

# 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](mailto:obgyn@greenjournal.org).

**Date:** Jul 27, 2020  
**To:** "Lorenzo Berra" [REDACTED]  
**From:** "The Green Journal" em@greenjournal.org  
**Subject:** Your Submission ONG-20-2020

RE: Manuscript Number ONG-20-2020

Benefits of Breathing High Concentrations of Nitric Oxide in Pregnant Patients with Severe COVID-19

Dear Dr. Berra:

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 July 29, 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).

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#### REVIEWER COMMENTS

Reviewer #1: This paper describes a novel potential method for supporting/treating pregnant women admitted with severe COVID 19 infection. This revised paper is a response to the reviewer's comments regarding their previous iteration, which included rewriting the piece to qualify as a Procedures and Instruments report. Issues to be addressed include:

##### 1. In the Methods section:

Under Study Design, when describing disease classification, instead of referencing two prior papers (which requires uninformed readers to try and look them up), please refer to your own Table, which includes the criteria (and add an explanation of severe vs critical to the caption underneath the table).

Under Nitric Oxide Delivery Device, following your explanation of how nitric oxide can damage epithelial cells, please add a brief explanation of how increased methemoglobin saturation occurs, its adverse effects, and how you reduce the level in this situation (since that is also an adverse effect that is mentioned several times but not explained).

Please indicate how frequently treatments were given (how many per day, and how many hours apart)

##### 2. Under Experience:

Please explain what you mean by "rescue therapy". This term implies that the patients were worsening despite standard therapy, but 2 of the patients in the study had had symptoms for only 3 days (and one of these had an SpO2 > 93%) and were categorized as severe, not critical.

In the text you state that heart rate was unchanged compared to baseline but in the caption underneath the figure you state that heart rate changed significantly (the latter appears to be more true, but the change cannot be described as [statistically] significant).

Despite the fact that you describe the beneficial effects of nitric oxide therapy as including improved oxygen delivery to the fetal circulation, and the fact that the fetal heart rate is considered part of the pregnant patient's vital signs, no information on fetal heart rate patterns is provided. Please report what happened to the FHR, if anything, during and after nitric oxide treatments (add data to the table or a cell to the figure, if possible, to stay within your word count).

The clinical details provided in under "Outcome and follow-up" (except the last sentence about discharge) are really about

the clinical course while receiving nitric oxide therapy, and should be moved into the "experience" section.

### 3. In the Discussion section:

You state for the first time that 83% of patients showed viral clearance by the time of discharge (within 28 days). This result belongs in the patient experience section. If possible, please report how quickly the virus cleared relative to nitric oxide therapy.

Figure 3 is a pictorial representation of the benefits of nitric oxide therapy, which are also listed in the text. This figure should be removed, and replaced by the clinical flow chart in the Appendix describing your nitric oxide protocol (and BTW, this figure implies that some patients received continuous nitric oxide therapy in addition to the periodic high dose treatments; if this is correct, please add to the Treatment section).

Reviewer #2: The authors present a Procedures and Instruments article describing the use of inhaled NO gas for pregnant women admitted with COVID infection. This was submitted previously as a different article type and reviewed and one of the suggestions was to change it to a Procedures and Instruments article type. The authors also revised the manuscript in accordance with the other recommendations made by the Editors and two reviewers. I have a few comments on the revised manuscript.

my comments all revolve around rewording the manuscript to read more like a Procedures and Instruments article than a Research article. The main difference is that the former is not intended to demonstrate/prove benefit, but rather present it as a viable option.

1. I would change the title. The main purpose of the article is to present NO as an option, not to demonstrate Benefits. Maybe something like "Nitric Oxide Therapy in Pregnant patients with Severe COVID-19"
2. for the abstract Methods, change from "to assess the therapeutic effects" to something more like "to report the use of".
3. for the abstract conclusion, change to something along the lines of: NO is an option, easy to use, appears to be well-tolerated, and might be of benefit.
4. the two figures from the supplementary digital content should be the ones included in the manuscript (the protocol for NO use, how it is hooked up), whereas the patient data and clinical outcomes should be the tables/figures moved to the supplemental content

### STATISTICAL EDITOR

Table 1: The number of NO sessions per patient were: 2,3,4,5,7 and 18. Only from the n=18 could a reasonable approximation of the IQR be estimated with any precision. Should cite NO dose as median(range), not median IQR and could include full enumeration in on-line material.

Fig 1a: It appears that the increase was due to the improvement in SpO<sub>2</sub>/FiO<sub>2</sub> for patient #1. Moreover, pts # 1,2,3 had differing numbers of NO sessions, totaling 26, but only 13 were used in Fig 1a. I suspect that each of the patients had differing counts of # of sessions, which means that they cannot be statistically considered as (1) 13 independent events and (2) must have a weighted analysis, based on the the relative number of sessions for each patient. Therefore the conclusion should be descriptive and not statistical, based on the analysis shown.

Fig 1b: Again, there are not 39 independent observations, in fact almost 1/2 observations were from one patient (#3), so adjustment should be made for correlation within each individual of RR.

Fig 1c and 1d: Again, the analysis appears to be based on assumption of independence for all the observations.

Figs 1b,c,d: These apparently show the median with IQR, but those are based on assumption of independence of all observations, ie, they were given equal weight mathematically, which is incorrect.

Fig 2a: It is not stated whether there were more than one measurement per patient, should so state and based on the number of patients, should use median(range) format.

