OBSTETRICS & GYNECOLOGY

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Questions about these materials may be directed to the *Obstetrics & Gynecology* editorial office: obgyn@greenjournal.org.

Date: Oct 24, 2019
To: "Ahmet A. Baschat" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-1768

RE: Manuscript Number ONG-19-1768

Obstetric and infant outcome following fetoscopic tracheal occlusion for severe congenital diaphragmatic hernia: a single center cohort study

Dear Dr. Baschat:

Your manuscript has been reviewed by the Editorial Board and by special expert referees. Although it is judged not acceptable for publication in Obstetrics & Gynecology in its present form, we would be willing to give further consideration to a revised version.

If you wish to consider revising your manuscript, you will first need to study carefully the enclosed reports submitted by the referees and editors. Each point raised requires a response, by either revising your manuscript or making a clear and convincing argument as to why no revision is needed. To facilitate our review, we prefer that the cover letter include the comments made by the reviewers and the editor followed by your response. The revised manuscript should indicate the position of all changes made. We suggest that you use the "track changes" feature in your word processing software to do so (rather than strikethrough or underline formatting).

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Nov 14, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: I think that this is a well-written and timely manuscript. While the generalizability is limited by the design (single center, cohort without control group), this is acknowledged by the authors and the study is recognized as a single data point in this field of research. There are several details that I recommend being addressed. Primarily, this would be to provide the reader who does not have experience in fetal diagnosis and therapy more context in which to consider these results.

Minor Recommended Revisions (in no particular order):

- Please include the end date to the enrollment period so that these results can be better compared to other trials.

- Why were patients with maternal depression diagnosed prior to enrollment excluded?

- As the authors point out in the discussion (lines 278-283), several strategies were employed in an attempt to decrease the risk of preterm delivery. However, I would have appreciated this to be more specifically addressed in the methods as deliberate goal of treatment (i.e. entry into the upper uterine quadrants versus lower uterine segment and needle puncture of balloon versus repeat fetoscope). Similarly, in lines 279-281, they describe that trans-placental IV administration was preferred for fetal medications, however, the wording should be consistent with description in methods, lines 138-139.

- Recently, use of cervical pessary for preterm birth prevention trials have largely shown minimal to no effect on preterm birth rates. Perhaps this should be mentioned in the discussion when methods for preterm birth prevention are discussed.

- What were cervical lengths prior to FETO? This could be included in Table 2. This would help the reader to understand how this population is from the women that we typically recommend the use of vaginal progesterone (CL <25mm). Was there any history of PTB in the women included in this study? Parity is also not described.

- Balloon removal is addressed in the "Post-FETO care" section of methods, so the titles of the methods sections should be amended. Also, there is no mention of why some cases were ultrasound-guided balloon puncture versus repeat fetoscope other than "if considered feasible" (line 171).

- In results, several important obstetrical outcomes are described (PPROM rate, preterm labor, Apgars) however these outcomes are not included in either Table 2 or Table 3. I would appreciate that the vaginal delivery rate be stated in the text as well (line 246) and Table 3 referenced. Similarly repeat operation rate for patch dehiscence (line 258) should be included in Table 3. Perhaps re-title Table 2 to "Obstetrical interventions and outcomes...".

- Lines 259-260 and Table 3 discuss neonatal survival and overall/hospital discharge survival, however I could not find any definition for neonatal survival to know what explains the difference between these rates.

- I would also appreciate at least some numbers for reference as to the preterm birth rate and survival for CDH at baseline (both without and with FETO procedures) to compare their outcomes, particularly as they focus the results and discussion on this aspect of their study.

- I appreciate the authors' point (lines 302-304) that it is tough to compare outcomes over time, however without any numbers it is difficult for readers (particularly those that are not familiar with fetal treatments as The Green Journal is for all OB/GYN) to put the current findings into context.

