Date: Aug 30, 2018
To: "Alireza Abdollah Shamshirsaz" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-18-1357

RE: Manuscript Number ONG-18-1357

An ethical framework for research on maternal-fetal intervention in the presence of maternal HIV or Hepatitis B and C seropositivity

Dear Dr. Shamshirsaz:

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 Sep 20, 2018, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:
The authors are to be congratulated for their discussion of the bioethical principles to be considered in the question of whether women who are HIV, hepatitis C, or hepatitis B seropositive should be excluded from clinical trials of fetal intervention.

The article could be much improved by attention to ambiguities in wording, keeping a clear focus, and consistency in message.

Introduction and background. There is a discordance between the procedures mentioned in the introduction and those listed in Figure 1. In the introduction, IUT, laser for TTTS, FETO, LUTO, and in utero repair of neural tube defects are listed. In Figure 1, additional fetal therapies—laser for chorioangiomas and vasa previa, valvuloplasty for aortic stenosis, and resections of fetal lung masses and sacrococcygeal teratomas are included. For consistency, it would seem appropriate to include the same fetal surgeries in both sections.

Lines 46-47 regarding repair of neural tube defects need revision . The fact that this in utero repair has come to the forefront in the mainstream media is not germane to this article; this phrase should be dropped.

In line 48-57 , the authors state that "for largely historical reasons HIV and hepatitis B and C seropositive pregnant women are excluded from consideration of their use and therefore from investigation". Clarification is needed. Are the authors discussing investigation or treatment here? Is it truly the case that seropositive women are excluded from the use of IUT? Or are the authors making the point that seropositive women are being excluded from investigational trials? If so, they should so state, and it would be helpful if they could provide more than a single reference. Is the MOMs study the only example?

At line 70, clarification is needed. The second sentence -- the authors are arguing for separate studies of fetal intervention in seropositive women. In the next sentence -- arguing that seropositive women should be included in phase 1 trials of fetal therapy. Later on in the article, (line 123-7) it sounds like they are arguing that seropositive women should be enrolled but only after "the maternal fetal intervention has been shown… …either to be life saving or to prevent serious and irreversible disease, injury, or disability…"

Table 1 seems incomplete -- "Potentially add data" occurs in the 4 boxes. Also, the "with intervention" for FETO needs clarification—does survival with intervention for severe cases of right CDH increase from 0 to 35%, or for all cases of right sided CDH?

Line 158—HAART needs to be defined.

Line 170-71: Why the emphasis on "well resourced countries like the US" rather than the intervention (vaccination and immunoprophylaxis). Recommend restating.

Line 189. Minimized or minimal?

Lines 208-10. This seems out of context. Are we recommending cesarean as part of treatment for seropositive women with low or undetectable viral loads? Unclear what direction the authors are suggesting for research here.

Lines 218-229 seem to be an editorial about treatment of HIV, and detracts from the article. Lines 245-250 state the justice argument well and succinctly.

Reviewer #2: Shamshirasz and colleagues present a clinical commentary focused on the ethics of research related to maternal-fetal intervention in seropositive women with HIV, hepatitis B and hepatitis C in pregnancy with low or undetectable viral loads. The commentary relies heavily on the previous work of 2 of the 9 authors (LBM and FAC). The discussion of the paper is very thorough and systematically approaches the relevant clinical and ethical issues related to fetal therapy in women with these perinatal infections. A concern with the paper if that the paper drifts from seropositive women with low or undetectable viral loads to generalized inference regarding seropositive women with viral load unspecified. A point-by-point critique of the paper follows:

1) On lines 70-71 of the paper the authors cite previous work from 2 of the co-authors of the paper (LBM and FAC). No citation is provided for this previous work. This should be included in the revised paper.

2) As noted above, it appears that the majority of the paper is based on the work of 2 of the authors. What was the role of the 7 other authors for this commentary?

3) In the section of related to autonomy, the focus is largely on maternal autonomy. Are there any paternal considerations? It would make the ethical discussion more robust to include some commentary related to any paternal role (ethically or legally) that paternal rights may play related to autonomy and decision making.

4) The paper begins with a discussion related to ethics of fetal intervention in seropositive women with low or undetectable viral load but the authors conclusions are more broadly stated to infer that their discussion equates to all seropositive women. The definition of "low" viral load and risks of vertical transmission with invasive fetal therapies has not been established and the authors conclusions from their ethical debate should be tempered to their original stated objective of this contemporary review. The reader could readily infer from the concluding paragraph of the document that these procedures may be ethically justifiable in any seropositive pregnant women when in fact the viral load of the respective infectious agent is a highly important piece of information to include in the ethical discussion and may significantly alter the balance of beneficence and autonomy.

Reviewer #3: This paper is an interesting discussion of the ethics of maternal fetal surgery in patients who are seropositive for HIV or hepatitis. While the discussion is worthwhile and interesting, as these patients have generally been excluded from such interventions, I have some questions and suggestions for the authors.

1. The premise is a discussion of the ethical framework for allowing seropositive women to participate in research on maternal fetal surgery. For interventions in which a benefit has been demonstrated (e.g. spina bifida repair), it seems that it is also important to consider whether they should be allowed to undergo in utero repair, not necessarily as part of a research trial. It seems unlikely that a research trial of the risks/benefits of in utero interventions on these women with viral infections will ever be undertaken, as the number of women who would be eligible would be vanishingly small. Even recruiting women to the MOMs trial from all women, or collecting enough outcomes to study transmission from amnio or CVS has been challenging; so a study of seropositive women with fetal myelo seems unlikely to ever be conducted and suggesting it as a requirement before allowing women to participate seems like an additional burden.

