Peer Review File

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Reviewer 1

Comments to the authors:

Clear and well-written. Kindly address 4 additional issues in the revised manuscript:

1. More outcomes data, esp. beyond mortality and gestational age at birth, would be helpful to the pediatrician readership. What is the current understanding of ECMO, length of stay, and quality of life. Given how long this has been studied, I suspect that there must be some data out there on this.
   Thank you for this suggestion. Unfortunately, most of the published literature focuses mainly on survival and gestational age at birth which is why that was the focus. However, there is some limited data about ECMO utilization, severity of pulmonary hypertension, and length of stay. Data that is known is included in a new table (Table 1) that includes available neonatal outcome data.
2. More attention to the question of selection criteria would enhance the paper since that was a huge problem with the NEJM trial. What is the impact of selection criteria as well as heterogeneity in the procedure itself? Is there agreement based on o/e LHR? What role does the MRI play?
   Thank you for this suggestion. The "patient inclusion criteria" is included in the table and varies among centers with most ultrasound data and a single center using MRI criteria.
3. Some have argued about the problems with the TOTAL trial, including slow enrollment and leakage of patients outside of the trial. These could impact the validity of the study and should be mentioned.
   Thank you for this suggestion. This has been added into the outcomes section.
4. A Table that reviews outcomes from the major tracheal occlusion trial would be very helpful for conveying the information.
   Thank you for this suggestion. We have added a new table that includes this information on both randomized controlled trials and case-control series.

Reviewer 2

Comments to the authors:

The authors provide a succinct, yet thorough review of FETO, and the history of fetal intervention for CDH, clearly a brave, innovative approach for a disease with sustained high mortality. I have a few comments which may render the article a bit easier for the non-fetal surgeon reader.

1. I would remove the transplacental sildenafil from the abstract as this is a very minor area of investigation without much human data. OK to leave as an area of expanded therapy under investigation in the discussion section.

Thank you for this review. We were asked specifically to discuss future directions so feel that keeping transplacental sildenafil within the abstract is important to the reader.

2. Line 46. Can remove word "fetal"….intrinsic to paper.
   Removed "fetal".
3. Line 53. Please give the reader a bit more background about the CDHSG. Many of their publications have a great few sentences of introduction which can be utilized.
   Thank you for this suggestion. Information about the CDHSG was added to the introduction.
4. Line 56. Please also include LHR alone as lung volumes estimates, which can be refined to o/e. May want to add a one sentence overview of how that measurement is obtained.
   Thank you. Also added this information to the introduction.
5. Line 61. Please include PPLV as alternative MRI measurements. May want to discuss there are many prenatal imaging predictors, but these are the most common.
   This was an oversight and new information has been added about fetal MRI measurements, including PPLV.
6. Line 67 and 93. Consider replacing "prematurity" with premature birth.
   Done
7. Line 71. Consider replacing "failures" with outcomes or results.
   Done
8. Line 81. Consider replacing "better" with improved.
   Done
9. Line 88. Duplicate "on placental bypass'
   Removed
10. Line 110. If just attributed to improved ventilator management ok to leave vs. the more broad improved perinatal care.
    Removed ventilator as it truly is due to a more broad "improved perinatal care".
11. Line 116. Consider changing "first-in-woman" trial to "human" etc.
    The authors wish to keep "first-in-woman" as this trial is limited to women and want to remain true to that.
12. Line 117. Add "weeks gestation".
    Done
13. Line 120. Change to "In 2009 this consortium reported….". Also the word "expected" in parentheses is confusing. Suggest FETO survival rates were compared to recent historic controls or even say how far back the control groups went as this is an important point…5 yrs? 10 yrs?
    Reworded as suggested in the first portion. The word "expected" remains as this was an estimated survival based on the regression equation of survival from o/eLHR in expectantly managed fetuses in the Antenatal CDH Registry.