Reviewer #2: THe report by Baschat et al is well written and concise. The results provide further promise to that fetal intervention (specifically fetal endoluminal tracheal occlusion, FETO) may prove to improve perinatal and long-term outcome in fetus/neonates affected with congenital diaphragmatic hernia. The modification in periopearative and antepartum management in this report is unique to others reports on the outcome following FETO, specifically vaginal progesterone administration. Further the suggest that avoiding lower uterine segment entry and removal via percutaneous puncture as adjuncts to reduced PPROM and prolonging gestation are points that should be taken into consideration. It will be interesting if similar findings are noted when results of the TOTAL Trail are reported, although the RCT does not include vaginal progesterone in the protocol.

There are a few points of clarification that I feel need to be addressed:

Introduction
- Page 4, lines 73-74: The randomized trial (TOTAL) is an international trial. that is currently underway in Europe, Japan and North America. ClinicalTrials.gov Identifier: NCT01240057 is for the Tracheal Occlusion To Accelerate Lung Growth (TOTAL) Trial for Severe Pulmonary Hypoplasia (TOTAL) is actively enrolling patients. The Randomized Controlled Trial of Fetoscopic Endoluminal Tracheal Occlusion With a Balloon Versus Expectant Management During Pregnancy in Fetuses With Left Sided Congenital Diaphragmatic Hernia and Moderate Pulmonary Hypoplasia. (TOTAL moderate), clinicaltrials.gov Identifier: NCT00763737, at the time of this writing is not longer actively enrolling patients. The analysis is waiting for the last patients enrolled (May 2019) to reach 6 months of age.

- Page 4, line 76-77: The authors have "The goal of this study was to determine the feasibility and safety of FETO in serve CDH cohort managed in a single Center". On the center's clinicaltrial page [ClinicalTrials.gov Identifier: NCT02710968] They have written that "our goal with this pilot study is to study the feasibility of implementing FETO therapy in the most severe group of fetuses with left CDH (O/E LHR < 30%). which will be considered in two subgroups. Those with and O/E LHR <25% (severe group) and those with an O/E between 25 to <30% (less severe group). Point here is that the report did not separate the results by LHR o/e cut-offs as outlined. It is expected that those with LHR o/e ≥25%-30% will have a better outcome than those ≤24%. Was this simply because of the "small number of cases treated?

Materials and Methods
- Page 10, lines 213-215: The authors have suggested that the FDA recommended enrollment of "at least" 10 patients with left CDH for feasibility with the option to enroll and (I believe they meant "an") additional 5 patient under compassionate request. I believe the suggest that the FDA required "at least 10 patients" be treated with FETO per protocol is in error. I think the authors meant to write that the FDA in the their initial submission allowed up to 10 cases. The compassionate use request would also have been under a separate submission, probably each separate request. Minor point but a clarification none the less.

Results:
- 14 patients underwent FETO. Table 1 indicates that 12 were left and 2 were right sided. The text states that "3 were under compassionate use". Based on the initial FDA approved protocol, one would assume that there was probably a petition to the FDA to extend the initial number of cases under the primary protocol to allow for 1 left CDH, and then there 2 were right sided CDH cases (one with a secondary lung lesion) who received FETO under compassionate use aplliation. Guessing that the last case was the other secondary lung lesions in a fetus with left CDH? It would be helpful if the authors clarified this.

Reference
The authors have included two reports by Ruano et al, #18 and #19. As there is some concern raised by others that there is overlap in the cases between the two reports. (Jani J & Nicoladies K.Fetal surgery for severe congenital diaphragmatic hernia? UOG 2012; 39: 7-9) Would suggest that the authors remove the earlier study (#19)

Table
The editor would pick this up, lines for ethnicity do not line up. "Ethnicity" or "maternal ethnicity" needs to be deleted

Discussion
The authors have acknowledged the limitations of the results in their "feasibility study" one in particular, lack of a control group. Rightfully, they noted that the comparison of the results from this study to what would be expected from historic controls may not address the impact of current postnatal management strategies, however it is interesting to noted that the survival to discharge in the present study, 85.7% is essenitally the same that was seen in a "comparable cohort" of espectnatlhy managed cases. Kay et al, from an affiliated John Hopkins program reported survived to discharge of 82% (71/87) in left sided CDH with liver herination. (J Am Coll Surg. 2016 Apr;222(4):459-70). The concept of a feasiblity study from the scientific community would be upon it completion, if there are promising results, then the progresson would be to test the investiatgional procedure (FETO in this case) against the established standard of care, expectant observation with postnatal intervention, idelally in a RCT. i would think that as part of the discussion/conclusion, the authors would acknowledged that they have (1) completed their feasiblity study, stating that their results may not be reproducible in other centers and that they will not longer be offering the investigational intervention outside of a RCT.