2. Do you have data on how many fetal centers exclude women with a history of hepatitis or HIV? Does this include women with an undetectable viral load?

3. The sentence from line 59-65 is convoluted and confusing, and should be rewritten.

4. Based on the principle of autonomy of the pregnant woman, you note that she should be allowed to choose to undergo a procedure even if seropositive. This seems right and I think should be emphasized. The alternative, that women should be excluded from these interventions solely because of HIV or hepatitis, is difficult to justify and, in fact, you don't

make the counter argument. What is the argument against allowing the pregnant woman herself to decide?

5. Line 95-7 states that most fetuses being considered for in utero intervention are previable. There are many interventions other than NTD repair where this is not the case, (FETO, some TTTS cases, many shunts), so I'd suggest removing this statement. Might require some reworking of this section.

6. The sentences from 183-86 need to be reworded; they don't make sense.

7. You divide procedures and risks of viral transmission into three categories (188-200). While it is logical and likely that different procedures pose different risks, it seems that your categories are not based on any data. I would not necessarily agree that laser poses a significantly lower risk than other procedures, and generally in the absence of any data, I think it is inappropriate to create these artificial categories. You appropriately note that it will be difficult to collect data on comparison transmission rates, although perhaps one can get some idea from alloimmunization as a proxy?

8. You note that the risks of seropositivity can be reduced to an "acceptable level" - (who decides what is acceptable?) by cesarean delivery. But generally cesarean is not recommended with a low viral load for these infections. I'm not sure what is meant here?

9. Line 114: should be "ratio" not ration

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.

- The Journal style does not include the use of the virgule (/) except in numeric expressions. Please edit here and in all instances.

- Please read the instructions for authors for guidance on manuscript organization, including allowable headings.

- have been...(line 46)

- wouldn't investigation come before use?

- Please note the requested crossed out text, as a deletion.

- why would it make sense in this case?

- Sentence from line 59-65 should be broken up into several shorter sentences.

- Please provide references for these contributions.

- The addition of "with low or undetectable viral loads" came as a bit of surprise to me as I read the introduction. It might be worthwhile to introduce importance of viral load to idea of vertical transmission here in the introduction rather than broad definition of fetal surgical procedures.

- appealing to THE ethical principals...

- you say "both" but then list 3 types of patients. Please edit

- check the punctuation in this quote.

- This would still be a vertical transmission--from mother to fetus. But you are comparing fetal interventions to normal biologic processes.

- You might consider making the arguement that the rate of transission with these procedures is not known and cannot be known without doing them, However, likely higher than rates for labor & delivery and amnio or cvs.

- The exact risk...

- please see instructions for authors about limits for current commentary references to make sure you are within them.

2. Please cite the three bullet points (lines 125-133).

3. 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, as well as subsequent author queries. 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:
1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.
2. OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries.

4. Each author on this manuscript must submit a completed copy of our revised author agreement form (updated in the August 2014 issue). Please note:

a) Any material included in your submission that is not original or that you are not able to transfer copyright for must be listed under I.B on the first page of the author agreement form.

b) All authors must disclose any financial involvement that could represent potential conflicts of interest in an attachment to the author agreement form.

c) All authors must indicate their contributions to the submission by checking the applicable boxes on the author agreement form.

d) The role of authorship in Obstetrics & Gynecology is reserved for those individuals who meet the criteria recommended by the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org):

* Substantial contributions to the conception or design of the work;
OR
the acquisition, analysis, or interpretation of data for the work;
AND
* Drafting the work or revising it critically for important intellectual content;
AND
* Final approval of the version to be published;
AND
* Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The author agreement form is available online at http://edmgr.ovid.com/ong/accounts/agreementform.pdf. Signed forms should be scanned and uploaded into Editorial Manager with your other manuscript files. Any forms collected after your revision is submitted may be e-mailed to obgyn@greenjournal.org.

5. All submissions that are considered for potential publication are run through CrossCheck for originality. The following lines of text match too closely to previously published works. Variance is needed in the following sections:

- Cite the three bullet points (Lines 125-133).

6. 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 will be transitioning as much as possible to use of the reVITALize definitions, and we encourage authors to familiarize themselves with them. The obstetric data definitions are available at http://links.lww.com/AOG/A515, and the gynecology data definitions are available at http://links.lww.com/AOG/A935.

7. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Current Commentary articles should not exceed 12 typed, double-spaced pages (3,000 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and appendixes).

8. Specific rules govern the use of acknowledgments in the journal. Please edit your acknowledgments or provide more information in accordance with 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 signature on the journal's author agreement 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, written in the present tense and stating 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: Current Commentary articles, 250 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. 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.

14. Figure 1 may be resubmitted as-is.

15. If you choose to revise your manuscript, please submit your revision via Editorial Manager for Obstetrics & Gynecology at http://ong.editorialmanager.com. It is essential that your cover letter list point-by-point the changes made in response to each criticism. Also, please save and submit your manuscript in a word processing format such as Microsoft Word.

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

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 Sep 20, 2018, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy C. Chescheir, MD
Editor-in-Chief

2017 IMPACT FACTOR: 4.982
2017 IMPACT FACTOR RANKING: 5th out of 82 ob/gyn journals

If you would like your personal information to be removed from the database, please contact the publication office.