Fig 2b: Was this patient (or any of the others) treated with dexamethasone or other steroids?

## EDITOR 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. For instance, there are no subheadings within the major headings, such as "Methods".

Numbers below refer to line numbers.

Title. Please delete "Benefits of" from the title.

69. Please note that your study was conducted from date 1 to date 2, not between those dates. As written, it would exclude the dates given. Also, please state if all were SARS-CoV-2 RT PCR positive.

79. Please note "were associated with improved systemic oxygenation and reduced tachypnea". As this is an observational report, not an RCT, please avoid causal language.

81. Do use single sentence paragraphs.

108. This sentence is unclear as written. There is no subject/verb agreement.

Perhaps this would work "Given well established benefit of NO for ARDS and pulmonary hypertension in adult patients prior to the COVID-19 pandemic and the lack of data to support other interventions, the multidisciplinary team of intensivists and maternal-fetal medicine physicians offered NO as rescue therapy to pregnant patients that the attending physician felt were rapidly declining. "

112 To whom did you describe this? Did you get specifically get consent for off-label use of NO? Did your IRB say this was not necessary?

160 Please provide units for FiO2

200. Virginia Apgar was an anesthesiologist who developed a scoring system to assess need for neonatal resuscitation. Please edit the spelling of this scoring system in your paper, as it is not an acronym and should be spelled "Apgar".

208. Update data on continuing pregnancies

227. I'm not an intensivist so please excuse a naïve question. It seems that the effect of treatment with NO is transient, as some of your patients (3) required multiple treatments. Do the treatments transiently result in vasodilation, bronchodilation? Its not expected that it would reverse or cure the process but allow for time for the inflammatory injury to resolve? If I'm remotely close here, or whatever mechanism is involved, can you describe? I think this is important since you treated at least one woman > 10 times.

229. How quickly did the hypoxemia and tachypnea return after cessation of treatment? (please put in results section).

239-242: please temper this. You cannot generalize about safety for either mother or infants based on 6 pregnancies. A plausible explanation might be that in other adults and newborns there is a reasonable safety profile. You did have 1 patient of 6 who developed AKI which should be noted.

Update Table 1 for any deliveries.

Figure 3. Where did this figure come from? Do we need to get permission for its' use?

Please label as "Potential beneficial" in title and figure legend.

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

\*The manuscript's guarantor.

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

4. Tables, figures, and supplemental digital content should be original. The use of borrowed material (eg, lengthy direct quotations, tables, figures, or videos) is discouraged. If the material is essential, written permission of the copyright holder must be obtained.

Both print and electronic (online) rights must be obtained from the holder of the copyright (often the publisher, not the author), and credit to the original source must be included in your manuscript. Many publishers now have online systems for submitting permissions request; please consult the publisher directly for more information. Permission is also required for material that has been adapted or modified from another source. Increasingly, publishers will not grant permission for modification of their material. Creative Commons licenses and open access have also made obtaining permissions more challenging. In order to avoid publication delays, we strongly encourage authors to link or reference to the material they want to highlight instead of trying to get permission to reprint it. For example, "see Table 1 in Smith et al" (and insert reference number). For articles that the journal invites, such as the Clinical Expert Series, the journal staff does not seek permission for modifications of material — the material will be reprinted in its original form.

When you submit your revised manuscript, please upload 1) the permissions license and 2) a copy of the original source from which the material was reprinted, adapted, or modified (eg, scan of book page(s), PDF of journal article, etc.).

If the figure or table you want to reprint can be easily found on the internet from a reputable source, we recommend providing a link to the source in your text instead of trying to reprint it in your manuscript.

5. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric 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.

6. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Procedures and Instruments articles 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.

7. 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).

8. Provide a short title of no more than 45 characters (40 characters for case reports), including spaces, for use as a running foot.

9. 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 Procedures and Instruments is 200 words. Please provide a word count.

10. 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.

11. 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.

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

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

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

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](http://edmgr.ovid.com/ong/accounts/table_checklist.pdf).

#### 14. Figures

Figure 1: What does the green represent? Please upload as a figure file on Editorial Manager.

Figure 2: What does the green represent? Please upload as a figure file on Editorial Manager.

Figure 3: Is this figure original to this manuscript or was this created by an illustrator for this manuscript? If it was created by an illustrator, please provide a letter of permission for use in print and online versions (an email is fine).

15. Each supplemental file in your manuscript should be named an "Appendix," numbered, and ordered in the way they are first cited in the text. Do not order and number supplemental tables, figures, and text separately. References cited in appendixes should be added to a separate References list in the appendixes file.

16. 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 <https://wkauthorservices.editage.com/open-access/hybrid.html>.

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.

Sincerely,

Nancy C. Chescheir, MD  
Editor-in-Chief

2019 IMPACT FACTOR: 5.524  
2019 IMPACT FACTOR RANKING: 6th out of 82 ob/gyn journals

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In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: <https://www.editorialmanager.com/ong/login.asp?a=r>). Please contact the publication office if you have any questions.

Nancy C. Chescheir, M.D.  
Editor-in-Chief,  
*Obstetrics & Gynecology*

Re: Submission of manuscript: **Benefits of Breathing High Concentrations of Nitric Oxide in Pregnant Patients with Severe COVID-19**

Dear Dr. Chescheir,

We are pleased to submit the revised version of our manuscript entitled: “**High Concentrations of Nitric Oxide Inhalation Therapy in Pregnant Patients with Severe COVID-19**”.

