OBSTETRICS & GYNECOLOGY

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- 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: Sep 30, 2019
To: "Molly McAdow" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-1602

RE: Manuscript Number ONG-19-1602

Oxytocin Rest Duration During Labor Induction and Its Association with Mode of Delivery

Dear Dr. McAdow:

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

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

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

REVIEWER COMMENTS:

Reviewer #1: The manuscript titled "Oxytocin Rest Duration During Labor Induction and Its Association with Mode of Delivery." by McAdow, et. al. examines the association between temporary cessation in oxytocin infusion (oxytocin rest) and mode of delivery in nulliparous women undergoing induction of labor with a protracted latent phase.

This was a retrospective single center study that included during 5 years a total of 977 nulliparous term singleton vertex presenting women in spontaneous or induced prolong (longer than 12 hours) latent phase (cervical dilation <6 cm). Of those 462 (47.4%) patients underwent an oxytocin rest. There were significant differences between those who had "Oxytocin Rest" and those who did not furthermore, within these that had an Oxytocin Rest 66% had it for less than 4 hours.

The authors have found that after adjusting for duration of the latent phase, gestational age, BMI and additional cervical ripening during oxytocin rest, the odds of CD for patients with oxytocin rest were increased with short rest but with longer rest i.e greater than 4/8 or 12 hours the risk of CD decreased.

The authors conclude that in a protracted latent phase during induction of labor, an oxytocin rest of at least 8 hours is associated with decreased odds of cesarean delivery.

The paper is well written. I have several general concerns:
1. There is a Delphi study regarding a core outcome set for trials on induction of labor - this paper details many more outcomes that should be addressed when examining the association between temporary cessation in oxytocin infusion (oxytocin rest) and mode of delivery in nulliparous women undergoing induction of labor with a protracted latent phase. I feel that this study will be much more powerful if other outcomes as suggested by this Delphi study would be added - i.e - chorioamnionitis, neonatal infection, PPH and so on.

2. I am missing a table comparing demographic and pregnancy and patient characteristics between groups of "oxytocin rest" groups - I can't tell if we are comparing oranges to apples or not.

3. Indeed, as the authors acknowledged certain information regarding patient care is missing - these could explain the outcomes and impact the Multivariable regression analysis results - i.e FHR at the time of oxytocin rest, induced labor vs. spontaneous labor, type of provider, indications for CD and so forth.

Title
1. Appropriate. If possible, add the term nulliparous

Précis
2. I would be more cautious and add the word may be associated with…. Otherwise the précis is appropriate.

Abstract
3. The abstract is specific and representative of the article.

4. Please add data regarding CD rates in each group of oxytocin rest to the abstract and not just OR.

5. The conclusion is more of a repeat of the findings and not conclusion.

Introduction
6. The introduction section is clear and states the purpose of the article in a concise, declarative statement. It does review the background in an appropriate length.

7. Line 63 - "to our knowledge" was a literature search performed?

8. The authors state that there is evidence from active phase of labor and oxytocin rest - however - they don't mention that the Cochrane result demonstrate non-significance difference with Oxytocin rest during active labor - they should consider adding it either in the introduction or at the discussion.
Materials and Methods:

9. Please see my above comment regarding data needed to be reported in studies reporting on IOL (Development of a core outcome set for trials on induction of labour: an international multistakeholder Delphi study. Dos Santos F, Drymiotou S, Antequera Martin A, Mol BW, Gale C, Devane D, Van't Hooft J, Johnson MJ, Hogg M, Thangaratinam S.)

10. Line 83 - please add indication for IOL, please add data regarding spontaneous labor or medically or mechanically induced labor as well?

11. Line 85 - this is not the true latent phase - however it does standardize the measurement, this should be acknowledged as another limitation.

12. Lines 99-101 - how many of the patient's charts were reviewed in detail?

13. Line 129 - it is unclear why were those parameters chosen for the multivariable analysis.

Results
14. line 139-144 should go into methods, figure is sufficient in describing patient breakdown.

15. Line 149 - it is only logical that women that had Oxytocin rest differed from those of did not - as such it also logical that characteristics would also differ based on time that women had oxytocin rest - however - I don't see this comparison.

16. lines 153-161 - as we know majority of women will have at some point during labor Category II tracing - and at times - Oxytocin would need to be held for that reason. Hence the longer the labor including latent phase the higher the chance there would need to be oxytocin rest - in short this study has to address FHR categories during labor and reasons for Oxytocin rest - otherwise it is noncontributory.

18. When looking at table 3 - essentially that there is only one group with a CD rate that differs clinically from the reference group and this is the 8-12 hours, otherwise it all looks quit the same clinically - 50-59.4% according to the group as opposed to 54.4% in the reference group.
Discussion

19. Lines 201-203 even though the findings described in this study are in accordance with what the authors have shown - some things are not in accordance with the literature- most likely oxytocin rest during active labor is not of importance (see above Cochrane), this study has not shown that post term labor is associated with higher risk of CD (Am J Obstet Gynecol. 2018 Feb;218(2):254.e1-254.e7. doi: 10.1016/j.ajog.2017.11.603. Epub 2017 Dec 7. A validated calculator to estimate risk of cesarean after an induction of labor with an unfavorable cervix. Levine LD1, Downes KL2, Parry S2, Elovitz MA2, Sammel MD3, Srinivas SK.).

References
20. Adequate.

Tables
21. No comments.

Reviewer #2:

1. The title and precis summarize the topic and findings very well.

2. Abstract. Well-written, faithful representation of the manuscript. The following are minor.
a. Would define protracted latent phase in the methods rather than in the results.
b. Would include the confounding variables for which adjustment was performed in the methods rather than in the results.

3. Introduction.
a. Lines 46-49. Here you write about prevalence of induction and indications. In the results, would include the proportion of births at your hospital during the study period for which induction was performed. Would also include the indications for induction and percentage of each (not merely because you started your paper with this but because it is directly relevant to your topic and the generalizability of your findings).
b. Lines 51-54. Might include something about appropriate circumstances for discontinuing oxytocin. When labor induction is medically indicated, it may not be appropriate to delay delivery.
c. Lines 63-65. Please include a Pubmed search, here or in the discussion (rather than "to our knowledge"). The authors mention that outcomes of oxytocin cessation during the active phase have been studied. What were the findings?
d. Lines 65-68. Would include the definition of protracted latent phase (more than 12 hours).

4. Methods.
a. Lines 71 and 77-79. The authors write that they studied women undergoing induction of labor, but they also write that women were in latent labor prior to starting oxytocin - which sounds like augmentation. Would clarify, because wording can differ from one hospital to another. Would include something about the role of cervical ripening agents at your center.
b. Were there any exclusion criteria?
c. Lines 80-83. Medical and obstetrical complications should be included, because women not eligible for oxytocin rest might also be less likely to achieve a vaginal delivery.
d. Would include more about the indication for stopping the oxytocin infusion. While I appreciate that discontinuation of 8 hours or more may have occurred for the purpose of allowing the patient to rest, stopping for < 2 or 4 hours may have occurred for a different reason. Did all women remain on L&D for the duration of the "rest"?
e. Because neonatal birth weight category is an outcome that is not known prior to delivery, it should not be used in a model intended to predict cesarean rate.

5. Results.
a. Lines 138-144. Here and in figure 1, the authors convey how many women received any oxytocin prior to delivery, and then they exclude women who did not meet study inclusion criteria (by virtue of search-criteria errors rather than because of exclusion criteria per se). This is not as helpful to readers who might want to implement oxytocin rest. Suggest beginning with all deliveries during the study period, then reporting the N (%) that were singleton nulliparous deliveries with cephalic presentation, then the N (%) with labor induction, and finally the N (%) of induced women with latent phase > 12 hrs.
b. Lines 149-151. The text should convey the direction of the relevant differences (e.g. women who rested had larger BMI). Please include preeclampsia, fetal growth restriction, and ruptured membranes in this table (indications for induction) or in a separate table.
c. Would include in the text that only 11% of the cohort had an oxytocin rest lasting 8 hours or longer.
d. Lines 158-159. If only women with latent phase > 12 hours were included, why report the oxytocin rest in 2 women with shorter latent phases?
e. Suggest providing a more complete description of table 3. The cesarean rates are quite high - ranging from 41% to 59% across the oxytocin rest cohorts, and none of the unadjusted odds ratios are statistically significant. I was surprised to see such a large difference between the unadjusted and adjusted odds ratios—what accounts for the difference. Please subtract oxytocin rest duration (hours) from the duration of the latent phase for the purposes of the regression model - otherwise the information is included twice.
f. Please include N (%) with adverse neonatal outcomes. It is important for readers to know that e.g. resting a patient won't result in increased risk for neonatal sepsis.