September 20, 2018

[redacted]

Manuscript #: ONG-18-1357

Dear editor in chief and associate editor of the Obstetrics and Gynecology,

Thank you for your consideration on the manuscript entitled: "**An ethical framework for research on maternal-fetal intervention in the presence of maternal HIV or Hepatitis B and C seropositivity**" and also for giving us the opportunity to address our comments on reviews. We took all the comments seriously and used them to improve the manuscript and fit the space requirements of the "Obstetrics and Gynecology". Hereby, we also thank the reviewers for their constructive comments and provide our answers.

Respectfully Yours,

Alireza A. Shamshirsaz M.D.

REVIEWER COMMENTS:

Reviewer #1:

The authors are to be congratulated for their discussion of the bioethical principles to be considered in the question of whether women who are HIV, hepatitis C, or hepatitis B seropositive should be excluded from clinical trials of fetal intervention.

The article could be much improved by attention to ambiguities in wording, keeping a clear focus, and consistency in message.

Introduction and background. There is discordance between the procedures mentioned in the introduction and those listed in Figure 1. In the introduction, IUT, laser for TTTS, FETO, LUTO, and in utero repair of neural tube defects are listed. In Figure 1, additional fetal therapies—laser for chorioangiomas and vasa previa, valvuloplasty for aortic stenosis, and resections of fetal lung masses and sacrococcygeal teratomas are included. For consistency, it would seem appropriate to include the same fetal surgeries in both sections.
Response: Agreed. Text was deleted in the revision in favor of space.

Lines 46-47 regarding repair of neural tube defects need revision. The fact that this in utero repair has come to the forefront in the mainstream media is not germane to this article; this phrase should be dropped.

Response: Text was deleted in the revision in favor of space.

In line 48-57, the authors state that "for largely historical reasons HIV and hepatitis B and C seropositive pregnant women are excluded from consideration of their use and therefore from investigation". Clarification is needed. Are the authors discussing investigation or treatment here? Is it truly the case that seropositive women are excluded from the use of IUT? Or are the authors making the point that seropositive women are being excluded from investigational trials? If so, they should so state, and it would be helpful if they could provide more than a single reference. Is the MOMs study the only example?

Response: Agreed. Text substantially revised as follow:

"Although it has been shown that women with low HIV viral loads have a minimal risk of transmitting the virus to their fetus, fetal centers remain hesitant to offer the full range of fetal interventions to pregnant women and their fetuses with evidence of HIV infection because of the hypothetical risk of iatrogenic viral transmission to the fetus. As a consequence, despite rapid advancements and expanding prevalence of use of fetal intervention procedures, HIV and Hepatitis B and C seropositive pregnant women are currently excluded from investigational studies. For instance, in the MOMs Trial maternal HIV or Hepatitis seropositive status was an exclusion criterion."

At line 70, clarification is needed. The second sentence -- the authors are arguing for separate studies of fetal intervention in seropositive women. In the next sentence -- arguing that seropositive women should be included in phase 1 trials of fetal therapy. Later on in the article, (line 123-7) it sounds like they are arguing that seropositive women should be enrolled but only after "the maternal fetal intervention has been shown…

…either to be life saving or to prevent serious and irreversible disease, injury, or disability…"

Response: Text substantially revised as follow:

"A recent study of investigators' views about including seropositive women identified the lack of ethical guidance as a challenge. To date, no such guidance exists. The purpose of this paper is to propose needed ethical guidance. We will show that it is ethically permissible to include HIV and Hepatitis B or C seropositive pregnant patients with low or undetectable viral loads in Phase I trials."

Table 1 seems incomplete -- "Potentially add data" occurs in the 4 boxes. Also, the "with intervention" for FETO needs clarification—does survival with intervention for severe cases of right CDH increase from 0 to 35%, or for all cases of right sided CDH?

Response: Agreed. Table has been completed appropriately. Also, the increase survival rate of 0-30% in right-sided CDH is correspondent to the severe ones. In fact, intervention is not recommended in mild cases. Text was deleted in the revision in favor of space.

Line 158—HAART needs to be defined.

Response: Agreed and corrected.

Line 170-71: Why the emphasis on "well resourced countries like the US" rather than the intervention (vaccination and immunoprophylaxis). Recommend restating.

Response: We thank the reviewer for the comment. We modified the sentence as follow:

"Vertical transmission for HBV has been decreased due to institution of postpartum neonatal HBV vaccination and immunoprophylaxis with hepatitis B immunoglobulin."

Line 189. Minimized or minimal?

Response: We thank the reviewer for the comment. The word 'minimal' has a technical meaning in the OHRP that does not apply to our paper. So with respect to the reviewer's comment we kept using the word 'minimized'.

Lines 208-10. This seems out of context. Are we recommending cesarean as part of treatment for seropositive women with low or undetectable viral loads? Unclear what direction the authors are suggesting for research here.

Response: Text was deleted in the revision in favor of space.

Lines 218-229 seem to be an editorial about treatment of HIV, and detracts from the article. Lines 245-250 state the justice argument well and succinctly.

Response: Lines 240-250 were deleted in the revision in favor of space and to avoid duplication.

