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: May 24, 2019
To: "David A Becker" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-822

RE: Manuscript Number ONG-19-822

Labor curve analysis of medically-indicated preterm induction of labor

Dear Dr. Becker:

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 Jun 14, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: This is a retrospective cohort study of live born, vaginally delivered neonates between 23 and 34 weeks after a medically indicated induction. Multiparous and nulliparous women were included. Rates of cervical change in 3 ranges was calculated and compared. Multiparous women had more rapid change between 3 and 6cm, but otherwise the rates of change was similar. The authors conclude that labor induction is shorter in multiparous women due to more rapid progression from 3 to 6 cm and that some women were capable of delivering vaginally despite long latent labor. Ways in which this manuscript could be improved include:

1. Lines 80-81: I would list your inclusion and exclusion criteria in this manuscript.

2. Lines 83-85: How many patients did this represent? I know you are trying to determine labor curves, but I think this data would be important to know for counseling these patients about risks.

3. Line 151: One has to wonder if 10cm dilation is really needed to be complete. It would certainly explain why this part of the labor curve was similar for both groups.

4. Line 186: What search terms did you use to exhaust your search.

Reviewer #2: The manuscript under review describes a retrospective cohort study of medically indicated inductions between 23 and 34 0/7 weeks gestation. 67 nulliparous and 69 multiparous women with vaginal delivery after induction were included.

1. Women with cervical exam
2. Is the cervical ripening phase considered a separate entity or are all women ripened with foley/pitocin? If someone with a closed cervix needed induction, were they excluded? In the results section, it is mentioned that multiparous women were less likely to receive ripening- define ripening.

3. Failed induction at your center is described as greater than 18 hours ruptured while on oxytocin without change. How many women were excluded for CD due to failed induction?

4. Arrest of dilation in active labor is diagnosed after no cervical change within 4 hours of adequate contractions, or 6 hours of adequate contractions. While most women fell well within this timeframe, this is a self-imposed limit on the labor curve assuming CD is performed at diagnosis of arrest. Indications for CD during first stage of labor should be described. If many were for arrest, this would result in a shorter labor curve.

5. The 95th centile for traverse time from 3-4cm was 26 hours for nulliparas and 7 hours for multiparous women. Could this be when ripening process is complete (foley bulb comes out). It may be important to point out that nulliparous women may take up to 26.5 hours for cervical change after ripening.

6. In discussion section, the authors state the the recommendation from ACOG to allow 12-18 hours after membrane rupture to define failed induction of labor is supported by this study. Was time of membrane rupture included in the data collection? Without time of rupture information, it is difficult to say this study supports that specific recommendation. The 95th centile traverse times to go from 1-6cm was 64 hours in nulliparous women and 42 hours in multiparous women, how long were women ruptured during this time?

7. In table 3, median times to go from 4-5cm are in hours, whereas traverse times from 5-6cm are in minutes. Could it be the active phase of labor starts at 5 in this cohort?

8. Table 3, traverse time row for 6-7cm is missing.

9. When inducing a preterm pregnancy, getting the patient into active labor is the most time consuming part of the process. It would be helpful if more description were included in this study regarding latent labor (ripening definition, ripening time, membrane rupture,etc). This would help further define failed induction in preterm patients and aid in clinical decision making.

Reviewer #3: The authors present a retrospective cohort study of successful vaginal deliveries following an induction of labor between 23-34 weeks' gestation. The methodology adjustments to improve prior studies is notable. However, this study is significantly limited by small sample size (less than 100 in each group, compared to thousands included in previous studies establishing labor curves, including those in preterm patients and preterm inductions) and wide CI, limiting the generalizability and validity of the results presented.

Abstract

1- Was the full labor induction time in each group reported?

2- What percentage of women delivered vaginally?

3- The conclusion that "some women deliver vaginally despite long latent labor" is quite vague, perhaps make a more specific conclusion based on your data. Additionally the exclusion of all those who had a CS means you cannot draw any conclusions regarding the success rate of preterm induction.

4- p value for 64.0 v 42.2h?

Introduction:

5- Can you describe the findings of Feghali and what you hope to find?

6- Describe in detail findings of previous labor curves in preterm patients and what you hope to add to existing literature.

7- What percentile is used to define "normal labor" for term patients, how does that compare to the methodology you have selected?

Methods:

8- Does exclusion of those with <=1 cervical exam skew your labor curve, with a selection bias against those with rapid labor?

9- Was the induction protocol consistent for the entire time period?

10- Does induction protocol include guidelines for timing of AROM?

11- In which settings were PPROM considered an induction vs augmentation?