6. Discussion.
a. Would address the lack of difference in cesarean rate when adjustment was not performed and discuss modifiability of each of the factors in the model.
b. Lines 205-220 and 240-242. The limitations are valid and clearly described. However, the fact that fields aren't searchable in an EMR is not a reason for not investing variables like fetal heart rate tracing abnormalities, ruptured membranes, and other reasons why it would be inappropriate to offer oxytocin rest. If the differences in odds ratios no longer hold up when women ineligible for oxytocin rest are excluded, the risk-benefit ratio may no longer favor the intervention (or worse, may put patients at unnecessary risk if neonatal adverse outcomes are increased).

Reviewer #3:

Description of the Study:
This is a retrospective cohort analysis examining the association of oxytocin rest with mode of delivery in women with term, cephalic, singleton pregnancies who are experiencing a protracted latent phase of labor following induction of labor. In multivariable analysis, oxytocin rest of 8 hours or greater increased the likelihood of vaginal delivery. Oxytocin rest of this duration was most commonly used in the setting of a latent phase >24 hours and for obese women.

Overall:
The finding that oxytocin rest improves the likelihood of vaginal delivery in the setting of induction of labor with a protracted latent phase is novel. The authors give a compelling biologic mechanism of action to support this finding. While this paper does a great job of stratifying women by duration of latent phase and BMI, it does not address the maternal and neonatal infectious morbidity potentially associated with this practice. Additionally, potential hemorrhagic complications are not addressed in the analysis.

1. Title and Precis: The title accurately represents the objectives of the paper. The precis concisely and accurately summarizes the major finding of the paper.

2. Abstract: The abstract clearly states the study design and the primary finding of the paper. The conclusion is not overstated. However, no mention is given to the benefit of this practice being most pronounced in obese women with latent phases >24 hours.

3. Introduction: The introduction provides adequate background to support the basis for the study. Additionally, it provides a biologic plausibility for the potential benefit of this practice. While a clear hypothesis is not offered, the objective of the study is clearly stated.

4. Materials and Methods: The study design is clearly delineated as is the selection of the final cohort. Prolonged latent phase is clearly defined. Oxytocin rest and how the duration of rest was calculated were clearly defined. Time of ascertainment of BMI is not defined. The study design is appropriate for the research question. However, the study does not address the potentially increased risk of maternal and neonatal morbidities associated with prolonged labor and exposure to uterotonic agents. The study also does not address total length of labor.

5. Results:
Selection of the study population is clearly described, as are demographic differences between the groups. The relationship between duration of oxytocin rest and likelihood of cesarean delivery is clearly demonstrated. The relationship between length of the latent phase and risk of cesarean is mentioned, but not clearly explained in either the text or Table 3. The modes of cervical ripening used during oxytocin rest were not stated. For example, was there a difference if a pharmacologic agent versus a mechanical dilation agent (ie foley balloon) was used?

Discussion: The conclusions of the study are not overstated in the discussion. However, more emphasis should be given to the groups who are most likely to benefit from prolonged oxytocin rest, which appear to be those with latent phase >24 hours and those with obesity. Again, the statement that cervical ripening did not improve likelihood of vaginal delivery is not well-explained or broken down by type of ripening or number of ripening agents used. Lastly, there is no discussion of the potential maternal and neonatal comorbidities that are known to increase with prolonged labor and duration of rupture of membranes.

6. Figures and Tables: All Tables and Figures are appropriate for inclusion.

7. References: The references are up-to-date, and are adequate to support the basis for the study and the arguments made in the paper.

STATISTICAL EDITOR COMMENTS:

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

Tables 1, 2, 3: The counts for numbers of CD among the 8-12 hr oxytocin rest duration and for the > 12 hr cohort were 40.5%x36= 15 and 72x51.4% = 37. Both of those counts were too few to allow for adjustment with the 4 variables included in the final regression model, particularly for the 8-12 hr cohort. The aORs are likely over fitted to the data. Likewise, for post-term, where the total N = 23, among which 73.9% had CD, is far too few for multiple variable adjustment of the OR.

Also, in Table 2, the duration of oxytocin rest categories are unevenly distributed. What was the basis for choosing those increments? What were the results if one were to divide the duration into quartiles, or quintiles? Those would have enough counts of CD per duration category to allow for proper aOR estimation.

EDITOR COMMENTS:

1. Thank you for your submission. While we are inviting you to revise your paper, there are several caveats to this invitation. The primary one is that it is important to include maternal and neonatal outcomes, beyond route of delivery. Prolonged labors are associated with increased risks, for instance, of postpartum hemorrhage, chorioamnionitis, endometriosis, neonatal respiratory morbidity and sepsis, as examples. Without having this information, while the improved cesarean birth rate is important, its not possible to have an adequate context to know if the risks outweigh the benefits. In addition, the important comments by the statistical editor need to be addressed and included.

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

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

- this is the theory behind an oxytocin rest. Is it known that a "reset" is actually happening or is it something else?

- please provide the literature search that supports this conclusion.

- "Affects" is causal language. As a retrospective study design, you can only describe associations, not causation. Please remove causal language from your paper when you are discussing your findings.

- can you describe the typical approach to cervical ripening? Are women for instance getting foley bulb + pitocin protocols?

- spell out abbreviations on first use

- Rather than saying they "differed" please tell us how they differed.

- Please include the data on lines 40-42 in their entirety here.

- This seems like a non-clinically significant difference. Can you tell us if there is a statistical difference?

- this is causal language.

- what about sleep, food, sense of control, etc.

3. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. 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.

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

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

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

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

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

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

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. 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%").

12. Line 63-65: 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 on the other hand, it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

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

14. The American College of Obstetricians and Gynecologists' (ACOG) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite ACOG documents in your manuscript, be sure the reference you are citing is still current and available. If the reference you are citing has been updated (ie, replaced by a newer version), please ensure that the new version supports whatever statement you are making in your manuscript and then update your reference list accordingly (exceptions could include manuscripts that address items of historical interest). If the reference you are citing has been withdrawn with no clear replacement, please contact the editorial office for assistance (obgyn@greenjournal.org). In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript (exceptions could include manuscripts that address items of historical interest). All ACOG documents (eg, Committee Opinions and Practice Bulletins) may be found via the Clinical Guidance & Publications page at https://www.acog.org/Clinical-Guidance-and-Publications/Search-Clinical-Guidance.

15. Figure 1: Please upload as a figure file on Editorial Manager.

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 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.

17. 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 21 days from the date of this letter. If we have not heard from you by Oct 21, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy C. Chescheir, MD
Editor-in-Chief

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

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Date: Nov 20, 2019
To: "Molly McAdow" molly.mcadow@gmail.com
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-1602R1

RE: Manuscript Number ONG-19-1602R1

Oxytocin Rest During Labor Induction of Nulliparous Women and Its Association with Mode of Delivery

Dear Dr. McAdow:

Your revised manuscript has been reviewed by the Statistical Editor. The Editors would like you to address these additional comments prior to making a final decision about your manuscript.

Your paper will be maintained in active status for 14 days from the date of this letter. If we have not heard from you by Dec 04, 2019, we will assume you wish to withdraw the manuscript from further consideration. Your next version should be submitted via Editorial Manager.