Reviewer #2:

Shamshirasz and colleagues present a clinical commentary focused on the ethics of research related to maternal-fetal intervention in seropositive women with HIV, hepatitis B and hepatitis C in pregnancy with low or undetectable viral loads. The commentary relies

heavily on the previous work of 2 of the 9 authors (LBM and FAC). The discussion of the paper is very thorough and systematically approaches the relevant clinical and ethical issues related to fetal therapy in women with these perinatal infections. A concern with the paper if that the paper drifts from seropositive women with low or undetectable viral loads to generalized inference regarding seropositive women with viral load unspecified. A point-by-point critique of the paper follows:

1) On lines 70-71 of the paper the authors cite previous work from 2 of the co-authors of the paper (LBM and FAC). No citation is provided for this previous work. This should be included in the revised paper.

Response: Text was deleted in the revision in favor of space.

2) As noted above, it appears that the majority of the paper is based on the work of 2 of the authors. What was the role of the 7 other authors for this commentary?

Response: We appreciate the reviewer's concern. However, we emphasize that all the authors meet the authorship criteria recommended by ICMJE. Since the topic of this article is multidisciplinary questions authors active with various disciplines including, maternal-fetal medicine, fetal intervention and surgery, perinatal research and applied ethics were involved; all authors had substantial contributions to the conception and design of the work, drafting the work and revising it critically for important intellectual content, final approval of the version to be published and agreement to be accountable for all aspects of the work.

3) In the section of related to autonomy, the focus is largely on maternal autonomy. Are there any paternal considerations? It would make the ethical discussion more robust to include some commentary related to any paternal role (ethically or legally) that paternal rights may play related to autonomy and decision making.

Response: Paternal consent continues to be a requirement of the OHRP regulations. Paternal consent, however, is not pertinent to the question of whether expanding inclusion criteria to include seropositive women in Phase I clinical trials is ethically permissible because the father is not a patient. We therefore made no changes.

4) The paper begins with a discussion related to ethics of fetal intervention in seropositive women with low or undetectable viral load but the authors conclusions are more broadly stated to infer that their discussion equates to all seropositive women. The definition of "low" viral load and risks of vertical transmission with invasive fetal therapies has not been established and the authors conclusions from their ethical debate should be tempered to their original stated objective of this contemporary review. The reader could readily infer from the concluding paragraph of the document that these procedures may be ethically justifiable in any seropositive pregnant women when in fact the viral load of the respective infectious agent is a highly important piece of information to include in the ethical discussion and may significantly alter the balance of beneficence and autonomy.

Response: Agreed. We used the term “seropositive with low or undetectable viral loads” instead of “seropositive” throughout the manuscript as appropriate.

Reviewer #3:

This paper is an interesting discussion of the ethics of maternal fetal surgery in patients who are seropositive for HIV or hepatitis. While the discussion is worthwhile and interesting, as these patients have generally been excluded from such interventions, I have some questions and suggestions for the authors.

1. The premise is a discussion of the ethical framework for allowing seropositive women to participate in research on maternal fetal surgery. For interventions in which a benefit has been demonstrated (e.g. spina bifida repair), it seems that it is also important to consider whether they should be allowed to undergo in utero repair, not necessarily as part of a research trial. It seems unlikely that a research trial of the risks/benefits of in utero interventions on these women with viral infections will ever be undertaken, as the number of women who would be eligible would be vanishingly small. Even recruiting women to the MOMs trial from all women, or collecting enough outcomes to study transmission from amnio or CVS has been challenging; so a study of seropositive women with fetal myelo seems unlikely to ever be conducted and suggesting it as a requirement before allowing women to participate seems like an additional burden.

Response: The main purpose of the paper was to show that including seropositive women in Phase I trials is ethically permissible. The point about multicenter trials is important and we have added a new third sentence to the conclusion to make this point.

2. Do you have data on how many fetal centers exclude women with a history of hepatitis or HIV? Does this include women with an undetectable viral load?

Response: This is a great question. Unfortunately there is no formal and published data available on this matter at this point. However, per oral informal discussions with majority of available centers, none offer interventions to such candidates.

3. The sentence from line 59-65 is convoluted and confusing, and should be rewritten.

Response: We merged the abovementioned paragraph and the next paragraph for the sake of space and clarity. The new paragraph is as follow:

> *"The ACOG Committee Opinion on Maternal-Fetal Intervention and Fetal Care Centers asserts a beneficence-based motivation to improve fetal and neonatal outcomes, which supports well designed and ethically permissible investigation to improve outcomes, especially in vulnerable populations of patients. A recent study of investigators' views about including seropositive women identified the lack of ethical guidance as a challenge. To date, no such guidance exists. The purpose of this paper is to propose needed ethical guidance. We will show that it is ethically permissible to include HIV and Hepatitis B or C seropositive pregnant patients with low or undetectable viral loads in Phase I trials."*

4. Based on the principle of autonomy of the pregnant woman, you note that she should be allowed to choose to undergo a procedure even if seropositive. This seems right and I think should be emphasized. The alternative, that women should be excluded from these interventions solely because of HIV or hepatitis, is difficult to justify and, in fact, you don't make the counter argument. What is the argument against allowing the pregnant woman herself to decide?

Response: The ethical principle of respect for autonomy is not adequate as a basis for the ethics of research for fetal benefit. Beneficence-based ethical obligations to the fetal patient must also be considered in analyzing the risk-benefit ratio, a task that is assigned to IRBs independently of the preferences of potential research subjects. We make the argument that excluding seropositive women is not permitted by the ethical principle of healthcare justice. The ethical principle of justice applies to populations of patients; respect for autonomy applies only to an individual patient, a further reason that respect for autonomy should not be considered the sole ethical principle for assessing the risk-benefit ratio. This is a large topic, about research ethics in general and the assessment of the risk-benefit ratio by IRBs. Addressing it would, we believe, dilute the focus of our paper on the ethical permissibility of including seropositive women and would require a number of words that would exceed the page limits stipulated in the Journal's instructions for authors.

