OBSTETRICS & GYNECOLOGY

NOTICE: This document contains correspondence generated during peer review and subsequent revisions but before transmittal to production for composition and copyediting:

- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*

**The corresponding author has opted to make this information publicly available.*

Personal or nonessential information may be redacted at the editor's discretion.

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

Date: Jun 08, 2020
To: "Carlota Rodo" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-1480

RE: Manuscript Number ONG-20-1480

Fetal transient skin edema in two pregnant women with COVID-19

Dear Dr. Rodo:

Your manuscript has been reviewed by the Editorial Board and by special expert referees. The Editors are interested in potentially publishing your revised manuscript in a timely manner. In order to have this considered quickly, we need to have your revision documents submitted to us as soon as you are able. I am tentatively setting your due date to June 10, 2020, but please let me know if you need additional time.

The standard revision letter text follows.

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).

REVIEWER COMMENTS:

Reviewer #1: This case report is well written and timely. With the addition of a few more details, it would add to current knowledge about COVID 19 in pregnancy:

1.Your report states that there was fetal edema but you provide only images of scalp edema. Since isolated scalp edema can have different etiologies than total body edema, please clarify: was there only scalp edema or was there truncal edema, edema of the feet, etc?

2. Since both skin edema and fetal tachycardia can be early signs of cardiac failure (and fetal cardiac decompensation is still a possible etiology for the edema in your cases), please specify what the serial fetal heart rates were (did the baseline fetal heart rates stay low, or was there a trend toward higher heart rates or episodes of tachycardia?).

3.Please edit lines 178-181 to make it clear that the ACE2 receptor is a SARS receptor.

4. Please clarify the sentence on lines 196-197; are you referring to maternal cytokines, fetal cytokines, or both?

5. You correctly state that current protocols recommend, for safety reasons, delaying ultrasound scans while pregnant women are positive for COVID19- yet you conclude your report by recommending close fetal surveillance for COVID 19 pregnancies. Are you recommending serial ultrasound exams as part of fetal surveillance, in contrast to current advice? If so, would this be for information purposes only or because you believe the results could alter pregnancy management? Please clarify.

Reviewer #2: The authors present 2 case reports of unexplained fetal skin edema in women with COVID-19 in Spain. I have several questions for the authors:

1. It would be helpful to report how many women with COVID-19 were seen in the ultrasound unit over the same time period, to get a sense of the incidence (and 95% confidence interval) of skin edema (2 out of 10? 2 out of 100? etc). since they scanned everyone weekly, their incidence should be relatively accurate.

2. similarly, it would be helpful to report how many women without COVID-19 (or suspected COVID-19) presented for second trimester ultrasound in the same time period and how many of them, if any, had fetal skin edema. this, plus the

data in #1 would be very useful to put this all into context

3. figure 2 should include more images of the skin edema for both cases, either different views of the same anatomical area, or different anatomical areas, if the edema was generalized.

Reviewer #3: The authors have submitted a case report with 2 cases of fetal skin edema that they are trying to tie into COVID-19. Couple of questions come immediately to mind: 1) how likely is this to be related and 2) how reliable are the findings (sonogram?)

1 - Introductory paragraph beginning line 66 could be shortened significantly as everyone is aware by now

2 - It is stated that the risk of M-M transmission (line 80) is controversial, but from what is known it seems vanishingly remote

3 - The many confounders as to what might have resulted in the skin edema are highlighted in line 102

4 - There is a lot of unnecessary info provided (line 110+ as an example)

5 - Is there any data of mothers pregnant in 2nd trimester being intubated for a week and whether you might see fetal skin edema from that alone?

6 - It was understandable in Case 1 why the patient was getting 'fetal wellbeing' scans on a daily basis, but why was an ultrasound performed (line 150) on Case 2 at this point? One would think it would not be ideal to bring a symptomatic COVID-positive pt to the clinic for a (elective?) scan only 8 days after diagnosis.

7 - Both patients got a big workup (including amnio) based on a sono finding. What was the leading diagnosis? What were the authors looking for?