Conclusion:

12- How do the times presented here compare to term labor curve and other published preterm labor curves? (median, 95%CI etc)

13- Line 215-217, see comment above in abstract re this concluding statement

14- Hard to conclude a sample of ~65 women provides normative data for a large population; the wide CI presented here further highlights the need for a larger sample size to account for the significant interindividual variability in order to better develop a normative population curve. Consider use of multi-site data in a modern time frame to increase your cohort size and strengthen your results and conclusions.

Reviewer #4: First, thank you for your changes and work involved in this revision.

However, I still question the use of a 9th-order polynomial in order to visually model these data. A ninth order polynomial requires estimation of 10 terms, 9 coefficients, plus the intercept. You have < 70 women's data each for nulliparous and multiparous cohorts, making such estimates imprecise and likely over fitting the model. The study referenced by Zhang et al used data from > 62,000 women, so there was more than sufficient data to evaluate various models in that study.

Clearly your data exhibit a non-linear relationship of dilation vs time, but I suspect that the improvement in model-fitting would be marginal beyond a cubic term. (eg, using goodness of fit criteria). Or, the data may fit a power or exponential function extremely well, also. Realizing the limitations of a modest size data set to estimate parameters or to build a model, it would be of interest for the reader to state the closeness of fit between observed and model predicted data for each of the cohorts. e.g, what were the R^2 values for the curves and the corresponding p-values?

Also, I agree with your response that slope is an imprecise term to use when referring to a non-linear function, since beyond a linear expression, the slope is constantly changing. However, a visual comparison is literally in the eyes of the beholder and imprecise. You could instead simply refer to the average slope in the interval from 6 to 10 cm. That appears to be ~ 1 hr for multiparous and ~ 2 hrs for nulliparous. So, the average slopes were ~ 4 and ~ 2 cm/hr, ie, the nulliparous average rate of dilation was ~ 1/2 as fast. Then leave it to the reader to decide whether those were "comparable".

Fig 2: I think this figure would be enhanced if data from the nulliparous could be included. Granted that including both cohorts for the <9 hr times would be visually distracting, but you could try including a different symbol for the nulliparous and just showing that data for ≥ 10 hours. This is just a suggestion, but I think it would add to your paper. Otherwise the reader has just the summary from the models to compare, rather than seeing all the data with the models.

Associate Editor
Please in your revision attend especially to the comments of Reviewer #4.

EDITORIAL OFFICE COMMENTS:

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

2. 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.

Any author agreement forms previously submitted will be superseded by the eCTA. During the resubmission process, you are welcome to remove these PDFs from EM. However, if you prefer, we can remove them for you after submission.

3. In order for an administrative database study to be considered for publication in Obstetrics & Gynecology, the database used must be shown to be reliable and validated. In your response, please tell us who entered the data and how the accuracy of the database was validated. This same information should be included in the Materials and Methods section of the manuscript.

4. Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluations of health interventions (ie, CHEERS), quality improvement in health care studies (ie, SQUIRE 2.0), and studies reporting results of Internet e-surveys (CHERRIES).

Include the appropriate checklist for your manuscript type upon submission. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at http://ong.editorialmanager.com. In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, CHEERS, SQUIRE 2.0, or CHERRIES guidelines, as appropriate.

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, tables, boxes, figure legends, and print appendixes) but exclude references.

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

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. 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.

12. 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.

13. The Journal's Production Editor had the following to say about the figures in your manuscript:

"Fig 2: The key is a bit confusing – “Nulliparous” has both white dots and dashed lines and “Multiparous” has both black dots and a line. The white dots are also hard to see so it might be better for the author to use another color."

When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint.

When you submit your revision, art saved in a digital format should accompany it. Please upload each figure as a separate file to Editorial Manager (do not embed the figure in your manuscript file).

If the figures were created using a statistical program (eg, STATA, SPSS, SAS), please submit PDF or EPS files generated directly from the statistical program.

Figures should be saved as high-resolution TIFF files. The minimum requirements for resolution are 300 dpi for color or black and white photographs, and 600 dpi for images containing a photograph with text labeling or thin lines.

Art that is low resolution, digitized, adapted from slides, or downloaded from the Internet may not reproduce.

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

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

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

If you submit a revision, we will assume that it has been developed in consultation with your co-authors 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 Jun 14, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

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

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We thank the reviewers for their thoughtful critiques. Below, please find our responses.