5. Line 95-7 states that most fetuses being considered for in utero intervention are previable. There are many interventions other than NTD repair where this is not the case, (FETO, some TTTS cases, many shunts), so I'd suggest removing this statement. Might require some reworking of this section.

Response: Text was deleted in the revision in favor of space.

6. The sentences from 183-86 need to be reworded; they don't make sense.

Response: Text was revised as follow:

"These viral infections are manageable, their mortality is not immediate, and it remains true that only a very small minority of infected women will vertically transmit with prophylaxis."

7. You divide procedures and risks of viral transmission into three categories (188-200). While it is logical and likely that different procedures pose different risks, it seems that your categories are not based on any data. I would not necessarily agree that laser poses a significantly lower risk than other procedures, and generally in the absence of any data, I think it is inappropriate to create these artificial categories. You appropriately note that it will be difficult to collect data on comparison transmission rates, although perhaps one can get some idea from alloimmunization as a proxy?

Response: We thank the reviewer for the comment. In the next paragraph (below) we emphasized that the risk assessment in each group can be determined by Phase I trials and study design should account for the viral load thresholds along this spectrum. Per Editor's suggestion we decided to resubmit Figure 1 with the revision with the purpose of visually presenting the spectrum of different fetal interventional procedures to our readers.

"Precise risk assessment can be determined only by investigating fetal outcomes in Phase I trials with seropositive pregnant women. Study design should account for viral load thresholds along this spectrum (i.e. require lower viral loads for Fetal Surgical procedures and permit higher viral loads for Placental and Ultrasound-Guided procedures). This can be based on current SMFM guidelines."

8. You note that the risks of seropositivity can be reduced to an "acceptable level" - (who decides what is acceptable?) by cesarean delivery. But generally cesarean is not recommended with a low viral load for these infections. I'm not sure what is meant here?

Response: Text was deleted in the revision in favor of space.

9. Line 114: should be "ratio" not ration

Response: Agreed and corrected.

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.

Response: We thank the Editor for the Editor's specific comments. We reviewed and considered the comments in the revised version of the manuscript (Manuscript file in track change form is also enclosed).

- The Journal style does not include the use of the virgule (/) except in numeric expressions. Please edit here and in all instances.

Response: Corrected.

- Please read the instructions for authors for guidance on manuscript organization, including allowable headings.

Response: Thanks for the comment. Per instruction for authors "Headings are not necessary in the body of the article but may be used if needed." We changed the first heading to "Introduction".

- have been...(line 46)

Response: Corrected.

- wouldn't investigation come before use?

Response: Corrected.

- Please note the requested crossed out text, as a deletion.

Response: Corrected.

- why would it make sense in this case?

Response: Agreed. We removed the sentence from the updated text.

- Sentence from line 59-65 should be broken up into several shorter sentences.

Response: Paragraph revised as follow:

> *"The ACOG Committee Opinion on Maternal-Fetal Intervention and Fetal Care Centers asserts a beneficence-based motivation to improve fetal and neonatal outcomes, which supports well designed and ethically permissible investigation to improve outcomes (9), especially in vulnerable populations of patients. A recent study of investigators' views about including seropositive women identified the lack of ethical guidance as a challenge. To date, no such guidance exists. The*

purpose of this paper is to propose needed ethical guidance. We will show that it is ethically permissible to include HIV and Hepatitis B or C seropositive pregnant patients with low or undetectable viral loads in Phase I trials."

- Please provide references for these contributions.

Response: Corrected.

- The addition of "with low or undetectable viral loads" came as a bit of surprise to me as I read the introduction. It might be worthwhile to introduce importance of viral load to idea of vertical transmission here in the introduction rather than broad definition of fetal surgical procedures.

Response: Agreed. We used the term "seropositive with low or undetectable viral loads" throughout the manuscript and abstract for consistency.

- appealing to THE ethical principals...

Response: Corrected.

- you say "both" but then list 3 types of patients. Please edit

Response: Corrected.

- check the punctuation in this quote.

Response: Corrected.

- This would still be a vertical transmission--from mother to fetus. But you are comparing fetal interventions to normal biologic processes.

Response: Agreed and corrected.

- You might consider making the arguement that the rate of transission with these procedures is not known and cannot be known without doing them, However, likely higher than rates for labor & delivery and amnio or cvs.

Response: We updated the paragraph as follow:

"For HIV and Hepatitis B and C, the risk of vertical transmission is very low in women with low or undetectable viral loads. This is considered in the current recommendations for invasive prenatal diagnosis methods such as amniocentesis and chorionic villous sampling. The risk of iatrogenic transmission via fetal intervention procedures is not known and cannot be known without doing them, however is potentially greater than the risk of transmission due to normal physiologic processes, and invasive prenatal diagnosis methods given the manipulation and instrumentation of maternal and fetal tissues."

- The exact risk...

Response: Corrected.

- please see instructions for authors about limits for current commentary references to make sure you are within them.

Response: We updated the references based on the instructions for authors

.

2. Please cite the three bullet points (lines 125-133).

Response: Text was deleted in the revision in favor of space.

Response: Text was deleted in the revision in favor of space.