8 - Paragraph beginning line 177 seems to give the impression COVID-19 has intrauterine transmission, but supported by a few anecdotes only, and since neither of the 2 cases had + amnios, nor did neonates in line 184 test positive the reader indirectly concludes this is not a common event

9 - Line 189 is relevant in pointing out is there any value in knowing that obvious COVID-19 pregnant women can have a transient fetal sono finding that goes away as the viral infection is cleared. The reader is unconvinced

10 - Line 206 not necessary to point out that COVID is a new disease. Also, hardly breaking news 'that fetuses may be affected in some way"

11 - How do the authors justify the teaching point claiming that 'fetal surveillance is strongly recommended'? They were scanning case 1 daily for fetal well-being as mom was intubated in ICU and case 2 only because of a study protocol - which itself seems quite hazardous to staff, other patients, etc when bringing in symptomatic COVID-19 moms for elective sono. The authors saw fetal skin edema in both cases, initiated a huge workup - including amnio - to identify nothing of importance and then the edema went away as COVID went away. More justification is needed for why they think the broader global community needs to conduct fetal surveillance that could/would in theory expose many providers etc unnecessarily to COVID-19

EDITOR'S COMMENTS:

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Numbers below refer to line numbers.

23. Rather than the more general background information about COVID-19 about which the readers will be aware, could you expand a bit re: vertical transmission? Just a statement or so about any evidence supporting it (placenta RNA? Neonatal + cases?)

28. Rather than say “we present” just give us the facts. We know you are presenting the caxes.

33. Would you consider substituting “abnormality” for “anomaly”? Skin edema is a physiologic finding, not a structural anomaly. Did the edema resolve? Do you have neonatal findings?

42. I agree with the reviewer who recommended tempering your conclusion that fetal surveillance is strongly recommended. There have been few cases in the literature as yet of maternal infections prior to the 3rd trimester and as you note, yours is the first case report of fetal findings out of what is likely 1000’s of infected pregnant women. What do you mean by “surveillance”? Regular antenatal testing like Non Stress Tests? One Ultrasound? Serial Ultrasounds? It would be fine to have only 1 teaching point and expand on these questions ein the manuscript.

66. The official name of the disease is “Coronavirus Disease (COVID-19)” so son’t include the “2019”.

71. Give the date and update the stats with your final submission.

72. This is a very broad, and not necessarily accurate, statement. Most maternal infections do not cause fetal injury. Also, (line 76) the fetus can become infected, for instance with GBS or herpes, through ascending infections. You could shorten this paragraph 72-29 quiete a bit for this readership. Instead of this paragraph, could you provide some background about # of pregnant women reported to date with information about evidence of placental infection? You could build on the statement about importance of gestational age at time of maternal infection for many infections and the paucity of reports of outcomes of pregnancy prior to the 3rd trimester for COVID-19. The sentence starting on line 7 and the one starting on 81 convey essentially the same information.

Case 1: Had the patient previously had a normal anatomic survey? Even though this pregnancy was conceived by donor egg, had she had preimplantation genetic testing, or cell free DNA or amnio/cvs earlier in the pregnancy? On line 128 you give the results of a microarray test that is sort of buried in the results of the infectious, inflammatory results. Would you consider moving these results up to line 124 at the beginning of the amnio results?

WG is not an acceptable abbreviation. Just spell out week of gestation.

142. Who tested positive? All 3 (husband and parents?)

156. These would have been diagnostic, not screening tests. Please state what tests you did.

160. Negativization is not a word.

162-164. Delete.

167: Don’t say “we report”.

168. Delete “In both fetuses” as these are the cases being presented.

175. Please edit out the “to our knowledge” or similar wording. As the readers cannot gauge the depth and breadth of your knowledge, this phrase does not add significant meaning. You can either reference your literature search details (database searched and search terms used) that informed your knowledge, or you could say something noting that your cited references provide limited information about this point.

177. Perhaps this could be shortened to “There is as yet inconclusive evidence of transplacentally-acquired fetal infection reported in the literature. A study investigated…..”

190 “which may result in lack of observation of transient fetal abnormalities”.

191: which pregnant women are you scanning weekly? IN case 1 you scanned her daily when she as in the ICU and case 2 was home. The study you describe was not the framework for your first ase.