We thank the editors and the reviewers for the comments and the suggestions, giving us the chance to improve our manuscript. We addressed all the points suggested by the Editors and Reviewer's. that has requested and revising the manuscript or explaining why no revisions were needed. In the following pages you will find the response to each of the received comments. We believe that the suggestions of the Editors and the Reviewer's have led to a significantly improved manuscript.

Dr. Lorenzo Berra 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. We confirm that we have read the instruction for the Authors.

We would like to thank you for your time and for allowing us to revise our manuscript and for considering it for publication. If there are any questions about the manuscript, please feel free to contact me and I will endeavor to respond at the earliest opportunity.

Sincerely

On behalf of all the authors,  
Lorenzo Berra, MD

A large black rectangular redaction box covering the signature and any accompanying text or contact information.



## REVIEWER COMMENTS

**Reviewer #1:** This paper describes a novel potential method for supporting/treating pregnant women admitted with severe COVID 19 infection. This revised paper is a response to the reviewer's comments regarding their previous iteration, which included rewriting the piece to qualify as a Procedures and Instruments report. Issues to be addressed include:

### 1. In the Methods section:

Under Study Design, when describing disease classification, instead of referencing two prior papers (which requires uninformed readers to try and look them up), please refer to your own table, which includes the criteria (and add an explanation of severe vs critical to the caption underneath the table).

Reply: We thank the Reviewer for helping us to clarify our methods and improve the manuscript. We have changed the classification to the description in the table and have also assessed the difference between severe and critical.

Methods, Page 3

*"Patients were classified into 2 categories (severe, and critical) according to the severity of respiratory, circulatory, and multiple organ involvement, as reported in **Table 1.**"*

### Appendix 1. Maternal baseline characteristics

General	Patient-1	Patient-2	Patient-3	Patient-4	Patient-5	Patient-6
Age, years	27	24	30	27	25	33
Gravida (Parity)	G1P0	G2P1	G1P0	G1P0	G3P1	G1P0
Gestational age at admission, weeks + days	18+3	29+4 (twins)	25	40	36+1	32+4
BMI, Kg/m <sup>2</sup>	35.1	34	25.1	33.3	30.3	32
Underlying chronic disease	Obesity	Obesity	None	Obesity Sickle-cell disease	Obesity	Obesity

<b>Known pregnancy complications</b>	None	Gestational Diabetes	None	None	None	None
<b>COVID-19 characteristics</b>						
<b>Days from onset of symptoms</b>	7	7	7	3	3	14
<b>Known positive SARS-CoV-2 test at admission</b>	Yes	No	Yes	Yes	No	Yes
<b>Days of SARS-CoV-2 positivity at admission</b>	1	0	5	4	0	9
<b>Disease severity by first NO administration</b>	Critical	Critical	Critical	Severe	Severe	Critical
<b>Respiratory Rate&gt; 30/min</b>	Yes	Yes	Yes	Yes	Yes	Yes
<b>SpO<sub>2</sub>&lt; 93%</b>	Yes	Yes	Yes	No	Yes	Yes
<b>Oxygen supplementation (Delivery methods)</b>	Nasal Cannula	Nasal Cannula	Nasal Cannula	Venturi Mask	Venturi Mask	Nasal Cannula
<b>Oxygen supplementation (L/min or %)</b>	6 L/min	4 L/min	4 L/min	31%	24%	3 L/min
<b>Lung infiltrates&gt; 50%</b>	Yes	Yes	No	Yes	Yes	Yes
<b>Severe respiratory distress</b>	Yes	Yes	No	No	No	Yes
<b>Shock</b>	No	Yes	Yes	No	No	No

<b>Multiple organ disfunction</b>	No	No	No	No	No	No
<b>Maternal Outcome</b>						
<b>Delivered to date</b>	No	Yes	No	Yes	Yes	No
<b>Gestational age at delivery</b>	-	30	36+2	40	36+1	38+2
<b>Type</b>	-	C-Section	Vaginal	Vaginal	C-Section	C-Section
<b>Intubated during hospital stay</b>	Yes	Yes	No	No	No	No
<b>MV Duration, days</b>	13	1	-	-	-	-
<b>NO sessions, n</b>	5	3	18	2	4	7
<b>NO dose, ppm-Median [Range]</b>	160 [160-160]	160 [160-200]	160 [160-160]	180 [160-180]	160 [160-160]	200 [200-200]
<b>Remdesivir, days</b>	0	7	3	0	0	0
<b>Hospital LOS, days</b>	25	9	12	2	6	6
<b>ICU LOS, days</b>	16	5	4	0	0	4
<b>Last available SARS-CoV-2 f/u test result</b>	Negative	Positive	Negative	Negative	Negative	Negative
<b>Days since first positive test/NO initiation</b>	23	28	17	26	21	23

BMI: Body Mass Index, SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2, NO: Nitric Oxide; MV: Mechanical Ventilation; ICU: Intensive Care Unit; LOS: Length of Stay; IQR: Interquartile Range; f/u: follow-up. Patients were classified as Severe if they presented with respiratory rate >30 and lung infiltrates >50%, while they were classified Critical if a severe organ insufficiency, identified as Severe respiratory distress, shock, or multiple organ dysfunction occur

**Under Nitric Oxide Delivery Device, following your explanation of how nitric oxide can damage epithelial cells, please add a brief explanation of how increased methemoglobin saturation occurs, its adverse effects, and how you reduce the level in this situation (since that is also an adverse effect that is mentioned several times but not explained).**