3. 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, as well as subsequent author queries. 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:

1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.

2. OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries.

Response: Yes, please publish my response letter and subsequent email correspondence related to author queries.

4. Each author on this manuscript must submit a completed copy of our revised author agreement form (updated in the August 2014 issue). Please note:

a) **Any material included in your submission that is not original or that you are not able to transfer copyright for must be listed under I.B on the first page of the author agreement form.**

b) All authors must disclose any financial involvement that could represent potential conflicts of interest in an attachment to the author agreement form.

c) All authors must indicate their contributions to the submission by checking the applicable boxes on the author agreement form.

d) The role of authorship in Obstetrics & Gynecology is reserved for those individuals who meet the criteria recommended by the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org):

*** Substantial contributions to the conception or design of the work;**

OR

the acquisition, analysis, or interpretation of data for the work;

AND

*** Drafting the work or revising it critically for important intellectual content;**

AND

*** Final approval of the version to be published;**

AND

*** Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.**

The author agreement form is available online at http://edmgr.ovid.com/ong/accounts/agreementform.pdf. Signed forms should be scanned and uploaded into Editorial Manager with your other manuscript files. Any forms collected after your revision is submitted may be e-mailed to obgyn@greenjournal.org.

Response: All authors signed author agreement forms.

5. All submissions that are considered for potential publication are run through CrossCheck for originality. The following lines of text match too closely to previously published works. Variance is needed in the following sections:

- Cite the three bullet points (Lines 125-133).

Response: Text was deleted in the revision in favor of space.

6. 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 will be transitioning as much as possible to use of the reVITALize definitions, and we encourage authors to familiarize themselves with them. The obstetric data definitions are available at http://links.lww.com/AOG/A515, and the gynecology data definitions are available at http://links.lww.com/AOG/A935.

Response: Thanks for the recommendation. We tried to stick with standardized obstetrics and gynecology data definitions throughout the manuscript.

7. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Current Commentary articles should not exceed 12 typed, double-spaced pages (3,000 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and appendixes).

Response: The revised manuscript fits the stated page and word limits above.

8. Specific rules govern the use of acknowledgments in the journal. Please edit your

acknowledgments or provide more information in accordance with 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 signature on the journal's author agreement 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).**

Response: Included as follow:

"Acknowledgments: Special thanks are due to the members of Fetal Therapy Board at Texas Children's Hospital for their support."

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, written in the present tense and stating 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."

Response: Included.

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.

Response: Checked.

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Current Commentary articles, 250 words. Please provide a word count.

Response: Checked (132 words).

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.

Response: Checked

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.

Response: Corrected.

13. 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.

Response: Checked and corrected.

14. Figure 1 may be resubmitted as-is.

Response: We resubmitted figure 1 as is.

15. If you choose to revise your manuscript, please submit your revision via Editorial Manager for Obstetrics & Gynecology at http://ong.editorialmanager.com. It is essential that your cover letter list point-by-point the changes made in response to each criticism. Also, please save and submit your manuscript in a word processing format such as Microsoft Word.

Response: Point by point changes are submitted separately in track-change form.

From: [redacted]
To: Randi Zung
Subject: Re: Your Revised Manuscript 18-1357R1
Date: Thursday, October 11, 2018 11:27:23 PM
Attachments: 18-1357R1 ms (10-9-18v5) Plain Text.docx
18-1357R1 ms (10-9-18v5) Revised.docx

Dear Randi,

We thank Dr. Chescheir for her valuable comments.
Please see the point-by-point responses attached in track changes and plaintexts. All comments are addressed in the text and below:

1. Running Foot: For the running foot, just Ethics of Maternal-Fetal Surgery is fine since seropositivity isn't quite correct.
Response: Confirmed.

2. Precis and elsewhere: Please note my prior concerns about talking about "serpositivity"-which denotes those with antibody. For Hep B and Hep C, being seropositive doesn't not necessarily mean there is active virus present. Throughout, please change seropositive to "infected."
Response: Corrected throughout.

3. Line 55: What conference? Perhaps, "....have a minimal risk of transmitting the virus to their fetus (1), anecdotally, fetal centers' leadership are hesitant to offer....."
Response: Text updated.

4. Line 61: Please spell out "MOMs" here.
Response: Corrected.

5. Lines 124-125: Please spell out "TTTS," "FETO," "LUTO," and "IUT" here. These appear to be the first use.
Response: Corrected.

6. Line 128: Please note the edit to make "address."
Response: Confirmed.

7. Line 151-152: The text actually needs to be deleted still. If the sentence that is struck-through is deleted, does the citation number (18) still needed here? Please make the edit directly to the text.
Response: Corrected.

8. Line 152: Do you mean Hepatitis B? Elsewhere, that is what you call it. Please be consistent.
Response: Corrected.

9. Page 17: The version of Table 1 that you sent back to me was inserted into the manuscript. Please review this to make sure it is correct.
Response: Confirmed.

10. General: The Editor has made edits to the manuscript using track changes. Please review them to make sure they are correct.

Response: Confirmed.