STATISTICAL EDITOR:

Regarding the issue of events per parameter:

While I agree that there is no generally agreed upon methodology for avoiding overfitting a model, the main issue here is the relative size of the two subsets (4-8 hrs) and (> 8 hrs) of oxytocin rest were comprised of n = 25 and n = 72 which respectively comprised 2% and 6% of the entire data set, with n = 12 and n = 35 events in each. That is, despite lines 158-162, the categories did not end up numerically balanced. So the main finding is based on a small proportion of the 1193 women in the study. Also, it is not clear how many parameters were initially considered in the adjustment model, only the final number of parameters was given.

If the Authors would like to justify the number of parameter estimates, I would suggest emulating the procedure outlined by Riley R.D. et al "Minimum sample size for developing a multivariable prediction model: Pat II - binary and time-to-event outcomes", Statistics in Medicine 38:1276-1296 (2019).

Since the Authors acknowledge that the oxytocin rest and the non-rest cohorts differed in important risk factors, it will only strengthen their argument if they corroborate the association of those longer rest periods with higher cesarean rates. Since there is ~ 9:1 ratio of controls:cases for the > 8 hr group and ~ 26:1 ratio for the 4-8 hr group, I would suggest matching the cases with controls to corroborate the association.

lines 360-362: Also, the statements regarding the lack of an association of > 8 hrs oxytocin rest with either higher maternal or neonatal morbidity after adjustment is based on 11 of 72 (15%) and 18 of 72 (25%) events vs unadjusted rates of 14% and 17% among the control group. The relative sizes of those groups vs the referent does not give sufficient power to generalize the NS findings.

Sincerely,

Nancy C. Chescheir, MD
Editor-in-Chief

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

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[redacted]

November 11, 2019

Obstetrics & Gynecology
409 12th Street, SW
Washington, DC 20024-2188

To the Editors of *Obstetrics & Gynecology*:

This is a cover letter regarding the re-submission of our manuscript "Oxytocin Rest During Labor Induction of Nulliparous Women and Its Association with Mode of Delivery," Manuscript Number ONG-19-1602. We have submitted solely to *Obstetrics & Gynecology*. This manuscript is not under consideration by another journal and will not be submitted unless a final negative decision is received from the Editors of *Obstetrics & Gynecology*. I have read the Instructions for Authors.

As the lead author (guarantor), I affirm 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 have been explained.

The work described in this manuscript was approved by the Yale University Human Investigation Committee and conducted in accordance with the application.

This work was previously presented as a poster presentation at the 66th Meeting of the Society for Reproductive Investigation in Paris, France, March 14-15, 2019.

I appreciate the opportunity from the Editors to revise our manuscript. While considering Reviewer #2's suggestion to subtract the duration of oxytocin rest from the duration of the latent phase and the suggestion to restructure Figure 1 in order to help the reader who is considering implementing oxytocin rest, we had the opportunity to revisit the inclusion and exclusion criteria that were used to identify our cohort from the original dataset. We were able to refine the study sample to only those women with exposure to oxytocin for at least 8 hours and who remained in latent labor (less than 6cm dilated) prior to oxytocin rest. Oxytocin rest was then subtracted from the total length of the latent phase. This adjustment makes the cohort more reflective of the clinical situation a provider might be faced with when deciding whether to implement an oxytocin rest. Because the cohort was revised, there are some

differences in the specific rates of patient characteristics and in the calculated odds ratios, though the principle findings have not changed.

The following are the comments from the reviewers, statistical editor, and editor with point-by-point responses in italics following.

Reviewer #1:
The manuscript titled "Oxytocin Rest Duration During Labor Induction and Its Association with Mode of Delivery." by McAdow, et. al. examines the association between temporary cessation in oxytocin infusion (oxytocin rest) and mode of delivery in nulliparous women undergoing induction of labor with a protracted latent phase.

This was a retrospective single center study that included during 5 years a total of 977 nulliparous term singleton vertex presenting women in spontaneous or induced prolong (longer than 12 hours) latent phase (cervical dilation <6 cm). Of those 462 (47.4%) patients underwent an oxytocin rest. There were significant differences between those who had "Oxytocin Rest" and those who did not furthermore, within these that had an Oxytocin Rest 66% had it for less than 4 hours.

The authors have found that after adjusting for duration of the latent phase, gestational age, BMI and additional cervical ripening during oxytocin rest, the odds of CD for patients with oxytocin rest were increased with short rest but with longer rest i.e greater than 4/8 or 12 hours the risk of CD decreased.

The authors conclude that in a protracted latent phase during induction of labor, an oxytocin rest of at least 8 hours is associated with decreased odds of cesarean delivery.

The paper is well written. I have several general concerns:
1. There is a Delphi study regarding a core outcome set for trials on induction of labor - this paper details many more outcomes that should be addressed when examining the association between temporary cessation in oxytocin infusion (oxytocin rest) and mode of delivery in nulliparous women undergoing induction of labor with a protracted latent phase. I feel that this study will be much more powerful if other outcomes as suggested by this Delphi study would be added - i.e - chorioamnionitis, neonatal infection, PPH and so on.
We appreciate this comment. We have reviewed the outcome measures outlined in Dos Santos et al (i.e., the Delphi study referred to by the reviewer) and agree that the findings of our study would be more clinically useful by including additional maternal and fetal outcomes. In response, we have evaluated maternal outcomes including hemorrhage, blood transfusion, intensive care unit (ICU) admission, chorioamnionitis and endometritis, venous thromboembolic disease, disseminated intravascular coagulation (DIC), cerebrovascular accident (CVA), and eclampsia and revised our manuscript. We have also added neonatal outcomes including neonatal infection, need for respiratory support, seizures, meconium aspiration, birth trauma, and neonatal ICU (NICU) admission. We were not able to evaluate some of the outcomes outlined by Dos Santos et al, especially maternal satisfaction and long-term outcomes because

such data were not available within our study. We did not detect a significant difference in any of the measured maternal outcomes. There was no association with neonatal infection. We do note a significant association with NICU admission in our treatment groups, but when we adjusted for maternal diabetes, neonates whose mother had oxytocin rest no longer had an increased risk of NICU admission, suggesting that the admission was for the hypoglycemia protocol. Additionally, as neonatal complications are very rare in the term population, our study may be underpowered to detect a difference in infection and other severe neonatal morbidity. We have revised our Methods section and Results section to reflect these additional analyses (pages 9-10, 13-14 in manuscript). Please also see new Table 3 that summarized the results on these maternal and neonatal outcomes.

2. I am missing a table comparing demographic and pregnancy and patient characteristics between groups of "oxytocin rest" groups - I can't tell if we are comparing oranges to apples or not.

We have re-structured Table 1 to reflect differences among those with continuous oxytocin, temporary oxytocin cessation (< 1 hr), oxytocin rest lasting 1 to less than 8 hours, and oxytocin rest 8 hours or longer. We kept the individual "short oxytocin rest" groups grouped together because they did not have a significant association with mode of delivery in our regression analysis. Please note that we also adjusted in multivariable analysis for all differences in these variables among the comparison groups when evaluating the association between duration of oxytocin rest and mode of delivery.

3. Indeed, as the authors acknowledged certain information regarding patient care is missing - these could explain the outcomes and impact the Multivariable regression analysis results - i.e FHR at the time of oxytocin rest, induced labor vs. spontaneous labor, type of provider, indications for CD and so forth.

We have improved our evaluation of confounding factors by incorporating the National Institute of Child Health and Human Development (NICHD) fetal heart rate category at the time of oxytocin rest into our analysis (described in the methods on page 6). We find that NICHD category at the time of oxytocin rest does contribute to an increased risk of cesarean among those patients with oxytocin turned off for less than 1 hour (displayed in Table 2 in the new version of the manuscript). However, after adjusting for NICHD at the time of oxytocin rest, the decreased odds of cesarean with oxytocin rest >8 hours persisted. In fact, the group that underwent oxytocin rest of 4-8 hours also demonstrated a significant association with mode of delivery after adjusting for NICHD category (these findings are described on pages 12-13). All patients in our sample are undergoing induction of labor and have been exposed to at least 8 hours of oxytocin without entering active labor (< 6cm); we have clarified this in our text and methods (page 7-8). Regarding type of provider, the patients in our sample are generally cared for by multidisciplinary teams including maternal fetal medicine, obstetrics, certified nurse midwives, and OB/GYN residents. It is not possible to assign a single type of provider in these circumstances.