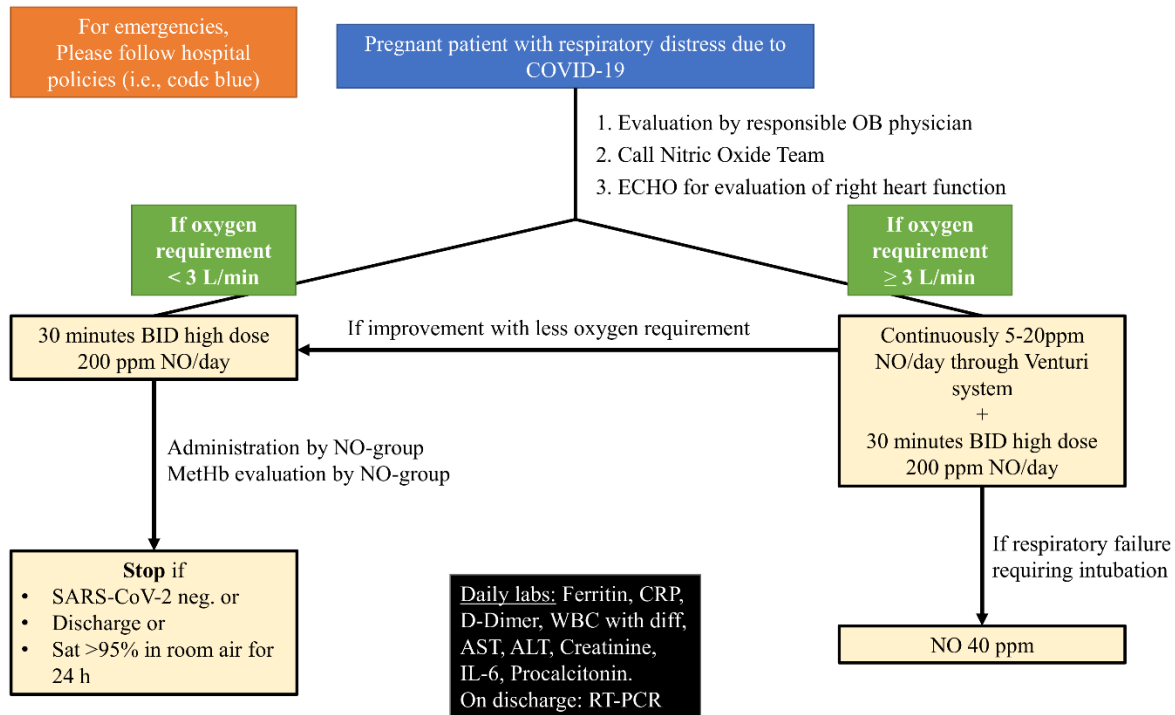
Reply: We have now added the following statement in the Methods.

Methods, Page 3

*“Before, during, and after each treatment session, peripheral oxygen ( $SpO_2$ ) and methemoglobin (MetHb) saturation, heart rate, and non-invasive blood pressure were continuously monitored. During NO breathing, MetHb is formed by oxidation of iron (from  $Fe^{2+}$  to  $Fe^{3+}$ ). Ferric hemoglobin (MetHb[ $Fe^{3+}$ ]) is unable to transport oxygen. To avoid tissue hypoxia in respiratory failure, our goal was to maintain MetHb level below <5%. MetHb levels was continuously monitored non-invasively with a transcutaneous pulse oximeter system (Masimo Corp., Irvine CA).”*

**Please indicate how frequently treatments were given (how many per day, and how many hours apart)**

Reply: As per the Reviewer’s suggestion, we have moved the protocol flowchart (**Figure 1**) from the digital supplement content to the main text.



**Figure 1**

## 2. Under Experience:

Please explain what you mean by “rescue therapy”. This term implies that the patients were worsening despite standard therapy, but 2 of the patients in the study had had symptoms for only 3 days (and one of these had an SpO<sub>2</sub> > 93%) and were categorized as severe, not critical.

Reply: We have now addressed this question by changing our Methods section.

Methods, Page 3

*“Given the well-established oxygenation and pulmonary vasodilation benefits of NO in ARDS and pulmonary hypertension prior to the COVID-19 pandemic, and the lack of data to support other respiratory interventions, the multidisciplinary team of intensivists and maternal-fetal medicine physicians offered NO as rescue therapy to prevent further respiratory deterioration of pregnant patients that the attending physician felt were rapidly declining.”*

In the text you state that heart rate was unchanged compared to baseline but in the caption underneath the figure you state that heart rate changed significantly (the latter appears to be more true, but the change cannot be described as [statistically] significant).

Reply: We thank the Reviewer for their suggestion. In the caption underneath the figure, we now say, “neither the (C) Mean Arterial Pressure (MAP) nor the (D) Heart Rate (HR) changed

*significantly.*” Also as per the Statistical reviewer suggestion, we are not formally testing the differences and we present descriptive data.

**Despite the fact that you describe the beneficial effects of nitric oxide therapy as including improved oxygen delivery to the fetal circulation, and the fact that the fetal heart rate is considered part of the pregnant patient’s vital signs, no information on fetal heart rate patterns is provided. Please report what happened to the FHR, if anything, during and after nitric oxide treatments (add data to the table or a cell to the figure, if possible, to stay within your word count).**

Reply: The Reviewer is correct. Unfortunately, recordings of those data are unavailable. This is one of the limitations of this study. This critical point will be addressed in future prospective studies. We acknowledged this as a limitation.