Thanks,
Shami

Alireza A. Shamshirsaz, M.D., FACOG

[redacted]

Science knows no country, because knowledge belongs to humanity, and is the torch which illuminates the world. Louis Pasteur (1822 - 1895)

On Tuesday, October 9, 2018 10:30:02 AM CDT, Randi Zung <RZung@greenjournal.org> wrote:

Dear Dr. Shamshirsaz:

Dr. Chescheir has reviewed your latest version. She has some additional comments for you to address. They are highlighted in yellow in the attached file and are listed below:

1. Running Foot: For the running foot, just Ethics of Maternal-Fetal Surgery is fine since seropositivity isn't quite correct.
2. Precis and elsewhere: Please note my prior concerns about talking about "serpositivity"-which denotes those with antibody. For Hep B and Hep C, being seropositive doesn't not necessarily mean there is active virus present. Throughout, please change seropositive to "infected."
3. Line 55: What conference? Perhaps, "....have a minimal risk of transmitting the virus to their fetus (1), anecdotally, fetal centers' leadership are hesitant to offer....."
4. Line 61: Please spell out "MOMs" here.
5. Lines 124-125: Please spell out "TTTS," "FETO," "LUTO," and "IUT" here. These appear to be the first use.
6. Line 128: Please note the edit to make "address."
7. Line 151-152: The text actually needs to be deleted still. If the sentence that is struck-through is deleted, does the citation number (18) still needed here? Please make the edit directly to the text.
8. Line 152: Do you mean Hepatitis B? Elsewhere, that is what you call it. Please be consistent.
9. Page 17: The version of Table 1 that you sent back to me was inserted into the manuscript. Please review this to make sure it is correct.

Please make your changes to v4 (attached). Please send me your next version when you are finished.

Thanks,
Randi

From: alireza shamshirsaz[redacted]
Sent: Sunday, October 7, 2018 11:59 AM
To: Randi Zung <RZung@greenjournal.org>; [redacted]
Subject: Your Revised Manuscript 18-1357R1

Dear Zung,

We would like to thank for the detailed comments and the opportunity to submit a revision.
Please see the attached files and below the point by point answers to the reviewers' comments.

Bests,
Shami

EDITORS' COMMENTS :

Your revised manuscript is being reviewed by the Editors. Before a final decision can be made, we need you to address the following queries. Please make the requested changes to the latest version of your manuscript that is attached to this email. **Please track your changes and leave the ones made by the Editorial Office.** Please also note your responses to the author queries in your email message back to me.

1. General: The Editor has made edits to the manuscript using track changes. Please review them to make sure they are correct.

Response: The changes are attached in track-change format.

2. Please submit an Author Agreement form for Dr. Aagaard with both the "Disclosure of Potential Conflicts of Interest" and "Authorship" sections completed.

Response: Attached to this email.

3. Line 23: Would you be more specific about how they contributed?

Response: Text updated.

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.

Please provide a signed version of this statement. A blank copy is attached.

Response: Attached to this email

5. Line 55: I moved the "with HIV infection" so that it is describing the mother (not her fetus) and deleted "evidence of" because she either has HIV disease or she doesn't…

Response: Confirmed.

6. Line 56: What is the data that supports this statement? How do you know that fetal centers are hesitant to do this?

Response: Text updated.

7. Line 56: On lines 56-61, you only describe HIV so when, on sentence on line 61 when you say "as a consequence" you have not supported anything that would "as a consequence" have anything to do with Hepatitis. You could get around this by saying something at the end of the of the sentence that ends on 61 like…"iatrogenic viral transmission to the fetus. Similar concerns exist in cases of active maternal Hepatitis B and C. As a consequence….". As a note—seropositive typically refers to having hepatitis antibodies. You specifically are concerned about women with the presence of hepatitis virus. Merriam Webster defines seropositive as "Definition of seropositive. : having or being a positive serum reaction especially in a test for the presence of an antibody." Please amend throughout as you are talking about women who have virus—detected by antigen testing or PCR—not just antibodies.

Response: Text updated.

8. Line 61: Please spell out all abbreviations on first use. It is reasonable to not use abbreviations for words that are seldom used in the paper. As well, please consult the Instructions for Authors regarding the use of abbreviations, and what constitutes an acceptable abbreviation. This is not an acceptable abbreviation. Please spell the words out throughout the manuscript.

Response: Corrected.

9. Line 68: I am confused by your use of Phase I trials here. Phase 1 is the initial introduction of an experimental drug or therapy to humans. This phase is the first step in the clinical research process involved in testing new or experimental drugs. (per Wikipedia). It would be important to define this in your paper (using some other reference than Wikipedia). Are you therefore specifically talking about Phase 1 trials of untested maternal-fetal interventions and that the presence of one of these active viral diseases should not be an exclusion criterium? Or are you saying that studies of existing procedures (such as laser, ONTD repair, IUT) should be done to study safety specifically in this population? I'm not sure that would be a phase 1 trial. Also, those studies have been done (or the interventions just accepted) so it's not that you would be "including" women with these viral diseases, but that you be doing a Phase 1 trial specifically in those populations—that is, women without these viruses would NOT be included.

Response: We used the term "Fetal intervention research studies" throughout the manuscript.

10. Line 72: Please avoid single sentence paragraphs. Also, you've used the word "ethical" three times in this one sentence. Could you edit this? Perhaps something like "Pertinent biomedical ethics principles include respect for autonomy of the pregnant patient, fetal status as a patient or not, balance of potential risks and benefits for the women, her fetus and the potential neonate, and the ethical principle of justice."

Response: Text updated.

1. Line 93: You need a reference here. Please make sure you renumber your in-text citations and reference list if you are adding a new reference.

Response: Reference inserted and the order refreshed in the plain text file.