192 What is the parenthetic information? Is that an IRB #? Just say “ in the framework of an IRB approved observational study…”

204. Given your normal multi-organ Doppler studies in both fetuses, what sort of direct fetal effect are you postulating that would cause isolated skin edema?

MANUSCRIPT EDITOR'S COMMENTS:

1. Add details of a literature search to lines 175-176.

2. Change line 220 from "To conclude, we report the first fetal complication potentially..." to read, "To conclude, we report a fetal complication potentially..."

3. Add a column heading to the first column in Table 1.

EDITORIAL OFFICE COMMENTS:

1. 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.

2. Electronic Copyright Transfer Agreement - Include for all manuscripts.***

Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA). 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.

3. 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 data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions and the gynecology data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

4. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Case Reports should not exceed 8 typed, double-spaced pages (2,000 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.

5. 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).

6. Provide a short title of no more than 40 characters, including spaces, for use as a running foot.

7. 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."

8. 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 limit for Case Reports is 125 words.

9. 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.

10. 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.

11. Line 175: Your manuscript contains a priority claim. We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

12. 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.

13. Figures:

Figure 1: Please upload as a figure file on Editorial Manager. Is this available in color? Please add tick marks along the x and y axes

Figure 2: Please upload high res figure files on Editorial Manager. Please remove the 1A-2B labels on them, these will be added back per journal style.

14. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at http://links.lww.com/LWW-ES/A48. The cost for publishing an article as open access can be found at http://edmgr.ovid.com/acd/accounts/ifauth.htm.

Please note that if your article is accepted, you will receive an email from the editorial office asking you to choose a publication route (traditional or open access). Please keep an eye out for that future email and be sure to respond to it promptly.

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If you choose to revise your manuscript, please submit your revision through Editorial Manager at http://ong.editorialmanager.com. Your manuscript should be uploaded in a word processing format such as Microsoft Word. Your revision's cover letter should include the following:

* 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 30 days from the date of this letter. If we have not heard from you by Jun 10, 2020, 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

_____

[redacted]

Dr. Nancy C. Chescheir
Editor-in-Chief
Obstetrics & Gynecology
June 11st, 2020

Dear Dr. Chescheir,

Please find enclosed the reviewed manuscript of the case report entitled “Fetal transient skin edema in two pregnant women with COVID-19”, which we would like to be considered for publication in Obstetrics & Gynecology. In this document, we report two cases of fetal skin edema during the follow-up of two pregnant women which were diagnosed with COVID-19 in their second trimester of pregnancy. Written consent was obtained from both patients to publish their data.

All the authors carefully read the manuscript and fully approved it. The manuscript is original and is not under consideration elsewhere. It will not be submitted elsewhere unless a final negative decision is made by the Editors of Obstetrics & Gynecology. We would, of course, be ready to provide further information about our data should you so desire. The authors declare not having conflicts of interests regarding this manuscript.

We have read with interest the valuable comments of the reviewers and editor and we have modified the manuscript accordingly. The specific answers to the reviewers’ comments are as follows.

I affirm that this manuscript is an honest, and transparent account of the cases being reported and that no important aspects have been omitted.
I confirm that we have read and followed the Instruction for Authors.
I confirm that all individuals cited in the Acknowledgements gave written permission to be named.
Please address any correspondence about the manuscript to me, as indicated in the first page of the manuscript.

We thank you for your kind consideration. We look forward to hearing from you.

Sincerely,

Carlota Rodo, MD, PhD
Maternal-Fetal Medicine Unit
Department of Obstetrics and Gynecology
Hospital Universitari Vall d'Hebron
Universitat Autònoma de Barcelona

REVIEWER COMMENTS:

Reviewer #1: This case report is well written and timely. With the addition of a few more details, it would add to current knowledge about COVID 19 in pregnancy:

1.Your report states that there was fetal edema but you provide only images of scalp edema. Since isolated scalp edema can have different etiologies than total body edema, please clarify: was there only scalp edema or was there truncal edema, edema of the feet, etc?

Thank you for your comment. In both cases, edema was generalized but scalp and truncal edema were more evident. We have added this information in both cases (lines 116-117).