Discussion, Page 7

*“This study is limited by the lack of fetal parameters during NO treatments as these data were not recorded.”*

**The clinical details provided in under “Outcome and follow-up” (except the last sentence about discharge) are really about the clinical course while receiving nitric oxide therapy, and should be moved into the “experience” section.**

Reply: We thank the Reviewer for the comment, we have moved those details as suggested.

### **3.In the Discussion section:**

**You state for the first time that 83% of patients showed viral clearance by the time of discharge (within 28 days). This result belongs in the patient experience section. If possible, please report how quickly the virus cleared relative to nitric oxide therapy.**

Reply: We thank the Reviewer for their suggestion. We have added this information to the discussion.

Discussion, Page 6

*“All participants in the cohort were successfully discharged within 28-days of hospitalization, and 5 out of 6 patients showed viral clearance on nasopharyngeal swabs. Viral clearance was obtained between day 9 and 21 after treatment initiation.”*

**Figure 3 is a pictorial representation of the benefits of nitric oxide therapy, which are also listed in the text. This figure should be removed, and replaced by the clinical flow chart in the Appendix describing your nitric oxide protocol (and BTW, this figure implies that some patients received continuous nitric oxide therapy in addition to the periodic high dose treatments; if this is correct, please add to the Treatment section).**

Reply: We thank the Reviewer for the suggestion. As suggested, we have moved the image to the online supplement materials and replaced it with the flowchart.

**Reviewer #2: The authors present a Procedures and Instruments article describing the use of inhaled NO gas for pregnant women admitted with COVID infection. This was submitted previously as a different article type and reviewed and one of the suggestions was to change it to a Procedures and Instruments article type. The authors also revised the manuscript in accordance with the other recommendations made by the Editors and two reviewers. I have a few comments on the revised manuscript.**

**my comments all revolve around rewording the manuscript to read more like a Procedures and Instruments article than a Research article. The main difference is that the former is not intended to demonstrate/prove benefit, but rather present it as a viable option.**

Reply: We thank the Reviewer for helping us improve the quality of our manuscript, increasing the adherence to the Procedure and Instruments article type.

**1. I would change the title. The main purpose of the article is to present NO as an option, not to demonstrate Benefits. Maybe something like “Nitric Oxide Therapy in Pregnant patients with Severe COVID-19”**

Reply: We have now changed the title to “*High Concentrations of Nitric Oxide Inhalation Therapy in Pregnant Patients with Severe COVID-19*”.

**2. for the abstract Methods, change from “to assess the therapeutic effects” to something more like “to report the use of”.**

Reply: We have now changed the language in the session method of the abstract to reflect the reviewer’s comment: Abstract, page 2 “**Method:** To report the use of 160-200 parts per million (ppm) inhaled nitric oxide (NO) for 30-60 minutes by mask twice per day in pregnant patients with COVID-19.”

**3. for the abstract conclusion, change to something along the lines of: NO is an option, easy to use, appears to be well-tolerated, and might be of benefit.**

Reply: We agree with the Reviewer’s suggestion. We have included this sentence in our abstract. Abstract, page 2. “*Conclusions: Nitric oxide at 160-200 ppm is easy to use, appears to be well-tolerated, and might be of benefit in pregnant COVID-19 patients with hypoxic respiratory failure.*”

**4. the two figures from the supplementary digital content should be the ones included in the manuscript (the protocol for NO use, how it is hooked up), whereas the patient data and clinical outcomes should be the tables/figures moved to the supplemental content**

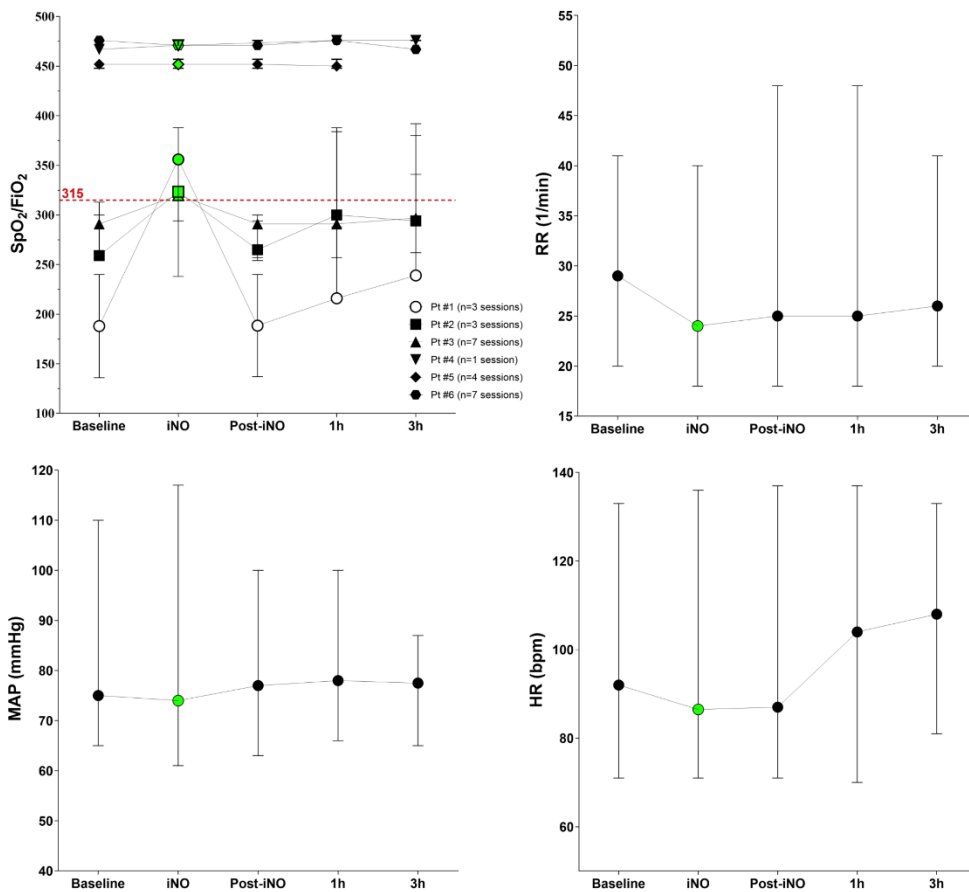
Reply: We moved both figures in the main text and the image about the beneficial effects of NO to the supplementary materials.