REVIEWER COMMENTS:

Reviewer #1: This is a retrospective cohort study of live born, vaginally delivered neonates between 23 and 34 weeks after a medically indicated induction. Multiparous and nulliparous women were included. Rates of cervical change in 3 ranges was calculated and compared. Multiparous women had more rapid change between 3 and 6cm, but otherwise the rates of change was similar. The authors conclude that labor induction is shorter in multiparous women due to more rapid progression from 3 to 6 cm and that some women were capable of delivering vaginally despite long latent labor. Ways in which this manuscript could be improved include:

1. Lines 80-81: I would list your inclusion and exclusion criteria in this manuscript.

We have added the inclusion and exclusion criteria from the Kuper et al. study to the materials and methods section.

2. Lines 83-85: How many patients did this represent? I know you are trying to determine labor curves, but I think this data would be important to know for counseling these patients about risks.

A flow diagram of the included and excluded patients is included in figure 1, and referenced at the beginning of our Results section.

3. Line 151: One has to wonder if 10cm dilation is really needed to be complete. It would certainly explain why this part of the labor curve was similar for both groups.

Thank you for this comment. In analysis of the traverse times according to gestational age (Table 4), we found no significant difference in the active phase of labor between GA <32 weeks and ≥32 weeks. However, we did observe a trend toward a greater traverse time in the ≥32 weeks group, and our small sample size may have prevented us from detecting a difference.

In clinical practice a patient is called “10cm” or “complete” when the provider has determined there is no cervix remaining, and the patient is ready to begin the second stage of labor. The dilation necessary to reach that stage may not be 10cm. We have provided additional commentary on this in the Discussion section.

4. Line 186: What search terms did you use to exhaust your search.

We performed a PubMed search of articles containing the words “labor” and “curve” in the Title/Abstract. We also searched MESH terms of labor and preterm. Abstracts were screened when the title of the article reflected a study that was potentially relevant. Although our intent was not a systematic review or metaanalysis, we do feel that the search identified the most relevant articles.

Reviewer #2: The manuscript under review describes a retrospective cohort study of medically indicated inductions between 23 and 34 0/7 weeks gestation. 67 nulliparous and 69 multiparous women with vaginal delivery after induction were included.

1. Women with cervical exam </= 1 were excluded. However, specific intervals of interest included 1cm increments from 1-3cm. Should the increment be 2-3 cm or should the exclusion criterion be < 1cm?

Interval censored regression analysis was used to estimate each traverse time presented, but traverse times could only be estimated if there were a sufficient number of exams at the dilation measured. This approach allowed us to determine the traverse times of the reported 1cm increments for the study population.

2. Is the cervical ripening phase considered a separate entity or are all women ripened with foley/pitocin? If someone with a closed cervix needed induction, were they excluded? In the results section, it is mentioned that multiparous women were less likely to receive ripening- define ripening.

The overwhelming majority of patients at our institution undergo cervical ripening using a transcervical Foley catheter along with concurrent oxytocin administration. Based on the cervical exam and membrane rupture status, the transcervical Foley catheter may not be utilized. At the attending physician's discretion, misoprostol may be substituted as the ripening agent. Women with a closed cervix prior to the start of the induction were not excluded and transcervical Foley catheter was utilized in the majority of these cases. We have provided a more detailed explanation of this process in our methods section.

3. Failed induction at your center is described as greater than 18 hours ruptured while on oxytocin without change. How many women were excluded for CD due to failed induction?

Failed induction is diagnosed at our institution when at least 18 hours have elapsed with ruptured membranes. Women are provided the opportunity to choose to continue labor if maternal and fetal status are reassuring. In the Kuper et al study from which we obtained our cohort, of the 331 women who had a planned induction of labor, 123 (37.2%) women had a cesarean and 19 (15.4%) of those had an indication of failed induction of labor. We have added this information to the discussion section.

4. Arrest of dilation in active labor is diagnosed after no cervical change within 4 hours of adequate contractions, or 6 hours of adequate contractions. While most women fell well within this timeframe, this is a self-imposed limit on the labor curve assuming CD is performed at diagnosis of arrest. Indications for CD during first stage of labor should be described. If many were for arrest, this would result in a shorter labor curve.

Thank you for this comment. We agree that when considering all women undergoing preterm induction of labor, the labor curve is shortened when excluding those who experienced an arrest of labor. However, our study's objective is to use a labor curve to describe the normal labor progression in this preterm population, for which all delivered vaginally.

5. The 95th centile for traverse time from 3-4cm was 26 hours for nulliparas and 7 hours for multiparous women. Could this be when ripening process is complete (foley bulb comes out). It may be important to point out that nulliparous women may take up to 26.5 hours for cervical change after ripening.

Thank you for this excellent insight. We have added this to the body of the results and our discussion.

