be included in order to decrease the rate of preterm delivery before 32 weeks' gestation from 40% to 26%”.

Agree. No comments. Thank you.

2) Background section of manuscript, lines 38 to 40, sentence beginning "It is obvious that the majority of cases...". I suggest changing this sentence to "Although many cases are delivered prematurely for medical indications (mainly selective intrauterine growth restriction), a large proportion also develop spontaneous preterm labour". You also need to give references for this sentence. I would then make your next sentence "Spontaneous preterm labour in TTTS may be partly due to overdistension of the uterus caused by polyhydramnios, or even uterine manipulation inherent to FLC procedures, neither of which can be avoided." Remove the sentence “These stressors can obviously not be avoided ab initio”
Agree. No comments. Thank you.

Sentence "Spontaneous preterm labour in TTTS may be partly due to overdistension of the uterus caused by polyhydramnios, or even uterine manipulation inherent to FLC procedures, neither of which can be avoided" removed.

3) Methods/design section, aims subsection, second paragraph. Better English expression would be "This is a multicenter study to be conducted in the Hospital Universitari Vall d'Hebron in Barcelona (Catalunya, Spain), the Universitaire Ziekenhuizen in Leuven (Belgium), and the University Medical Centre Hamburg-Eppendorf (UKE) in Hamburg (Germany). All centers have approval from the respective Medical Ethics Committees to conduct the trial." As I presume you have prospectively registered this clinical trial in a clinical trial registry, this should also be stated in this paragraph, and the website details and the clinical trial number/unique trial identifier should be given.

Agree. Thank you.

As suggested, I added the comment: The trial was registered in ClinicalTrials.gov in December 4th, 2011 (https://clinicaltrials.gov/ct2/results?term=pecep+laser&Search=Search). The trial identifier is NCT01334489.

4) Methods section, intervention subsection, first sentence (lines 14-15) - The term "exploration room" is not familiar to me. Do you mean the minor procedures/assessment room on your regular antenatal ward, Delivery Suite or outpatients Department? (the sort of room where you could insert a cervical catheter, have an examination bed to do proper speculum examination etc?). If yes then "in the assessment room of antenatal ward/Delivery Suite/outpatients" (use whichever term is the correct one) I think will be more easily understood by most readers. For the following sentence I would also suggest "the operating theatres" rather than "a surgery room".

Agree. Thank you.

5) Methods section, intervention subsection, line 19 - "with clinical controls every two weeks" - again, I am not quite sure what this means here. I think you most like mean clinical review and ultrasound every two weeks, so I would say that instead.

Agree. Thank you.

6) Methods section, outcome subsection, first sentence - rather than "main outcome" "primary outcome". For the next sentence, where the secondary outcomes are listed, I would also suggest that rather than "neonatal morbidity (with a composite of intraventricular haemorrhage.....)" to use "and composite neonatal morbidity (any of intraventricular haemorrhage,.....)".

Agree. Thank you.
7) Methods section, Statistics subsection, expected sample size paragraph" - The first sentence here is confusing. Suggest to replace with "From a pilot study (reference 18), we based our sample size calculations on the assumption that the pessary will reduce the primary outcome (preterm birth <32 weeks) from 40% in the control group to 26% in the pessary group." Then you can continue with the sentence about study power, although instead of "drop out retain" use "drop out rate", instead of "requested sample size" "required sample size", and "has been estimated to 352 patients" "has been estimated to be 352 patients”.

Agree. Thank you.

8) Methods section, Data analysis, last paragraph (lines 25-26): suggest add a few words to clarify here "We also intend to perform a subgroup analysis according to the cervical length before laser surgery: over 25mm, 15 to 25mm, and less than 15mm”.

We decided to perform the subgroup analysis with these cut-off lengths because 25 mm is around the 5th centile for cervical length for twins less than 22 weeks’ gestation and some groups perform cervical cerclage in TTTS patients with CL below 15 mm


9) Methods section, interim analysis paragraph: The O'Brien and Fleming rule needs to be referenced.


10) Discussion, second paragraph (lines 50-51) - I would leave "no matter the reason" out of this sentence. You also need to give the references regarding the high rate of delivery by 32 weeks in these babies (not just say that many authors have published before). For the next sentence "given the fact that most of these twins are electively delivered at 34 weeks", please also give a reference or references to support this statement.


11) Discussion, 3rd paragraph, line 60 - need reference for statement that rate of spontaneous preterm delivery is very high even if cervical length normal at the time of surgery.


12) Discussion, 4th paragraph, lines 1-3. Again, references regarding bed rest not being useful in twins, and use of cerclage being questioned (I agree these are all correct statements about current knowledge, but they still need to be referenced!).


Reviewer #2:

1) Background well written.

2) Methods: Aims: Well done

3) Participants: The exclusion criteria should be more detailed as: Are the authors including patient that are dilated cervix as>2 cm, TTTS with selective IUGR, patient who have documented contraction on monitor ...etc.


4) Intervention: The author mentioned that cerclage should not be introduced for study patient. What are indications for cerclage in patients who failed pessary? Define pessary failure. If cerclage will be offered for patient with physical exam dilated cervix esp if failed pessary. Esp after the article that is published in Jan 2016 in AJOG about twin cerclage in physical exam indicated patient vs. expectant management.
We do not consider a failure of the pessary. In our experience, in PECEP Trial we had to remove the pessary in only one case because she was a multiparous woman and the pessary was not big enough for her. In PECEP TWINS trial 2 cases required replacement of the pessary but there were no cases of failure.

In spite of recent publications about better outcomes of cerclage indicated by physical exam in twins, cerclage will not be offered. This item was largely discussed when designing the study (before this recent publications) and it was considered that cerclage could mask the results of the trial.

5) Statistics, interim analysis and discussion all are appropriately written.