## STATISTICAL EDITOR

**Table 1:** The number of NO sessions per patient were: 2,3,4,5,7 and 18. Only from the n=18 could a reasonable approximation of the IQR be estimated with any precision. Should cite NO dose as median(range), not median IQR and could include full enumeration in online material.

Reply: Please find attached below the median (range) data as suggested by the Statistical Reviewer (image produced for reviewer's only view). Due to the small number of patients enrolled in our study, we present individual data as it is more informative from a physiological point of view. We hope this is agreeable to the Statistical Editor as well.



**Fig 1a:** It appears that the increase was due to the improvement in SpO<sub>2</sub>/FiO<sub>2</sub> for patient #1. Moreover, pts # 1,2,3 had differing numbers of NO sessions, totaling 26, but only 13 were used in Fig 1a. I suspect that each of the patients had differing counts of # of sessions, which means that they cannot be statistically considered as (1) 13 independent events and (2) must have a weighted analysis, based on the the relative number of sessions for each patient. Therefore the conclusion should be descriptive and not statistical, based on the analysis shown.

**Fig 1b:** Again, there are not 39 independent observations, in fact almost 1/2 observations were from one patient (#3), so adjustment should be made for correlation within each individual of RR.

**Fig 1c and 1d:** Again, the analysis appears to be based on assumption of independence for all the observations.

**Figs 1b,c,d:** These apparently show the median with IQR, but those are based on assumption of independence of all observations, ie, they were given equal weight mathematically, which is incorrect.

Reply: We thank the Statistical Editor for their important suggestions. We now present descriptive physiological data for each patient in the new figure. The P value has been removed. We have also tempered our conclusion in the main text as suggested by the Editor and the Reviewers.

**Fig 2a:** It is not stated whether there were more than one measurement per patient, should so state and based on the number of patients, should use median(range) format.

Reply: We have changed the image inserting median and range format.

**Fig 2b:** Was this patient (or any of the others) treated with dexamethasone or other steroids?

Reply: We thank the Statistical Editor for their suggestions. The patient referred to by the Editor received Betamethasone because of concern for indicated preterm delivery. In total, 3 out of 6 patients received steroids (2 Betamethasone and one Methylprednisolone).

## EDITOR 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. For instance, there are no subheadings within the major headings, such as “Methods”.**

Reply: We thank the Editor for letting us submit our manuscript as a Procedure and Instrument article. We removed the subheadings.

**Numbers below refer to line numbers.**

**Title. Please delete “Benefits of” from the title.**

Reply: We thank the Editor for the suggestion. We have removed the “Benefit” from the title.

Title, page 1

*“High Concentrations of Nitric Oxide Inhalation Therapy in Pregnant Patients with Severe COVID-19”.*

**69. Please note that your study was conducted from date 1 to date 2, not between those dates. As written, it would exclude the dates given. Also, please state if all were SARS-CoV-2 RT PCR positive.**

Reply: We thank the Editor for the suggestion. We have corrected the time frame identification and stated the positivity of the patients.

Abstract, page 2

*“Six pregnant patients were admitted with severe or critical COVID-19 at Massachusetts General Hospital from April to June 2020 and received inhalational NO therapy.”*

**79. Please note “were associated with improved systemic oxygenation and reduced tachypnea”. As this is an observational report, not an RCT, please avoid causal language.**

Reply: We have corrected the language as also suggested by Reviewer #1.

Abstract, page 2

*“Conclusions: Nitric oxide at 160-200 ppm is easy to use, appears to be well-tolerated, and might be of benefit in pregnant COVID-19 patients with hypoxic respiratory failure.”*

**81. Do use single sentence paragraphs.**

Reply: We believe the Editor intended to suggest that we do not use single-sentence paragraphs. As indicated, we no longer include single sentence paragraphs in the manuscript.

**108. This sentence is unclear as written. There is no subject/verb agreement.**

**Perhaps this would work “Given well established benefit of NO for ARDS and pulmonary hypertension in adult patients prior to the COVID-19 pandemic and the lack of data to support other interventions, the multidisciplinary team of intensivists and maternal-fetal medicine physicians offered NO as rescue therapy to pregnant patients that the attending physician felt were rapidly declining. “**

Reply: We thank the Editor for the suggestion. We have corrected it in the revised version as suggested.