Title

1. Appropriate. If possible, add the term nulliparous

We have added the word nulliparous to the title.

Précis

2. I would be more cautious and add the word may be associated with…. Otherwise the précis is appropriate.

We agree and have added the words "may be associated" to the précis.

Abstract

3. The abstract is specific and representative of the article.

Thank you.

4. Please add data regarding CD rates in each group of oxytocin rest to the abstract and not just OR.

Thank you for this suggestion. Due to the word count limit, we are not able to include cesarean delivery rates to the abstract.

5. The conclusion is more of a repeat of the findings and not conclusion.

We appreciate this feedback and have revised the text to say, "An oxytocin rest of at least 8 hours is a clinical tool that may reduce the risk of cesarean delivery among women with protracted latent labor without significantly increasing maternal or neonatal morbidity."

Introduction

6. The introduction section is clear and states the purpose of the article in a concise, declarative statement. It does review the background in an appropriate length.

Thank you.

7. Line 63 - "to our knowledge" was a literature search performed?

We performed a comprehensive review of the literature but did not perform a systematic review. We acknowledge that it is possible work has been done on this topic that we are unaware of and have adjusted our wording accordingly. We have clarified the text to say "Evidence examining [oxytocin rest] in latent labor is limited" on page 5.

8. The authors state that there is evidence from active phase of labor and oxytocin rest - however - they don't mention that the Cochrane result demonstrate non-significance difference with Oxytocin rest during active labor - they should consider adding it either in the introduction or at the discussion.

We agree and have clarified the finding of the Cochrane review in the introduction. The studies described in the Cochrane review found a non-significant difference in mode of delivery when evaluating complete cessation of oxytocin, but they do not examine oxytocin rest (resumption of oxytocin). We have revised the text to say, "Complete cessation of oxytocin during the active phase of labor has no effect on mode of delivery" (page 5). This statement is based on the Cochrane Review finding. As discussed in response to comment 19, the studies included in the Cochrane Review looked at the effect of discontinuation of oxytocin in the active phase of labor,

not an oxytocin rest (i.e. discontinuation followed by resumption).

Materials and Methods:

9. Please see my above comment regarding data needed to be reported in studies reporting on IOL (Development of a core outcome set for trials on induction of labour: an international multistakeholder Delphi study. Dos Santos F, Drymiotou S, Antequera Martin A, Mol BW, Gale C, Devane D, Van't Hooft J, Johnson MJ, Hogg M, Thangaratinam S.)
We appreciate the suggestion of adding these important outcome measures in order to interpret the clinical utility of our findings and have revised our manuscript to evaluate many of the additional outcome measures suggested. The additional data were added to the manuscript. Please see our detailed response to Reviewer #1 Comment 1 above.

10. Line 83 - please add indication for IOL, please add data regarding spontaneous labor or medically or mechanically induced labor as well?
We have clarified in our methods that all subjects in this sample were admitted without signs of active labor and began oxytocin. Each subject was exposed to at least 8 hours of oxytocin and remained in latent phase (<6cm dilated) at the 8 our time point. We adjusted for maternal comorbidities and pregnancy complications to account for indication for induction in the analysis. We have added a description the typical course of labor induction at our institution on page 7, which states, "At our institution, patients who present with an unripe cervix first undergo cervical ripening prior to initiation of oxytocin. Intrauterine balloons are most frequently used, while pharmacologic agents (vaginal misoprostol) are also used when an intrauterine balloon cannot be placed. During the years comprising this analysis, nulliparous patients rarely underwent concurrent mechanical ripening and oxytocin."

11. Line 85 - this is not the true latent phase - however it does standardize the measurement, this should be acknowledged as another limitation.
We agree and have specified the definition as such in the text. In the discussion, we have added "Lastly, it should be noted that while we included patients who had been on oxytocin without entering the active phase for 8 hours, this is not the definition of a protracted latent phase."

12. Lines 99-101 - how many of the patient's charts were reviewed in detail?
Eleven patients' charts were reviewed in detail to check the coding and calculations of the exposure and outcome variables, including the duration of oxytocin rests, dilation and NICDH fetal heart rate categories at the time of oxytocin start and stop, medical comorbidities, and other potential confounders. We have revised the relevant text to clarify this. The text now states, "To confirm that these calculations correctly identified episodes and duration of oxytocin rest, eleven patients were identified at random and their medical record reviewed in detail, which validated the statistical and mathematical coding using the raw data from the EMR."

13. Line 129 - it is unclear why were those parameters chosen for the multivariable analysis.

We analyzed variables that we hypothesized could affect the mode of delivery and/or the use or duration of oxytocin rest during induction of labor based on clinical experience and evidence in the literature. The final multivariable regression model included gestation age, BMI, and duration of the latent phase. The remaining variables did not contribute significantly to our model. The text now states, "Potential confounding variables that were hypothesized to be associated with mode of delivery included gestational age category, maternal BMI category, maternal race or ethnicity, maternal comorbidities (chronic hypertension, gestational hypertension, preeclampsia, superimposed preeclampsia, type I diabetes mellitus, type II diabetes mellitus, gestational diabetes), obstetric risk factors (pre-labor rupture of membranes, oligohydramnios, and fetal growth restriction), neonatal birth weight category, duration of the latent phase, and additional cervical ripening that occurred during oxytocin rest. We used a stepwise backward elimination process to determine the variables retained in the final model."

Results

14. line 139-144 should go into methods, figure is sufficient in describing patient breakdown.
Thank you for this suggestion. The text now states, "A cohort of 3,136 nulliparous, term, vertex-presenting, singleton patients underwent induction of labor during the study period (Figure 1). Of those, 1193 patient remained in the latent phase after 8 hours of continuous oxytocin. 642 patients experienced no interruption of oxytocin infusion, 284 had oxytocin discontinuation for less than 1 hour, and 267 oxytocin rest of at least 1 hour" (page 11).

15. Line 149 - it is only logical that women that had Oxytocin rest differed from those of did not - as such it also logical that characteristics would also differ based on time that women had oxytocin rest - however - I don't see this comparison.
We have broken down the subgroups within Table 1. Comparison groups are now listed as continuous oxytocin, oxytocin rest less than 1 hour, oxytocin rest 1-8 hours (patients for whom oxytocin rest was not associated with mode of delivery), and oxytocin rest 8 hours or longer. Please note that all differences across these variables have been evaluated and adjusted for in the multivariable regression model.

16. lines 153-161 - as we know majority of women will have at some point during labor Category II tracing - and at times - Oxytocin would need to be held for that reason. Hence the longer the labor including latent phase the higher the chance there would need to be oxytocin rest - in short this study has to address FHR categories during labor and reasons for Oxytocin rest - otherwise it is noncontributory.
We agree that fetal heart rate (FHR) category is an important consideration. In particular, those patients whose oxytocin was discontinued for short durations might represent those with fetal compromise, as the goal was to re-start oxytocin once the tracing improved. Including patients whose oxytocin was interrupted for a short duration might have led to an increased cesarean rate among our reference group. Therefore, in the revised analysis presented here, patients whose oxytocin was discontinued for less than 1 hour were treated as a separate group and compared to those who had no oxytocin rest, reflecting reassuring maternal and fetal status. Indeed, in this new analysis, we identified an increased risk of cesarean among those with less than 1 hour of oxytocin discontinuation. When we adjusted for NICHD fetal heart rate category

at the time of oxytocin rest, the increased risk of cesarean was no longer statistically significant. The reduced odds of cesarean among patients with oxytocin rest greater than 8 hours persisted even after adjusting for the NICHD fetal heart rate category.

18. When looking at table 3 - essentially that there is only one group with a CD rate that differs clinically from the reference group and this is the 8-12 hours, otherwise it all looks quit the same clinically - 50-59.4% according to the group as opposed to 54.4% in the reference group.
Thank you for this question. The raw cesarean rate among each group does not appear clinically different because it does not take into account all of the significant and clinically meaningful confounding variables that contribute to the odds of cesarean delivery. We have kept the raw cesarean rate in the table (now Table 3), but if the Editor thinks this information is confusing to readers and distracts from the finding of the multivariable regression analysis, we could remove it from the table.