6. In discussion section, the authors state the the recommendation from ACOG to allow 12-18 hours after membrane rupture to define failed induction of labor is supported by this study. Was time of membrane rupture included in the data collection? Without time of rupture information, it is difficult to say this study supports that specific recommendation. The 95th centile traverse times to go from 1-6cm was 64 hours in nulliparous women and 42 hours in multiparous women, how long were women ruptured during this time?

Thank you. We initially did not include time of membrane rupture because some women were induced for preterm premature rupture of membranes, which would falsely lengthen the time from rupture to labor. However, excluding women with PPROM, we have calculated the time from rupture to delivery and the time from rupture to 6-cm.

EXCLUDING PPROMS (32 excluded)
Here are the descriptives for time from ROM to delivery, in hours :
For nullips: median (5th-95th): 7.8 (0.1 – 271.5) mean (sd): 27.8 (78.4)
For multips: median (5th-95th): 3.3 (0.0 – 101.3) mean (sd): 17.9 (36.6)
Overall: median (5th-95th): 6.4 (0.1 – 101.3) mean (sd): 23.4 (63.2)

p-values for the Wilcoxon rank-sum test to compare nullup and multip medians: p=0.004

Here are the descriptives for time from ROM to first documented 6 cm, in hours:
For nullips: median (5th-95th): 7.0 (0 – 269.7) mean (sd): 26.9 (78.4)
For multips: median (5th-95th): 2.6 (0.0 – 101.1) mean (sd): 17.4 (36.6)
Overall: median (5th-95th): 6.1 (0 – 101.0) mean (sd): 22.7 (63.2)

p-values for the Wilcoxon rank-sum test to compare nullup and multip medians: p=0.008

7. In table 3, median times to go from 4-5cm are in hours, whereas traverse times from 5-6cm are in minutes. Could it be the active phase of labor starts at 5 in this cohort?

For the purposes of the manuscript, we defined the active phase of labor as beginning at 6cm. But this is an excellent point. We have added this to the body of the results and the discussion.

8. Table 3, traverse time row for 6-7cm is missing.

We have added this row to demonstrate that not enough data was present to calculate this traverse time

9. When inducing a preterm pregnancy, getting the patient into active labor is the most time consuming part of the process. It would be helpful if more description were included in this study regarding latent labor (ripening definition, ripening time, membrane rupture,etc). This would help further define failed induction in preterm patients and aid in clinical decision making.

Thank you for this comment. Our group has previously published a study of early versus delayed rupture of membranes in the preterm population (Parrish et al, Am J Perinatology). As our cervical ripening policy is fairly uniform, we are unable to explore the impact of cervical ripening in this population. We focused rather on expectations for a normal time in latent and active phases of preterm labor.

Reviewer #3: The authors present a retrospective cohort study of successful vaginal deliveries following an induction of labor between 23-34 weeks' gestation. The methodology adjustments to improve prior studies is notable. However, this study is significantly limited by small sample size (less than 100 in each group, compared to thousands included in previous studies establishing labor curves, including those in preterm patients and preterm inductions) and wide CI, limiting the generalizability and validity of the results presented.

Abstract

1- Was the full labor induction time in each group reported?
For nullips: median (5th-95th): 19.7 (4.7 – 43.3) mean (sd): 21.4 (11.8)
For multips: median (5th-95th): 10.1 (3.2 – 24.4) mean (sd): 11.2 (6.7)
Overall: median (5th-95th): 14.6 (3.4 – 40.4) mean (sd): 16.2 (10.8)
p-values for the Wilcoxon rank-sum test to compare nullup and multip medians: $p<0.0001$

2- What percentage of women delivered vaginally?

In the Kuper et al study from which we obtained our cohort, of the 331 women who had a planned induction of labor, 208 (62.8%) women delivered vaginally.

3- The conclusion that "some women deliver vaginally despite long latent labor" is quite vague, perhaps make a more specific conclusion based on your data. Additionally the exclusion of all those who had a CS means you cannot draw any conclusions regarding the success rate of preterm induction.

We have edited our conclusion in the abstract to more appropriately state the length of latent labor at the 95th percentile, which was 64.0 hours for nulliparous women and 42.2 hours for multiparous women. We are not drawing a conclusion about the success rate of induction of labor in preterm gestations. Instead we are simply showing that prolonged latent labor is not prohibitive of success in these women.

4- p value for 64.0 v 42.2h?

This is the 95th percentile traverse times for nulliparous and multiparous women, thus a p-value is not applicable. We have clarified this information.

Introduction:

5- Can you describe the findings of Feghali and what you hope to find? Describe in detail findings of previous labor curves in preterm patients and what you hope to add to existing literature.