Methods, page 3

*“Given well established benefit of NO for ARDS and pulmonary hypertension prior to the COVID-19 pandemic, and the lack of data to support other interventions, the multidisciplinary team of intensivists and maternal-fetal medicine physicians offered NO as rescue therapy to prevent further deterioration of pregnant patients that the attending physician felt were rapidly declining.”*

**112 To whom did you describe this? Did you get specifically get consent for off-label use of NO? Did your IRB say this was not necessary?**

Reply: For the purposes of the current study, any spontaneous breathing pregnant patient with COVID-19 was eligible to receive NO gas if the patient was deteriorating despite best supportive care due to COVID-19. This was done only if the clinical obstetrician agreed with the use of NO as rescue therapy. This primarily because pregnant patients cannot be included in other experimental protocols (e.g., most randomized trial specifically exclude pregnant patients). Therefore, our institutional IRB deemed formal consent was not necessary for the off-label use of NO.

Currently, FDA has only approved NO therapy for the treatment of neonatal hypoxic respiratory failure associated with pulmonary hypertension. The majority of clinical use of the NO gas (especially in the adult population) is off label (cardiac surgery, ARDS, cystic fibrosis etc.) as in the cases presented. Prior to COVID-19 at our institution, we typically deliver NO gas off-label

in spontaneous breathing patients with a similar methodology illustrated here, specifically in Catheterization Laboratory, in all adult ICUs and in the Pediatric department.

The IRB at our Institution was consulted and, based on the above and on the nature of treatment (e.g., absence of randomization), a formal IRB process was not felt necessary.

#### **160 Please provide units for FiO<sub>2</sub>**

Reply: We thank the Editor for the suggestion. We included the unit for FiO<sub>2</sub>

Experience, page 5

*“(SpO<sub>2</sub>/fraction of inspired oxygen [FiO<sub>2</sub>%] ratio < 315, corresponds to the arterial partial pressure of oxygen [PaO<sub>2</sub>]/FiO<sub>2</sub> < 300 mmHg).”*

**200. Virginia Apgar was an anesthesiologist who developed a scoring system to assess need for neonatal resuscitation. Please edit the spelling of this scoring system in your paper, as it is not an acronym and should be spelled “Apgar”.**

Reply: We thank the Editor for the suggestion. We have corrected the typographical error in the revised version.

#### **208. Update data on continuing pregnancies**

Reply: We have updated the paragraph with the available information.

Experience, page 6: *“Three of the 6 women remain pregnant after hospital discharge (GA: 22, 26, and 33 weeks, respectively). Patient-1 follow-up at 27w6d has been reassuring while Patient-3 and Patient-6 delivered the baby at respectively 36w2d and 38w2d without any complication.”*

**227. I’m not an intensivist so please excuse a naïve question. It seems that the effect of treatment with NO is transient, as some of your patients (3) required multiple treatments. Do the treatments transiently result in vasodilation, bronchodilation? Its not expected that it would reverse or cure the process but allow for time for the inflammatory injury to resolve? If I’m remotely close here, or whatever mechanism is involved, can you describe? I think this is important since you treated at least one woman > 10 times.**

Reply: We thank the Editor for their comments. We believe that the fastest mechanism of relief is caused by the physiological effect of nitric oxide gas in improving ventilation-perfusion matching, bronchodilation, vasodilation, and modulation of inflammation. The observed clinical benefit in our case series would suggest the use of a continuous low-dose along with the high-dose treatment. The rationale behind the use of high-dose, is also supported by a recent publication by Hedenstierna et al. (Nitric Oxide 103 (2020) 1-3, June 23, 2020). The pathophysiologic basis is the possible antiviral effect of nitric oxide, as shown for a prior similar

coronavirus strain (Akerstrom, Journal of Virology 2005). The antiviral effect of NO is pleiotropic and is likely dose, and time-dependent. The reason to only give a high-dose for the short term is to avoid high levels of methemoglobin.

**229. How quickly did the hypoxemia and tachypnea return after cessation of treatment? (please put in results section).**

Reply: We thank the Editor for the suggestion. Reviewing the data chart, we could find that while the hypoxemia present before the treatment returned soon after the cessation of the treatment. For the patients that were tachypneic before the treatment, the return of tachypnea occurred after a median of 3 hours, and this ranged from 0 (immediately after the treatment) to ~16 hours after the treatment. We have inserted the results in the main text

Experience, page 5: *“The NO inhalation provided rapid subjective relief of shortness of breath in all patients and respiratory rates decreased (Fig. 3B) returning to be tachypneic 3 hours after the treatment (ranging from 0-16 hours after the treatment).”*

**239-242: please temper this. You cannot generalize about safety for either mother or infants based on 6 pregnancies. A plausible explanation might be that in other adults and newborns there is a reasonable safety profile. You did have 1 patient of 6 who developed AKI which should be noted.**

Reply: We thank the Editor for helping us in tempering our claims. As suggested, we have removed the 2 points that specifically addressed safety, and we tempered suggesting a reasonable safety profile also based on the previous literature. As suggested by the Reviewer #2 we acknowledge our limitation due to the absence of Fetal monitoring during the treatment. We also acknowledge in the discussion the presence of 1 patient who developed acute kidney injury.