Discussion

19. Lines 201-203 even though the findings described in this study are in accordance with what the authors have shown - some things are not in accordance with the literature- most likely oxytocin rest during active labor is not of importance (see above Cochrane), this study has not shown that post term labor is associated with higher risk of CD (Am J Obstet Gynecol. 2018 Feb;218(2):254.e1-254.e7. doi: 10.1016/j.ajog.2017.11.603. Epub 2017 Dec 7. A validated calculator to estimate risk of cesarean after an induction of labor with an unfavorable cervix. Levine LD1, Downes KL2, Parry S2, Elovitz MA2, Sammel MD3, Srinivas SK.).
At our institution, we have a very low rate of pregnancies that go past 41 weeks. There are only 26 patients (2%) in our cohort, which likely explains the wide confidence interval for this gestational age category in the version of the analysis that was previously submitted. In the current analysis with the revisions to how the cohort was built, post-term pregnancies were now associated with an increased odds of cesarean delivery.

The Cochrane review evaluated randomized controlled trials that studied the role of discontinuing oxytocin infusion for patients in the active phase of labor. In those studies, resuming oxytocin (an oxytocin rest) was considered non-compliance with the intended protocol rather than the intervention of interest. In the 7 studies that reported whether oxytocin was resumed (i.e. whether the patient had an oxytocin rest), 3.8-46.4% of the patients assigned to the oxytocin discontinuation had oxytocin resumed due to lack of progression. Whether this "oxytocin rest" in the active phase had an effect on mode of delivery was not specifically evaluated.

References
20. Adequate.
Thank you.

Tables
21. No comments.

Thank you

Reviewer #2:

1. The title and precis summarize the topic and findings very well.
Thank you.

2. Abstract. Well-written, faithful representation of the manuscript. The following are minor.
a. Would define protracted latent phase in the methods rather than in the results.
The text was revised. That sentence now reads, "Among patients who were exposed to 8 hours of continuous oxytocin yet remained in the latent phase of labor (i.e. protracted latent labor), episodes of oxytocin rest were identified."

b. Would include the confounding variables for which adjustment was performed in the methods rather than in the results.
We agree and have edited the text accordingly. In the methods section, it now reads, "Multivariable logistic regression analysis was performed to determine the association between duration of oxytocin rest and mode of delivery while adjusting for duration of the latent phase, gestational age, maternal body mass index category, additional cervical ripening during oxytocin rest, maternal and obstetric risk factors, and fetal heart rate category."

3. Introduction.
a. Lines 46-49. Here you write about prevalence of induction and indications. In the results, would include the proportion of births at your hospital during the study period for which induction was performed. Would also include the indications for induction and percentage of each (not merely because you started your paper with this but because it is directly relevant to your topic and the generalizability of your findings).

We appreciate this suggestion. However, because our dataset did not include all births at our hospital, we are not able to assess the proportion of all births for which induction of labor was performed. We have added an analysis of the indication for induction of labor. Please see Table 1 for these new findings.

b. Lines 51-54. Might include something about appropriate circumstances for discontinuing oxytocin. When labor induction is medically indicated, it may not be appropriate to delay delivery.
We agree that oxytocin rest should not be pursued in certain circumstances and conclude the paper by stating, "When it is medically safe to do so, our results suggest that oxytocin rest for more than 8 hours may optimize a woman's chance of vaginal delivery." Due to space limitations in the discussion, we were not able to discuss this further.

c. Lines 63-65. Please include a Pubmed search, here or in the discussion (rather than "to our

knowledge"). The authors mention that outcomes of oxytocin cessation during the active phase have been studied. What were the findings?
We performed a comprehensive Pubmed search but did not perform a systematic review and acknowledge there may be studies we are unaware of. We have edited our wording to reflect this limitation. We have also clarified the findings from the Cochrane review. In the introduction, we now state, "Despite this evidence from the basic science literature, the clinical efficacy of oxytocin rest during induction of labor remains unclear. Evidence examining its use in latent labor is limited. Complete cessation of oxytocin during the active phase of labor has no effect on mode of delivery" on page 5.

d. Lines 65-68. Would include the definition of protracted latent phase (more than 12 hours).
Thank you for this suggestion. The sentence now reads, "Our objective was to assess whether oxytocin rest during a protracted latent phase during induction of labor, here defined as 8 hours of oxytocin without entering active phase, is associated with the mode of delivery among parturients, and, if so, to identify the duration of oxytocin rest associated with lowest risk of cesarean delivery.

4. Methods.
a. Lines 71 and 77-79. The authors write that they studied women undergoing induction of labor, but they also write that women were in latent labor prior to starting oxytocin - which sounds like augmentation. Would clarify, because wording can differ from one hospital to another. Would include something about the role of cervical ripening agents at your center.
We agree that wording was confusing and have edited it to clarify. We have also included a paragraph to describe how cervical ripening is typically performed at our institution. We state, "At our institution, patients who present with an unripe cervix first undergo cervical ripening prior to initiation of oxytocin. Intrauterine balloons are most frequently used, while pharmacologic agents (vaginal misoprostol) are also used when an intrauterine balloon cannot be placed. During the years comprising this analysis, nulliparous patients rarely underwent concurrent mechanical ripening and oxytocin" on page 7.

b. Were there any exclusion criteria?
Inclusion criteria were nulliparous patients undergoing induction of labor at term. Patients were excluded if they were not on at least 8 hours of continuous oxytocin prior to discontinuation of their oxytocin.

c. Lines 80-83. Medical and obstetrical complications should be included, because women not eligible for oxytocin rest might also be less likely to achieve a vaginal delivery.
We appreciate this comment. We have included an analysis of the more common medical and obstetric complications and found that actually there was a trend of increased comorbidities among the patients who had oxytocin rest compared to those who did not, such as chronic hypertension, preeclampsia, and Type II diabetes.

d. Would include more about the indication for stopping the oxytocin infusion. While I appreciate that discontinuation of 8 hours or more may have occurred for the purpose of allowing the patient to rest, stopping for < 2 or 4 hours may have occurred for a different reason. Did all women remain on L&D for the duration of the "rest"?
We appreciate the reviewer's comment and the fact that oxytocin may have been discontinued due to the fetal tracing. Therefore, we have adjusted for NICHD fetal heart rate category in the analysis. Please see Table 2. Women remained on Labor and Delivery during their oxytocin rest.

e. Because neonatal birth weight category is an outcome that is not known prior to delivery, it should not be used in a model intended to predict cesarean rate.
We appreciate the reviewer's comment that because birth weight is not known prior to delivery, it is not helpful in the pre-rest clinical decision making. However, we used birth weight as a proxy for estimated fetal weight in our analysis. In our multivariable regression analysis, birth weight was not significantly associated with the risk of cesarean delivery and thus it was not retained in the final model and was removed from Table 1.