14. Please consider in prose or table form the current inclusion for FETO from NIH.gov for the reader. Is amnio needed, etc.
    We have included this information within the procedure description.
15. Line 141. Remove the word "at"
    Done
16. Line 144. Consider changing to "The procedure can be performed under local …".
    Changed
17. Line 148. Tell the reader more directly this is percutaneous, or transcutaneous as readers may not be proceduralists. i.e., goes through maternal skin, abdominal wall, punctures placenta, etc.
    Reworded
18. Line 165. Describe how centers choose how to remove balloon. Is this standardized in the trial or left up to each center?
    There are standards in place and most centers do either ultrasound guided puncture or fetoscopic retrieval with the other options remaining for emergencies. We have added a sentence into the description to help the reader understand.
19. Line 174-5. I don't understand the increased survival with a mean gestational age????
    These are the results of the systematic review. There was a trend towards better survival (OR of 13.32) with FETO. However, this was accompanied by a mean gestational age of 35.6 at delivery. We have reworded to make it more clear.
20. Line 186. Can remove "problems".
    Done
21. Line 187/188. Not sure I understand this….
    There has been much critique of FETO and the different trials, including the systematic reviews. This is one of the reasons that a multi-institutional randomized controlled trial (e.g. TOTAL) is needed and we are awaiting those results at this time.
22. Line 189. The response to FETO should be included earlier in the disc section as far as prenatal results. Then go to postnatal effects of the balloon such as tracheomegaly, a barky cough, etc. Same for the line 209 part about FETO stimulating vasc growth.
    Thank you for this suggestion. We moved the prenatal lung changes and tracheal effects to the beginning of the outcomes section. We also added more neonatal variables and a table (Table 1) after suggestion by other reviewers. We hope that you find this section better organized and more complete now.
23. I'd consider minimizing sildenafil use for now.
    The editors asked us to specifically discuss novel therapies and future directions. We think the research is exciting and adds to this manuscript.
24. Line 202. Please articulate what anomalies were included. This also goes along

with the current inclusion criteria for the FETO for both mom and fetus.
The authors reported 2 cases: one with Tetralogy of Fallot identified post-balloon and a congenital lung lesion identified prior to the procedure. This information was added to the discussion.

25. Figure 1. The 3 circles that show the catheter down the device are confusing. Please label what is being demonstrated or remove.
We have added descriptions of what the pictures represent into the figure legend.
26. Figure 4. Consider….Equipment needed for the procedure (from top to bottom) includes:
Added, thank you for the suggestion.

Reviewer 3

Comments to the authors:

This is a well-written review of the history and current status of fetal intervention for CDH. The technical details of FETO are nicely explained. This is a useful summary, though the information has been presented thoroughly elsewhere (but could use an update which this paper provides).

ll. 50-51: "in many series the outcome for these fetuses is associated with lower survival and less favorable long-term outcomes" – lower and less than what? (those without a prenatal diagnosis, which is not clear). Also why is this the case? (larger defects)
Thank you. We have added "than those diagnosed postnatally" so the reader better understands. We have also added a sentence about prenatally diagnosed CDH being correlated with larger defect sizes.

l. 88 typo "on placental bypass"
Removed, thank you for identifying.

l. 127: would add that the center for this trial did not have standard postnatal resuscitation capability including availability of ECMO, and hence the survival seen here with and without FETO is not applicable at other centers. In fact, without a standard accepted resuscitation algorithm, FETO outcomes may be better or worse than "traditional" management depending on individual center experience and resources. It is extremely important to note in the outcomes section that even with any positive findings from the FETO trial, advances in postnatal resuscitation may outpace any benefit seen with FETO, without the risk to mother and risk of prematurity (as was seen in the 2003 UCSF trial). The FETO trial cannot be described as a panacea or endpoint but rather as a next step.
Thank you. This was added to the Outcomes section as we agree that FETO is not an endpoint but rather an adjunct to care for these complex patients.