Discussion, page 7

*“While this is a preliminary report on the use of NO gas from a small cohort of spontaneously breathing pregnant patients with COVID-19, there are several plausible reasons for using NO in this population as graphically illustrated in Appendix 5, together with previous study on adults<sup>17</sup> and newborns<sup>18</sup> including: (I) reasonable safety profile (II) potential antiviral, anti-inflammatory, and mild bronchodilatory action, and selective pulmonary vasodilation which improves maternal and, thereby, placental oxygenation. This study is limited by the lack of fetal parameters during NO treatments as these data were not recorded. One patient developed AKI after caesarian section, but causal relationship about development of AKI and administration of NO cannot be derived from our data.”*

**Update Table 1 for any deliveries.**

Reply: We have updated the table with the available data.

**Figure 3. Where did this figure come from? Do we need to get permission for its' use?**

Reply: We thank the Editor for the question. This image is original for this manuscript, created by an illustrator. As required by the Editorial office, we attached the letter of permission and acknowledged the illustrator in the acknowledgment.

**Please label as “Potential beneficial” in title and figure legend.**

Reply: We thank the Editor for the suggestion. We have moved the figure in the supplementary materials and revised the title and the figure legend

Supplemental Digital content, page 4

*“Potential beneficial mechanisms of breathing NO in pregnancy.”*

## **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:**

Reply:

A. OPT-IN: Yes, please publish my point-by-point response letter.

**2. 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.**

Reply: We thank the editorial office for clarifying the steps through the eCTA. We have checked among the authors about the disclosures

**3. Our journal requires that all evidence-based research submissions be accompanied by a transparency declaration statement from the manuscript's lead author. The statement is as follows: "The lead author\* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained." \*The manuscript's guarantor. If you are the lead author, please include this statement in your cover letter. If the lead author is a different person, please ask him/her to submit the signed transparency declaration to you. This document may be uploaded with your submission in Editorial Manager.**

Reply: We thank the editorial office for the clarification. We have included this statement in the cover letter.

**4. Tables, figures, and supplemental digital content should be original. The use of borrowed**



material (eg, lengthy direct quotations, tables, figures, or videos) is discouraged. If the material is essential, written permission of the copyright holder must be obtained.

Both print and electronic (online) rights must be obtained from the holder of the copyright (often the publisher, not the author), and credit to the original source must be included in your manuscript. Many publishers now have online systems for submitting permissions request; please consult the publisher directly for more information. Permission is also required for material that has been adapted or modified from another source. Increasingly, publishers will not grant permission for modification of their material. Creative Commons licenses and open access have also made obtaining permissions more challenging. In order to avoid publication delays, we strongly encourage authors to link or reference to the material they want to highlight instead of trying to get permission to reprint it. For example, “see Table 1 in Smith et al” (and insert reference number). For articles that the journal invites, such as the Clinical Expert Series, the journal staff does not seek permission for modifications of material — the material will be reprinted in its original form.

When you submit your revised manuscript, please upload 1) the permissions license and 2) a copy of the original source from which the material was reprinted, adapted, or modified (eg, scan of book page(s), PDF of journal article, etc.).

If the figure or table you want to reprint can be easily found on the internet from a reputable source, we recommend providing a link to the source in your text instead of trying to reprint it in your manuscript.

Reply: We thank the editorial office for the clarification. All tables, figures, and supplemental digital contents are original

5. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women’s Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric 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.

Reply: We thank the editorial office for the clarification. The use of reVITALize definitions is not problematic

6. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Procedures and Instruments articles 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.**

Reply: We have reformatted to adhere to the length restrictions

**7. 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).**

Reply: We agree to comply with the abovementioned requirements.

**8. Provide a short title of no more than 45 characters (40 characters for case reports), including spaces, for use as a running foot.**

Reply: The short title is "Nitric oxide in COVID-19 pregnant patients" (42 characters, including the spaces). It is also presented on the title page.

**9. 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 Procedures and Instruments is 200 words. Please provide a word count.**

Reply: We thank the editorial office for the suggestion. We have checked the consistency of the abstract with the main text and word counts.

**10. 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.**

Reply: We thank the editorial office for the clarification. All the abbreviations and the acronyms have been spelled out.

**11. 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.**

Reply: We thank the editorial office for the clarification. We have rephrased our text according to the journal requirements

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

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

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

Reply: The reduced sample size and the distribution of the data don't allow us to run major statistical analysis. Moreover, as suggested by the Statistical Editor, we now are more focused on the description of the data than the verification of the statistical significance since the small amount of patients and the distribution of the data in any case couldn't allow us to state any conclusion.

**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](http://edmgr.ovid.com/ong/accounts/table_checklist.pdf).

#### **14. Figures**

**Figure 1: What does the green represent? Please upload as a figure file on Editorial Manager.**

**Figure 2: What does the green represent? Please upload as a figure file on Editorial Manager.**

Reply: The green dot represents the timing in which the patient was receiving the treatment. We have included this information in the figure description. Thanks for helping to clarify our figure.

**Figure 3: Is this figure original to this manuscript or was this created by an illustrator for this manuscript? If it was created by an illustrator, please provide a letter of permission for use in print and online versions (an email is fine).**

Reply: This image is original for this manuscript, created by an illustrator. As required, we have attached the letter of permission (email) and acknowledged the illustrator in the acknowledgments

**15. Each supplemental file in your manuscript should be named an “Appendix,” numbered, and ordered in the way they are first cited in the text. Do not order and number supplemental tables, figures, and text separately. References cited in appendixes should be added to a separate References list in the appendixes file.**

Reply: We have corrected all the names being consistent with the editing requirements.

**16. 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 <https://wkauthorservices.editage.com/open-access/hybrid.html>.**

**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.**

Reply: Thank you for clarifying the process.