5. Results.
a. Lines 138-144. Here and in figure 1, the authors convey how many women received any oxytocin prior to delivery, and then they exclude women who did not meet study inclusion criteria (by virtue of search-criteria errors rather than because of exclusion criteria per se). This is not as helpful to readers who might want to implement oxytocin rest. Suggest beginning with all deliveries during the study period, then reporting the N (%) that were singleton nulliparous deliveries with cephalic presentation, then the N (%) with labor induction, and finally the N (%) of induced women with latent phase > 12 hrs.
We appreciate the reviewer's recommendation and have re-structured figure 1 to make it more helpful clinically.

b. Lines 149-151. The text should convey the direction of the relevant differences (e.g. women who rested had larger BMI). Please include preeclampsia, fetal growth restriction, and ruptured membranes in this table (indications for induction) or in a separate table.
We have evaluated the variables suggested and they were added to Table 1. There was a significant association among the groups for preeclampsia with a higher percentage of women in the oxytocin rest group having preeclampsia. There was also a significant association of PROM and oxytocin rest with fewer patients with PROM having undergone oxytocin rest. There was not a significant association with fetal growth restriction. The text and table were amended as suggested by the reviewer. On page 11, we now state, "Certain baseline characteristics differed significantly across the exposure groups (Table 1). A larger percentage of patients who had an oxytocin rest delivered at 37 to less than 39 weeks, were black, and had a BMI of 40kg/m^2 or greater. Patients who had an oxytocin rest also had higher rates of chronic hypertension, preeclampsia, and type II diabetes mellitus. They were more likely to have a latent phase lasting at least 24 hours. They were less likely to have had PROM."

c. Would include in the text that only 11% of the cohort had an oxytocin rest lasting 8 hours or longer.
We rebuilt our cohort in accordance with some other comments from the reviewers, which now results in 6% of the cohort having an oxytocin rest lasting longer than 8 hours. This is now stated in the text. Please see page 11 in the manuscript.

d. Lines 158-159. If only women with latent phase > 12 hours were included, why report the oxytocin rest in 2 women with shorter latent phases?
In our revised cohort, we recalculated the latent phase according to the reviewer's point e below by subtracting out the duration of oxytocin rest from the calculated latent phase. This created an opportunity to examine the distribution of duration of latent phase prior to oxytocin rest and refine the study sample to women with exposure to oxytocin for at least 8 hours who remained in latent phase during induction. Oxytocin rests (>1 hour) prior to 8 hours were very unusual, whereas after 8 hours, 22.3% of the sample underwent oxytocin rest. This makes sense from a clinical practice standpoint and also creates an appropriate sample to analyze. We no longer included only patients with total length of latent phase longer than 12 hours.

e. Suggest providing a more complete description of table 3. The cesarean rates are quite high - ranging from 41% to 59% across the oxytocin rest cohorts, and none of the unadjusted odds ratios are statistically significant. I was surprised to see such a large difference between the unadjusted and adjusted odds ratios—what accounts for the difference. Please subtract oxytocin rest duration (hours) from the duration of the latent phase for the purposes of the regression model - otherwise the information is included twice.
We appreciate the reviewer's suggestion to subtract the oxytocin rest duration from the duration of the latent phase and have done so in the analysis. This prevents oxytocin rest from being counted in the model twice. We believe that these cesarean rates in the 40-50% range are to be expected among nulliparous women with protracted induction of labor courses. The overall cesarean rate is much lower at our institution when all-comers are considered (when including parous women and those without protracted induction of labor). The large difference between the unadjusted and adjusted odds ratios is the result of several important confounding factors for mode of delivery. In particular, BMI, gestational age, and duration of latent phase all contributed significantly to mode of delivery in our cohort. Without adjusting for these important confounding variables, we are not able to detect the benefit of an oxytocin rest. We have removed the unadjusted odds ratios from the new Table 2 to reduce this confusion.

f. Please include N (%) with adverse neonatal outcomes. It is important for readers to know that e.g. resting a patient won't result in increased risk for neonatal sepsis.
We agree and have added information about neonatal and maternal outcomes as secondary outcomes measures. Please see Table 3 in the revised manuscript. There is not a measurable increased risk of neonatal sepsis, meconium aspiration, or need for respiratory support.

6. Discussion.

a. Would address the lack of difference in cesarean rate when adjustment was not performed and discuss modifiability of each of the factors in the model.
Because numerous factors contribute to the mode of delivery of a woman undergoing induction of labor, there is a large difference between the unadjusted and adjusted analysis. Gestational age, BMI, and the duration of latent phase are all significantly associated with a patient's odds of cesarean.

b. Lines 205-220 and 240-242. The limitations are valid and clearly described. However, the fact that fields aren't searchable in an EMR is not a reason for not investing variables like fetal heart rate tracing abnormalities, ruptured membranes, and other reasons why it would be inappropriate to offer oxytocin rest. If the differences in odds ratios no longer hold up when women ineligible for oxytocin rest are excluded, the risk-benefit ratio may no longer favor the intervention (or worse, may put patients at unnecessary risk if neonatal adverse outcomes are increased).
We appreciate this comment. In our revised manuscript, we have included NICHD fetal heart rate category at the time of oxytocin rest and pre-labor rupture of membrane (PROM) status in our analysis. The main findings remained robust even after adjusting for these factors. Please see Table 2 in the revised manuscript.

Reviewer #3:

Description of the Study:
This is a retrospective cohort analysis examining the association of oxytocin rest with mode of delivery in women with term, cephalic, singleton pregnancies who are experiencing a protracted latent phase of labor following induction of labor. In multivariable analysis, oxytocin rest of 8 hours or greater increased the likelihood of vaginal delivery. Oxytocin rest of this duration was most commonly used in the setting of a latent phase >24 hours and for obese women.

Overall:
The finding that oxytocin rest improves the likelihood of vaginal delivery in the setting of induction of labor with a protracted latent phase is novel. The authors give a compelling biologic mechanism of action to support this finding. While this paper does a great job of stratifying women by duration of latent phase and BMI, it does not address the maternal and neonatal infectious morbidity potentially associated with this practice. Additionally, potential hemorrhagic complications are not addressed in the analysis.

1. Title and Precis: The title accurately represents the objectives of the paper. The precis concisely and accurately summarizes the major finding of the paper.
Thank you.

2. Abstract: The abstract clearly states the study design and the primary finding of the paper.

The conclusion is not overstated. However, no mention is given to the benefit of this practice being most pronounced in obese women with latent phases >24 hours.
We had not previously performed an analysis to look at that interaction but appreciated the idea. We have now tested for the interaction between BMI, length of the latent phase, and length of oxytocin rest. There were no significant interactions (P values ranged 0.41 to 0.57 for those variables).

3. Introduction: The introduction provides adequate background to support the basis for the study. Additionally, it provides a biologic plausibility for the potential benefit of this practice. While a clear hypothesis is not offered, the objective of the study is clearly stated.
Thank you.

4. Materials and Methods: The study design is clearly delineated as is the selection of the final cohort. Prolonged latent phase is clearly defined. Oxytocin rest and how the duration of rest was calculated were clearly defined. Time of ascertainment of BMI is not defined. The study design is appropriate for the research question. However, the study does not address the potentially increased risk of maternal and neonatal morbidities associated with prolonged labor and exposure to uterotonic agents. The study also does not address total length of labor.
The text on page 6 was updated to reflect the time of ascertainment of BMI, which was the time of admission for delivery. Pre-pregnancy BMI was not available for our entire cohort due to patients whose providers did not use the EMR, transfers of care into our healthcare system, and patients with late entry to care.

We appreciate the reviewer's suggestion to evaluate the risks of maternal and neonatal morbidities as well as the total length of labor and agree about the importance of those outcomes in interpreting our findings. We have performed these analyses and updated the manuscript accordingly, see new Table 3 and results on page 13-14. It should be noted that during oxytocin rest, myocytes theoretically have the opportunity to up-regulate oxytocin receptors, which might reduce the risk of hemorrhage and re-sensitize the body to the uterotonic agent.

5. Results:
Selection of the study population is clearly described, as are demographic differences between the groups. The relationship between duration of oxytocin rest and likelihood of cesarean delivery is clearly demonstrated. The relationship between length of the latent phase and risk of cesarean is mentioned, but not clearly explained in either the text or Table 3. The modes of cervical ripening used during oxytocin rest were not stated. For example, was there a difference if a pharmacologic agent versus a mechanical dilation agent (ie foley balloon) was used?
Thank you. On page 12 we now state, "The duration of a patient's latent phase was significantly associated with her odds of cesarean delivery. For each additional hour of a patient's latent phase, her odds of cesarean delivery increased 1.58-fold."

Since further cervical ripening was not found to be a significant factor affecting mode of delivery, we did not further stratify the results by mode of cervical ripening. Among the 65 patients who had additional cervical ripening during their oxytocin rest, 54.7% had misoprostol, 35.9% had an intrauterine balloon placed, and 9.4% had both. This was added to the results section on page 13.