2. Since both skin edema and fetal tachycardia can be early signs of cardiac failure (and fetal cardiac decompensation is still a possible etiology for the edema in your cases), please specify what the serial fetal heart rates were (did the baseline fetal heart rates stay low, or was there a trend toward higher heart rates or episodes of tachycardia?).

Fetal heart rate was always within the normal range (added in lines 113-114 & 154-155).

3.Please edit lines 178-181 to make it clear that the ACE2 receptor is a SARS receptor.

It has been reworded. Thank you.

4. Please clarify the sentence on lines 196-197; are you referring to maternal cytokines, fetal cytokines, or both?

We are referring to maternal cytokines. Added in line 214.

5. You correctly state that current protocols recommend, for safety reasons, delaying ultrasound scans while pregnant women are positive for COVID19- yet you conclude your report by recommending close fetal surveillance for COVID 19 pregnancies. Are you recommending serial ultrasound exams as part of fetal surveillance, in contrast to current advice? If so, would this be for information purposes only or because you believe the results could alter pregnancy management? Please clarify.

We believe that given these findings and the lack of reports of COVID-19 in the first and second trimesters, a close follow-up of these pregnancies may help to understand the impact on the fetus.

Reviewer #2: The authors present 2 case reports of unexplained fetal skin edema in women with COVID-19 in Spain. I have several questions for the authors:

1. It would be helpful to report how many women with COVID-19 were seen in the ultrasound unit over the same time period, to get a sense of the incidence (and 95% confidence interval) of skin edema (2 out of 10? 2 out of 100? etc). since they scanned everyone weekly, their incidence should be relatively accurate.
We scanned 31 COVID-19 pregnant women. Fetal skin edema was seen in two cases (6,5%; 95% confidence interval, 1,8% to 20,7%) (lines 208-210).

2. Similarly, it would be helpful to report how many women without COVID-19 (or suspected COVID-19) presented for second trimester ultrasound in the same time period and how many of them, if any, had fetal skin edema. This, plus the data in #1 would be very useful to put this all into context.
During the peak of the pandemic, 491 non-COVID-19 women had presented to the Maternal Fetal Unit for the second trimester ultrasound, and none of them had fetal skin edema.

3. Figure 2 should include more images of the skin edema for both cases, either different views of the same anatomical area, or different anatomical areas, if the edema was generalized.
We have added another image for each case.

Reviewer #3: The authors have submitted a case report with 2 cases of fetal skin edema that they are trying to tie into COVID-19. Couple of questions come immediately to mind: 1) how likely is this to be related and 2) how reliable are the findings (sonogram?)

1 - Introductory paragraph beginning line 66 could be shortened significantly as everyone is aware by now

Done. Thank you.

2 - It is stated that the risk of M-M transmission (line 80) is controversial, but from what is known it seems vanishingly remote

Thank you for your opinion. Since new evidence has arisen recently of the presence of the virus in placenta (references 5-8), we still think that vertical transmission remains controversial.

3 - The many confounders as to what might have resulted in the skin edema are highlighted in line 102

This is discussed in the “limitations” paragraph. We state that fetal edema is a non-specific finding (line 229). Furthermore, the patient from case 2 did not receive any drugs for COVID-19.

4 - There is a lot of unnecessary info provided (line 110+ as an example)

Thank you for your opinion. All information provided is intended to reflect the differences in the severity of COVID-19 for each woman, and how similar the fetal edema is, despite the maternal status.

5 - Is there any data of mothers pregnant in 2nd trimester being intubated for a week and whether you might see fetal skin edema from that alone?

Our hospital is a tertiary care facility and we treat pregnant women with severe pathology. We have around 100 pregnant women per year who require admission to intensive or semi-intensive care units. However, intubation is rare. Even so, it is the first time that we noticed this finding in a fetus; and after a search in PubMed, we are not aware of any other similar reports in the literature.

6 - It was understandable in Case 1 why the patient was getting 'fetal wellbeing' scans on a daily basis, but why was an ultrasound performed (line 150) on Case 2 at this point? One would think it would not be ideal to bring a symptomatic COVID-positive patient to the clinic for a (elective?) scan only 8 days after diagnosis.