Reviewer #3: To assess safety, feasibility, maternal and infant outcome after fetoscopic tracheal balloon occlusion (FETO) in patients with severe congenital diaphragmatic hernia (CDH).

This is a review of their first 15 patients

Introduction: Enhance the readers understanding of tracheo-occlusion by adding more fetal physiology for the reader: some examples the concept of "plug and unplug" Why wait until 26 weeks and why remove at 34 weeks ? Animal models response to tracheal occlusion ?observations in laryngeal atresia?

Materials and Methods: well done and detailed . This is where diagrams and art could be helpful

Can you describe maneuvers used in order to obtain proper fetal positioning? What was the optimal fetal position

Discussion: should tell more about the large RCT (or two parallel RCTS that are ongoing and past feasibility. How is your protocol different?

Can you explain why placing of trocar in the upper uterus is less risky than the LUS regarding risk of PPROM or PTB

Can you explain the thinking behind abandoning EXIT procedures since the earlier studies used EXIT.

What next? WIll you do anything different after the first 15 patients? Any changes in protocols?

Consider adding this reference: It is very applicable when you expand the discussion. I am interested to know what is different about your protocols than that in the Trials?

Gynecol Surg. 2018; 15(1): 9. Published online 2018 May 8. doi: 10.1186/s10397-018-1041-9
PMCID: PMC5940711/ PMID: 29770109
Fetoscopic endoluminal tracheal occlusion and reestablishment of fetal airways for congenital diaphragmatic hernia
Lennart Van der Veeken,1 Francesca Maria Russo,1 Luc De Catte,1 Eduard Gratacos,2,3 Alexandra Benachi,2,4,14 Yves Ville,2,5 Kypros Nicolaides,2,6 Christoph Berg,2,7,8 Glenn Gardener,2,9 Nicola Persico,2,10 Pietro Bagolan,2,11,14 Greg Ryan,2,12 Michael A. Belfort,2,13 and Jan Deprest corresponding author1,2,14

STATISTICAL EDITOR COMMENTS:

The Statistical Editor makes the following points that need to be addressed:

General: The total N and subset samples are small, so the %s should be rounded to nearest integer %, there is no basis for precision to nearest 0.1%

lines 44-45: The point estimates of survival and survival to hospital discharge need to include CIs: 93% (49-100%) and 88%(44-100%), to put the results in context.

Tables 1, 2, 3: Need to round %s to nearest integer %.

Fig 1: Were the 5 patients who declined participation but who were otherwise suitable for inclusion different in baseline characteristics from the N = 14 in any characteristic which might limit generalization of the conclusions?

lines 215-216: Should cite how ties were analyzed in the M-W U test procedure, and given the relatively small samples, how many ties were there?

EDITOR COMMENTS:

1. Thank you for your submission to Obstetrics & Gynecology. In addition to the comments from the reviewers above, you are being sent a notated PDF that contains the Editor's specific comments. Please review and consider the comments in this file prior to submitting your revised manuscript. These comments should be included in your point-by-point response cover letter.

The notated PDF is uploaded to this submission's record in Editorial Manager. If you cannot locate the file, contact Randi Zung and she will send it by email - rzung@greenjournal.org.

- We no longer require that authors adhere to the Green Journal format with the first submission of their papers. However, any revisions must do so. I strongly encourage you to read the instructions for authors (the general bits as well as those specific to the feature-type you are submitting). The instructions provide guidance regarding formatting, word and reference limits, authorship issues, and other things. Adherence to these requirements with your revision will avoid delays during the revision process, as well as avoid re-revisions on your part in order to comply with the formatting.

- Unable to assess safety w/ 14 patients

- either side CDH?

- Do not begin a sentence w/ a numeral.

- at time of FETO or later?

- Again, you cannot assess safety. As well, you have provided no information about maternal well-being in the abstract.