Discussion: The conclusions of the study are not overstated in the discussion. However, more emphasis should be given to the groups who are most likely to benefit from prolonged oxytocin rest, which appear to be those with latent phase >24 hours and those with obesity. Again, the statement that cervical ripening did not improve likelihood of vaginal delivery is not well-explained or broken down by type of ripening or number of ripening agents used. Lastly, there is no discussion of the potential maternal and neonatal comorbidities that are known to increase with prolonged labor and duration of rupture of membranes.

As stated above, we did not find a significant interaction between BMI, length of the latent phase, and length of oxytocin rest.

With respect to cervical ripening, we wish to clarify that we were only looking at cervical ripening during oxytocin rest to evaluate whether we were measuring the effect of oxytocin rest, not additional measures taken during that time. Among the 65 patients who had additional cervical ripening during their oxytocin rest, 54.7% had misoprostol, 35.9% had an intrauterine balloon placed, and 9.4% had both. This was added to the results on page 13.

We agree with the reviewer about the importance of additional comorbidities and have incorporated those analyses and the role of PROM in our study. We found no significant association with maternal morbidities. We found no increased rate of neonatal infections. There was an association with NICU admission among oxytocin rest groups, but this association was driven by maternal diabetes and need for the infant to be on the hypoglycemia protocol. On page 14, we have added that "after adjusting for maternal diabetes, this association was eliminated: oxytocin rest 1 to less than 8 hours aOR1.62 (1.0-2.5) and oxytocin rest 8 hours or greater aOR 1.10 (0.56-2.15)."

6. Figures and Tables: All Tables and Figures are appropriate for inclusion.
Thank you.

7. References: The references are up-to-date, and are adequate to support the basis for the study and the arguments made in the paper.
Thank you.

STATISTICAL EDITOR COMMENTS:

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

Tables 1, 2, 3: The counts for numbers of CD among the 8-12 hr oxytocin rest duration and for

the > 12 hr cohort were 40.5%x36= 15 and 72x51.4% = 37. Both of those counts were too few to allow for adjustment with the 4 variables included in the final regression model, particularly for the 8-12 hr cohort. The aORs are likely over fitted to the data. Likewise, for post-term, where the total N = 23, among which 73.9% had CD, is far too few for multiple variable adjustment of the OR.

We appreciate this comment. However, we would like to clarify that the "number of events per parameter" requirement refers to the number of events in the overall sample, not stratified by each covariate. As suggested in Hosmer and Lemeshow (2000)[*], a minimum of 10 events per parameter are needed to appropriately estimate coefficients when fitting a logistic regression model. In our study, among the total sample of 1,193 patients included, 561 had a cesarean delivery, which should be able to accommodate 561/10=56 covariates in the regression model. Hence our sample size should be sufficient to support the multivariable logistic regression presented, which included five covariates (oxytocin rest categories, gestational age categories, BMI categories, duration of latent phase, and additional cervical ripening).

** Hosmer DW, Lemeshow S. Applied Logistic Regression. Second Edition. 2000. John Wiley & Sons, Inc. Hoboken, NJ. Page 346-347.*

Also, in Table 2, the duration of oxytocin rest categories are unevenly distributed. What was the basis for choosing those increments? What were the results if one were to divide the duration into quartiles, or quintiles? Those would have enough counts of CD per duration category to allow for proper aOR estimation.

The durations of oxytocin rest categories were selected based on clinical relevance and an evaluation of the empirical distribution of the variable. The cutoffs were chosen to ensure meaningful interpretation clinically while ensuring a reasonable sample size for each category. This was clarified in the text. Please see manuscript pages 8-9.

EDITOR COMMENTS:

1. Thank you for your submission. While we are inviting you to revise your paper, there are several caveats to this invitation. The primary one is that it is important to include maternal and neonatal outcomes, beyond route of delivery. Prolonged labors are associated with increased risks, for instance, of postpartum hemorrhage, chorioamnionitis, endometriosis, neonatal respiratory morbidity and sepsis, as examples. Without having this information, while the improved cesarean birth rate is important, its not possible to have an adequate context to know if the risks outweigh the benefits. In addition, the important comments by the statistical editor need to be addressed and included.

Thank you for this suggestion. We have obtained further outcome data for women in our sample and were able to present these in our analysis.

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

- this is the theory behind an oxytocin rest. Is it known that a "reset" is actually happening or is it something else?
Based on our review of the literature, it is not known whether or when a "reset" actually happens on the molecular level. This sentence has been edited to say, " In these circumstances, some clinicians temporarily discontinue the oxytocin infusion ("oxytocin rest") with the theory that it will re-sensitize the myocyte's response to oxytocin.

- please provide the literature search that supports this conclusion.
A comprehensive literature search was performed, but we did not perform a systematic review. The text has been amended to reflect the possibility that there are some data that we could not find. In the introduction, we now state, "Despite this evidence from the basic science literature, the clinical efficacy of oxytocin rest during induction of labor remains unclear. Evidence examining its use in latent labor is limited. Complete cessation of oxytocin during the active phase of labor has no effect on mode of delivery (11)." Reference 11 is the Cochrane review discussed in response to Reviewer 1, #8.

- "Affects" is causal language. As a retrospective study design, you can only describe associations, not causation. Please remove causal language from your paper when you are discussing your findings.
Thank you for this important reminder. We have revised the wording in the manuscript to reflect that our findings are associations rather than necessarily causal.

- can you describe the typical approach to cervical ripening? Are women for instance getting foley bulb + pitocin protocols?
The text has been amended to further describe the typical approach to cervical ripening at our institution. In the methods, we have added the following paragraph: "At our institution, patients who present with an unripe cervix first undergo cervical ripening prior to initiation of oxytocin. Intrauterine balloons are most frequently used, while pharmacologic agents (vaginal misoprostol) are also used when an intrauterine balloon cannot be placed. During the years comprising this analysis, nulliparous patients rarely underwent concurrent mechanical ripening and oxytocin."

- spell out abbreviations on first use
Thank you. We have spelled out abbreviations on first use in this revision.

- Rather than saying they "differed" please tell us how they differed.
Thank you for this suggestion. This paragraph on page 11 now states, "Certain baseline characteristics differed significantly across the exposure groups (Table 1). A larger percentage of patients who had an oxytocin rest delivered at 37 to less than 39 weeks, were black, and had a BMI of 40kg/m^2 or greater. Patients who had an oxytocin rest also had higher rates of chronic hypertension, preeclampsia, and type II diabetes mellitus. They were more likely to have a latent phase lasting at least 24 hours. They were less likely to have had PROM."

- Please include the data on lines 40-42 in their entirety here.
All results of the multivariable regression analysis are now included here. On page 12, we now write, "After adjusting for the confounding factors, our multivariable regression analysis showed that cessation of oxytocin less than 1 hour was associated with increased odds of cesarean delivery with adjusted odds ratio (aOR) of 1.41, 95% CI 1.05-1.89. Short durations of oxytocin rest were not associated with the odds of cesarean: 1 hour to less than 2 hours aOR 0.99 (95%CI 0.63-1.55), 2 hours to less than 4 hours aOR 0.89 (95% CI 0.50-1.56), 4 hours to less than 8 hours aOR 0.43 (95% CI 0.17-1.13). However, patients who had an oxytocin rest 8 hours or longer had a reduced risk of cesarean, aOR 0.31 (95%CI 0.12-0.84)."

- This seems like a non-clinically significant difference. Can you tell us if there is a statistical difference?
This result was not statistically significant in our regression analysis. We have edited the text to convey more clearly that finding. It now states, "In our multivariable regression analysis, additional cervical ripening during oxytocin rest was not associated with the odds of cesarean delivery, aOR 1.33 (95% CI 0.56-3.14)."

- this is causal language.
The text was edited to convey correctly that this is an association, that our retrospective study cannot ascertain a causal relationship. We have endeavored to correct the causal language throughout the text.

- what about sleep, food, sense of control, etc.
We agree with the editor that there may be additional reasons why oxytocin rest is associated with mode of delivery. Our full discussion of these benefits was limited by the word count limit in the discussion.

3. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. 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. We OPT-IN: Yes, please publish my point-by-point response letter.

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

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

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

We have adhered to revitalize definitions in the use of these terms in our manuscript.