12. Line 101: Again, I argue that if the interventions have been accepted clinical practice, then you are not talking about a phase 1 trial. I think you need to be really clear about what you are proposing. I think you are suggesting doing a safety study of established interventions in women with active viral disease with low or non-detectable viral load. If that is the case, it might be clearer to say something more clearly like. "These criteria support safety studies of maternal-fetal interventions that have become accepted clinical practice in women with HIV, Hepatitis B or Hepatitis C in order to evaluate the risk of vertical transmission.

If that is not your intent, then please do be clearer.

Response: Per comment #9, we used the term "Fetal intervention research studies" throughout the manuscript.

13. Line 102: Perhaps its sufficient to say something like "Table 1 summarizes the data on risks and benefits for some established maternal-fetal interventions. We are advocating for study of these procedures in women with active HIV, Hepatitis B or C with low or undetectable viral loads." And delete the rest of line 120-123.

I'm unclear what you are saying in lines 124-130. If I understand it properly perhaps something like the following would be clearer? Prior studies of these interventions limited to women without HIV, Hepatitis B or Hepatitis C have shown an acceptable level of risk of both maternal and fetal death or neonatal death or morbidity. Proposed study of these interventions in pregnant women with low or undetectable levels of HIV, Hepatitis B or C would explore whether these procedures increase rates of vertical transmission, the degree of harm caused by vertical transmission, and whether the outcomes from the intervention are otherwise similar to those done in uninfected women". Is this what you mean?

Response: Text updated.

14. Line 115: Please expand this.

Response: Corrected.

15. Line 116: Not clear what this means. If you remove the dependent clauses this reads: “Viral transmission is probably because of very effective post-natal treatments….”. That doesn’t really make sense. Vertical transmission doesn’t depend on post-natal treatment. Yes—HAART can render the infected individual to have an undetectable viral load but doesn’t eliminate the disease. Hep C can be cured now but I don’t think its use has been studied in neonates. Perhaps it’s worth noting that the theoretic risk of vertical transmission is related to exposure of the fetal circulation to infected amniotic fluid or maternal blood.

Response: Text deleted.

16. Line 119: This reads as if you are saying “the data for viral transmission relates to the risk of transmission”. What do you mean?

Response: Text updated.

17. Line 120: What is the vertical transmission rate of the 8500 women? I think you could shorten this discussion a bit.

- Describe the rate (25-28%) in HIV + women delivered vaginally without treatment
- Women with viral loads < 1,000 have < 2% risk of transmission to the fetus (by any route?)
- Increasing risk with increasing viral burden
- Multicenter study of invasive prenatal diagnosis procedures in women on HAART (viral loads known???) with no transmission.

Response: Text updated.

18. Line 137: The struck-through sentence not relevant to discussion. Please delete this from the text and update your in-text citation and reference numbering.

Response: Text deleted.

19. Line 147: See comments earlier regarding exposure of fetal circulation to maternal compartment with virus.

Response: Addressed.

20. Line 150-156: Although each of these viral infections can be treated with resulting complete cure in the case of Hepatitis C or control of HIV disease and Hepatitis B, there is limited understanding of the use of the medications required to for so in the neonatal patient, their effectiveness and potential side effects.

Response: Agreed.

21. Line 158: Not sure what you mean with this sentence. What do you mean “minimized to current level”?? What current level.

Please pull the information about risk of transmission all to one section. You have it scattered in several places. Then you can organize it better, avoid redundancy, etc.

Response: Text edited.

22. Line 161: What data? Do you have references?
Response: Text deleted.

23. Line 162: Again, tissue manipulation is important, but infection is going to occur for these primarily blood-borner disorders only if fetal blood is exposed to infected maternal tissue (such as amniotic fluid, maternal blood).
Response: Text updated.

24. Line 165: How do you consider FETO a placental procedure? I agree with the reviewer who commented that this rubric is perhaps artificial. You may have a sense of the likely outcomes of the different procedures, but that is to be determined by the study you are proposing. You don't really know. I've seen IUTs where there have been several attempts at cordocentesis with the needle going in and out of the Amniotic fluid before gaining fetal venous access. This may have a higher risk than some of the open procedures.
Response: Agreed. Figure 1 updated.

25. Line 173: As noted above, I think this is premature. You have some hypotheses about risk for vertical transmission along the lines you describe, but we really don't know.
Response: Text updated.

26. Line 177: How is this relevant?
Response: Text deleted.

27. Line 196: I'm not entirely clear how this whole description relates to justice.
Response: Text updated.

Science knows no country, because knowledge belongs to humanity, and is the torch which illuminates the world. Louis Pasteur (1822 - 1895)

From: [redacted]
To: Stephanie Casway
Subject: Re: O&G Art Revision: 18-1357
Date: Wednesday, October 10, 2018 9:45:04 PM

Look great.

Thanks

Sent from my iPhone

On Oct 9, 2018, at 10:23 PM, Stephanie Casway <SCasway@greenjournal.org> wrote:

> Good Afternoon Dr. Shamshirsaz,
>
> Your figure has been edited, and PDFs of the figure and legend are attached for your review. Please review the figure and legend CAREFULLY for any mistakes.
>
> PLEASE NOTE: Any changes to the figures must be made now. Changes made at later stages are expensive and time-consuming and may result in the delay of your article's publication.
>
> To avoid a delay, I would be grateful to receive a reply no later than Thursday, 10/11. Thank you for your help.
>
> Best wishes,
>
> Stephanie Casway, MA
> Production Editor
> *Obstetrics & Gynecology*
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