As explained in lines 193-195, at our center we are performing an IRB approved observational study (PR(AMI)181/2020), which includes weekly microbiological sampling and ultrasound examinations in pregnant women with COVID-19. We adapted an independent clinic, with a parallel circuit, that allows minimum contact between COVID and non-COVID patients.

7 - Both patients got a big workup (including amniocentesis) based on a sonographic finding. What was the leading diagnosis? What were the authors looking for?

Nuchal edema in the second trimester is in itself an indication to perform additional studies. We aimed to rule out genetic anomalies and infections, including SARS-CoV-2 (lines 123-130 & 159-165).

8 - Paragraph beginning line 177 seems to give the impression COVID-19 has intrauterine transmission, but supported by a few anecdotes only, and since neither of the 2 cases had + amniocentesis, nor did neonates in line 184 test positive the reader indirectly concludes this is not a common event.

Lines 198-200 refer to other reports different from ours.

We agree with the reviewer that this is not a common event.

9 - Line 189 is relevant in pointing out is there any value in knowing that obvious COVID-19 pregnant women can have a transient fetal sonographic finding that goes away as the viral infection is cleared. The reader is unconvinced.

Removed sentence.

10 - Line 206 not necessary to point out that COVID is a new disease. Also, hardly breaking news 'that fetuses may be affected in some way".

Deleted. Thank you.

11 - How do the authors justify the teaching point claiming that 'fetal surveillance is strongly recommended'? They were scanning case 1 daily for fetal well-being as mom was intubated in ICU and case 2 only because of a study protocol - which itself seems quite hazardous to staff, other patients, etc when bringing in symptomatic COVID-19 moms for elective sono.

The authors saw fetal skin edema in both cases, initiated a huge workup - including amnio - to identify nothing of importance and then the edema went away as COVID went away. More justification is needed for why they think the broader global community needs to conduct fetal surveillance that could/would in theory expose many providers etc unnecessarily to COVID-19.

Thank you for your comment. We think that these pregnancies should be closely followed-up, not while SARS-CoV-2 remains positive but when it turns negative. All public health recommendations regarding patients and healthcare providers were followed. We assessed these pregnancies on a weekly basis as a part of a study, and we had a separated clinic and a different medical team for positive-SARS-CoV-2 women.

EDITOR'S COMMENTS:

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 relevant topics. Adherence to these requirements with your revision will avoid delays during the revision process by avoiding re-revisions on your part in order to comply with formatting.

Numbers below refer to line numbers.

Done. Thank you.

23. Rather than the more general background information about COVID-19 about which the readers will be aware, could you expand a bit re: vertical transmission? Just a statement or so about any evidence supporting it (placenta RNA? Neonatal + cases?)

Thank you, we have modified this paragraph.

28. Rather than say “we present” just give us the facts. We know you are presenting the cases.

Reworded paragraph (lines 43-45).

33. Would you consider substituting “abnormality” for “anomaly”? Skin edema is a physiologic finding, not a structural anomaly. Did the edema resolve? Do you have neonatal findings?

Reworded paragraph (lines 45-48).

42. I agree with the reviewer who recommended tempering your conclusion that fetal surveillance is strongly recommended. There have been few cases in the literature as yet of maternal infections prior to the 3rd trimester and as you note, yours is the first case report of fetal findings out of what is likely 1000’s of infected pregnant women. What do you mean by “surveillance”? Regular antenatal testing like Non-Stress Tests? One Ultrasound? Serial Ultrasounds? It would be fine to have only 1 teaching point and expand on these questions in the manuscript.

We meant maternal and fetal surveillance: weekly SARS-CoV-2 RT-PCR, clinical follow-up and ultrasound. We reworded the conclusion in order to clarify this point.

66. The official name of the disease is “Coronavirus Disease (COVID-19)” so don’t include the “2019”.

Removed. Thank you.

71. Give the date and update the stats with your final submission.

Numbers in Spain are updated (lines 62-64).