- We now use the reVITALize terminology. Please note the PROM is officially prelabor rupture of the membranes.

- retrospective or prospective?

- How reliable is this method given associated small AC's with severe CDH?

- was amnio required? If a woman declined, did you do cell free testing?

- Here is this information. However, again, if they patient decided to forego amnio did you accept cell free?

- Since most women it seems remained pregnant after tracheal occlusion and you required that they agree to get neonatal care at your center, did you assist them with accommodations post occlusion?

- at any time or just at time of FETO?

- What's the basis for this given the lack of evidence to support long term tocolysis?

- Not clear here: Do you mean you each were primary surgery on some cases or was one of you always the primary surgeon and the other assisted?

- What did you do for women with an anterior placenta without a free window?

- by "membrane status" do you specifically mean chorioamnion separation or for rupture, which is what most non MFM might think. Obviously US not the best tool for PROM assessment.

- why? why did you look weekly at the cervical length? What results of this examination would alter your management and how?

- please elaborate on "sparingly". How often? To what EGA?

- spell out iNO and all abbreviations on first use.

- why?

- in all patients?

- Didn't you only identified women whose fetuses had severe CDH. You didn't actually dx diaphragmatic agenesis prenatally, did you? Please clarify.

- Please discuss your primary outcome first, followed by secondary ones.

- please comment about how this would decrease punctures if placental insertion is posterior.

- All of this of course is conjecture given the lack of randomized interventions in your study. Its fine to hypothesize that this contributed to your GA at delivery, but you should set up the paragraph discussing this with the caveat that the numbers of small, EGA at delivery was broad, and that the interventions you did have not been studied in a randomized fashion. You discuss all of this, but the caveats about lack of evidence needs to come first in order to emphasize that.

- note extra parenthesis. please give EGA at delivery in this table as well.

- Given your emphasis on avoiding preterm birth, please provide information about individual's EGA at delivery. You've reported the EGA as a median in your paper and I assume that is what you are reporting here. We need more information about this.

2. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:
A. OPT-IN: Yes, please publish my point-by-point response letter.
B. OPT-OUT: No, please do not publish my point-by-point response letter.

3. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page.

4. Our journal requires that all evidence-based research submissions be accompanied by a transparency declaration statement from the manuscript's lead author. The statement is as follows: "The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained." *The manuscript's guarantor.

If you are the lead author, please include this statement in your cover letter. If the lead author is a different person, please ask him/her to submit the signed transparency declaration to you. This document may be uploaded with your submission in Editorial Manager.

5. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric and gynecology data definitions at https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

6. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.

7. Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). Do not structure the title as a declarative statement or a question. Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles. Abbreviations, jargon, trade names, formulas, and obsolete terminology also should not be used in the title. Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," or "A Systematic Review," as appropriate, in a subtitle. Otherwise, do not specify the type of manuscript in the title.

8. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

* All financial support of the study must be acknowledged.
* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis,

writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.
* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

9. Provide a précis on the second page, for use in the Table of Contents. The précis is a single sentence of no more than 25 words that states the conclusion(s) of the report (ie, the bottom line). The précis should be similar to the abstract's conclusion. Do not use commercial names, abbreviations, or acronyms in the précis. Please avoid phrases like "This paper presents" or "This case presents."

10. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Original Research articles, 300 words. Please provide a word count.

11. Only standard abbreviations and acronyms are allowed. A selected list is available online at http://edmgr.ovid.com /ong/accounts/abbreviations.pdf. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

12. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

13. In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.

If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts.

Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1%").

14. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.

15. Figures

Figure 1: This figure may be resubmitted as-is.

Figure 2: Is this figure available at a higher resolution?

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* A confirmation that you have read the Instructions for Authors (http://edmgr.ovid.com/ong/accounts/authors.pdf), and
* A point-by-point response to each of the received comments in this letter.

If you submit a revision, we will assume that it has been developed in consultation with your co-authors and that each author has given approval to the final form of the revision.

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Nov 14, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy C. Chescheir, MD
Editor-in-Chief

2018 IMPACT FACTOR: 4.965
2018 IMPACT FACTOR RANKING: 7th out of 83 ob/gyn journals