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

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).
All financial support has been acknowledged (there was no associated funding). We have acknowledged the individual and office at our institution who assisted us in data acquisition. She has provided written permission for this acknowledgment. This work was presented at the Society for Reproductive Investigation Annual Meeting, which is noted on page 1.

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 limits for different article types are as follows: Original Research articles, 300 words. Please provide a word count.
Thank you for this caution. We have reviewed the abstract to ensure that it reflects the revisions made to the paper. The abstract word count is 295.

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.
Thank you. We have reviewed the list of approved abbreviations and edited the manuscript to assure compliance including ensuring that abbreviations are spelled out the first time and no abbreviations are used that are on the "do not use" list.

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.
The virgule symbol was removed from the manuscript except in the case of units of measure.

11. 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%").

Thank you. We have adhered to these guidelines.

12. Line 63-65: 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 on the other hand, it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.
Thank you. We have performed an extensive review of the literature but not a systematic review. We have revised the wording in the manuscript text to reflect this as described above in the response to reviewer 1. On page 5, the text now reads, "Despite this evidence from the basic science literature, the clinical efficacy of oxytocin rest during induction of labor remains unclear. Evidence examining its use in latent labor is limited. Complete cessation of oxytocin during the active phase of labor has no effect on mode of delivery."

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.
Thank you. We have confirmed that our tables conform to the journal style.

14. The American College of Obstetricians and Gynecologists' (ACOG) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite ACOG documents in your manuscript, be sure the reference you are citing is still current and available. If the reference you are citing has been updated (ie, replaced by a newer version), please ensure that the new version supports whatever statement you are making in your manuscript and then update your reference list accordingly (exceptions could include manuscripts that address items of historical interest). If the reference you are citing has been withdrawn with no clear replacement, please contact the editorial office for assistance (obgyn@greenjournal.org). In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript (exceptions could include manuscripts that address items of historical interest). All ACOG documents (eg, Committee Opinions and Practice Bulletins) may be found via the Clinical Guidance & Publications page at https://www.acog.org/Clinical-Guidance-and-Publications/Search-Clinical-Guidance.
We have referenced ACOG Practice Bulletin Number 107 which is the current and available version of the document.

15. Figure 1: Please upload as a figure file on Editorial Manager.
Figure 1 was uploaded as a figure file on the Editorial Manager.

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 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.
Thank you. We will await the Editor's decision and if accepted will look for this email.

17. 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.

Thank you for the opportunity to revise our manuscript. We have read the instructions for authors. We appreciate the comments from each reviewer and the Editors and believe those comments have given us the opportunity to improve this manuscript. We have submitted our revision through the Editorial manager along with this letter.

Sincerely,

Molly McAdow, MD, PhD

[redacted]

December 4, 2019

Obstetrics & Gynecology
409 12th Street, SW
Washington, DC 20024-2188

To the Editors of *Obstetrics & Gynecology*:

This is a cover letter regarding the re-submission of our manuscript "Oxytocin Rest During Labor Induction of Nulliparous Women and Its Association with Mode of Delivery," Manuscript Number ONG-19-1602. We have submitted solely to *Obstetrics & Gynecology*. This manuscript is not under consideration by another journal and will not be submitted unless a final negative decision is received from the Editors of *Obstetrics & Gynecology*. I have read the Instructions for Authors.

As the lead author (guarantor), I affirm 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 have been explained.

The work described in this manuscript was approved by the Yale University Human Investigation Committee and conducted in accordance with the application.

This work was previously presented as a poster presentation at the 66th Meeting of the Society for Reproductive Investigation in Paris, France, March 14-15, 2019.

The statistical editor has raised the concern that we are at risk for over-fitting our model of the association between oxytocin rest and cesarean delivery because the number of oxytocin rests in our retrospective cohort lasting 4 to 8 hours and 8 hours or greater is low and the absolute number of cesarean deliveries is therefore low in those two groups. We appreciate this concern and have read with interest the article referenced by the statistical editor, Riley *et al* 2019. That paper describes an approach that can be taken to avoid over-fitting a model when developing a prediction model for diagnosis or prognosis, such as the Wells score for pulmonary embolism. In Riley et al, in order to avoid over-fitting the model, the authors propose following three criteria: reducing optimism by ensuring a high shrinkage factor, a small absolute difference between apparent and adjusted Nagelkerke's R^2score, and precise estimation of the rate of the outcome in the sample.

We have responded to the statistical editor's concerns in several steps. First, we reexamined the univariate analysis of duration of oxytocin rest to determine how the oxytocin rest groups could be more equally distributed and determined that among patients who had an oxytocin rest, three tertiles could be delineated among those with >= 1 hour of oxytocin rest, the exposure of interest. By combining these with our reference group of subjects unexposed to oxytocin rest and the group of subjects exposed to < 1 hour of oxytocin, we have created 5 comparison groups, which are less amenable to incremental comparison of durations of rest, but also less arbitrary given the sample size. The third quintile included patients with oxytocin rest duration up to 2 hours. The fourth quintile included patients with oxytocin rest duration up to 8 hours, and the fifth quintile greater than eight hours This resulted in groups of 284 patients, 106 patients, 89 patients, and 72 patients. We feel that to further break up the first group into half hour increments would not be meaningful clinically and therefore kept that group as one larger group. A fifth group consists of patients whose oxytocin was never discontinued, which comprises 642 patients as in our previously submitted model. We have also evaluated oxytocin rest as a continuous variable and found that the association between increased duration oxytocin rest and decreasing cesarean rates persists and remains strong with a P value for trend of 0.0017. While matching or propensity scoring is a possible way to further reduce the number of subjects in the shorter oxytocin exposure groups, we feel that our model is a good fit and has been found to be robust.

Second, we have followed the procedure as outlined in Riley *et al.* In order to minimize the degrees of freedom in our analysis and therefore risk over-fitting our model, we converted maternal age, gestational age, body mass index, and duration of latent phase to continuous variables (see revised Table 1). We also grouped patients with similar indications to increase the number of subjects with the exposure of interest. Therefore, chronic hypertension, gestational hypertension, preeclampsia, and superimposed preeclampsia were grouped together as "hypertension." Type I diabetes mellitus, Type II diabetes mellitus, and gestational diabetes were likewise grouped together as "diabetes." Based on our findings in table 1 of significant differences in baseline characteristics, we then developed an initial regression model for mode of delivery including the following parameters: oxytocin rest duration, age, gestational age, body mass index (BMI), latent phase duration (on a logarithmic scale to normalize the data), hypertension, diabetes, prelabor rupture of membranes (PROM), additional cervical ripening during oxytocin rest, and National Institute of Child Health and Human Development (NICHD) fetal heart rate category at time of oxytocin rest. With these ten parameters (and 13 degrees of freedom), according to the equations in Riley *et al*, we have a global Shrinkage factor of 0.91 and an apparent Nagelkerke's R^2 of 0.153. The difference between the adjusted and apparent Nagelkerke's R^2 is 0.014. Both of these numbers conform to the criteria specified in Riley *et al* to avoid including too many parameters in an initial model or over-fitting the model. Using the partial-F statistic to evaluate the full and reduced models, we subsequently eliminated additional cervical ripening, hypertension, and PROM sequentially to remove parameters that do not meaningfully contribute to the model, which resulted in an improved fit of the model and optimized parsimony. This refined model had global shrinkage

factor of 0.93 and absolute difference in Nagelkerke's $R^2$of 0.01. Lastly, the third criterion asks that the association between the exposure and the outcome be precisely measured.

Additionally, the statistical editor has pointed out that our study is not powered to evaluate the secondary outcomes of maternal and neonatal morbidity and therefore we cannot draw conclusions from the non-significant findings. We evaluated those secondary outcomes in response to the questions from the other reviewers and the editor. However, we agree with this concern. Because the neonatal composite was driven by neonatal intensive care unit (NICU) admissions, we have pulled ICU admissions out of the composite to evaluate that outcome separately and have adjusted the text to accurately reflect this limitation in the analysis of our secondary outcomes.

Sincerely,

Molly McAdow, MD, PhD