72. This is a very broad, and not necessarily accurate, statement. Most maternal infections do not cause fetal injury. Also, (line 76) the fetus can become infected, for instance with GBS or herpes, through ascending infections. You could shorten this paragraph 72-29 quite a bit for this readership. Instead of this paragraph, could you provide some background about # of pregnant women reported to date with information about evidence of placental infection? You could build on the statement about importance of gestational age at time of maternal infection for many infections and the paucity of reports of outcomes of pregnancy prior to the 3rd trimester for COVID-19. The sentence starting on line 7 and the one starting on 81 convey essentially the same information.

Thank you for your suggestions, we have modified the paragraph accordingly.

Case 1: Had the patient previously had a normal anatomic survey? Even though this pregnancy was conceived by donor egg, had she had preimplantation genetic testing, or cell free DNA or amnio/cvs earlier in the pregnancy?

Added (line 91).

On line 128 you give the results of a microarray test that is sort of buried in the results of the infectious, inflammatory results. Would you consider moving these results up to line 124 at the beginning of the amnio results?

Moved to lines 123-125.

WG is not an acceptable abbreviation. Just spell out week of gestation.

Done. Thank you.

142. Who tested positive? All 3 (husband and parents?)

Corrected.

156. These would have been diagnostic, not screening tests. Please state what tests you did.

Described in lines 160-164.

160. Negativization is not a word.

Corrected.

162-164. Delete.

Done. Thank you.

167: Don't say "we report".

Done. Thank you.

168. Delete "In both fetuses" as these are the cases being presented.

Done. Thank you.

175. Please edit out the "to our knowledge" or similar wording. As the readers cannot gauge the depth and breadth of your knowledge, this phrase does not add significant meaning. You can either reference your literature search details (database searched and search terms used) that informed your knowledge, or you could say something noting that your cited references provide limited information about this point.

Sentence removed.

177. Perhaps this could be shortened to "There is as yet inconclusive evidence of transplacentally-acquired fetal infection reported in the literature. A study investigated….."

Added in lines 188-189. Thank you for your suggestion.

190 "which may result in lack of observation of transient fetal abnormalities".

Changed in lines 204-205. Thank you for your suggestion.

191: Which pregnant women are you scanning weekly? IN case 1 you scanned her daily when she as in the ICU and case 2 was home. The study you describe was not the framework for your first case.

Women admitted into the ICU were scanned daily to assess fetal vital signs, as we normally do in clinical practice. A complete ultrasound scan was performed weekly by MMF in the framework of the study (lines 111-113).

192 What is the parenthetic information? Is that an IRB #? Just say "in the framework of an IRB approved observational study…"

Done (line 206). Thank you for your suggestion.

204. Given your normal multi-organ Doppler studies in both fetuses, what sort of direct fetal effect are you postulating that would cause isolated skin edema?

Sorry, this is a misunderstanding due to Spanish translation. It has been reworded.

MANUSCRIPT EDITOR'S COMMENTS:

1. Add details of a literature search to lines 175-176.

Sentence removed.

2. Change line 220 from "To conclude, we report the first fetal complication potentially..." to read, "To conclude, we report a fetal complication potentially..."

Done (line 262). Thank you.

3. Add a column heading to the first column in Table 1.

Done (line 324). Thank you.

EDITORIAL OFFICE COMMENTS:

1. 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.

We opt for OPT-IN.

2. Electronic Copyright Transfer Agreement - Include for all manuscripts.***

Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA). 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.

3. Standard obstetrics 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 data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions and the gynecology data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

Already revised. Thank you.

4. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Case Reports should not exceed 8 typed, double-spaced pages (2,000 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.

Done. Thank you.

5. 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.

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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).

Acknowledgements reported (lines 26-31).

6. Provide a short title of no more than 40 characters, including spaces, for use as a running foot.

Done (line 24).

7. 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."

Done (lines 32-33). Thank you.

8. 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 limit for Case Reports is 125 words.

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9. 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.

Revised. Thank you.

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Sentence removed.

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Thank you, it has been reviewed.

13. Figures:

Figure 1: Please upload as a figure file on Editorial Manager. Is this available in color? Please add tick marks along the x and y axes.

Figure 1 is available in color.

Figure 2: Please upload high res figure files on Editorial Manager. Please remove the 1A-2B labels on them, these will be added back per journal style.

We added two more images to figure 2. Labels have been removed and the footnote has been rephrased.

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