In Feghali's analysis of the NICHD Consortium on Safe Labor, women were included regardless of ultimate mode of delivery and immediate neonatal outcome. It can be argued that labor was abnormal in women who required a cesarean and those who gave birth to neonates with low Apgar scores or acidosis as measured by arterial cord pH. We chose to exclude these women in order to analyze our outcomes in women with a normal labor course - those who delivered a normal neonate vaginally regardless of how long it may have taken. In addition, we provide cervical dilation traverse times, which Feghali did not present. This rationale has been added to our introduction.

6- What percentile is used to define "normal labor" for term patients, how does that compare to the methodology you have selected?

We consider normal labor progression to be any labor course which ends in a vaginal delivery of a neonate with a normal immediate outcome. We present median traverse times as well as the ranges for the 5^{th}-95^{th} percentile. We considered the 95^{th} percentile to be the upper limit of normal labor, as presented by Zhang et al, although we recognize women can have uncomplicated vaginal deliveries beyond the 95^{th} percentile (Harper et al).

Methods:

8- Does exclusion of those with <=1 cervical exam skew your labor curve, with a selection bias against those with rapid labor?

Thank you for this comment. We have added this limitation to our discussion section as this my bias against those with a rapid labor; however, labor curves are not calculable with only one exam or fewer and was necessary for the analysis.

9- Was the induction protocol consistent for the entire time period?

The protocol as described was consistent during the study period.

10- Does induction protocol include guidelines for timing of AROM?

Timing of AROM is left to the discretion of the treating physicians.

11- In which settings were PPROM considered an induction vs augmentation?

All patients with preterm PROM in the Kuper et al study from which this population was derived from were non-laboring and had either laboratory confirmation of fetal lung maturity or an indication for delivery (chorioamnionitis, vaginal bleeding) All charts were reviewed by a physician to confirm that the patient was induced (no contractions or cervical change) rather than augmented.

Conclusion:

12- How do the times presented here compare to term labor curve and other published preterm labor curves? (median, 95%CI etc)

Labor curves associated with induction of labor were examined in the referenced studies by Feghali et al and Harper et al. In the Feghali study, traverse times were not provided, this we cannot make any comparisons. In the Harper study, 1cm traverse times were calculated beginning at 3cm dilation and only included term patients. Thus, we are unable to make a comparison for most of the traverse times we calculated. Traverse times in our preterm nulliparous women were longer compared to Harper's term nulliparous women. For example, our 3-4cm median traverse time was 4.6 hours and 95th percentile of 26.5 hours versus a median of 1.4 hours and 95th percentile of 8.1 hours for term women. That difference was not observed in the multiparous women.

13- Line 215-217, see comment above in abstract re this concluding statement

Please see our response to comment #3.

14- Hard to conclude a sample of ~65 women provides normative data for a large population; the wide CI presented here further highlights the need for a larger sample size to account for the significant interindividual variability in order to better develop a normative population curve. Consider use of multi-site data in a modern time frame to increase your cohort size and strengthen your results and conclusions.

Thank you for this comment. We acknowledge this limitation in our discussion. The only existing database that would potentially have a large enough preterm population is the Consortium on Safe Labor. Applying our methods to that database could be a worthy follow-up study.

Reviewer #4: First, thank you for your changes and work involved in this revision.

However, I still question the use of a 9th-order polynomial in order to visually model these data. A ninth order polynomial requires estimation of 10 terms, 9 coefficients, plus the intercept. You have < 70 women's data each for nulliparous and multiparous cohorts, making such estimates imprecise and likely over fitting the model. The study referenced by Zhang et al used data from > 62,000 women, so there was more than sufficient data to evaluate various models in that study.

We appreciate the reviewer's caution and we hope to remedy this concern. The strategy here is to fit curves to the data that closely follow the local trends including the lower and upper boundaries of labor duration. We elected to do this with high-order polynomials rather than a loess-type locally weighted regression approach. The 9th order polynomials do indeed overfit the data and a 3rd order polynomial would suffice. This is evidence by the marginal drop in AIC values as we move from a 3rd to 9th order model: 1619.3 to 1413.1 in nulliparous and 1291.3 to 1150.9 in multiparous. However, the models do converge. The benefit of the overly complex models is that they effectively illustrate the slower progression of labor in the early phase and the expedited progression of labor up to 10cm in the later phase. We generated a figure with the cubic curves and unfortunately the fitted lines do not go all the way up to 10 cm at the upper boundaries. This may introduce questions about inadequate fits. Nevertheless, if instructed to do so we will substitute a figure with a 3rd order polynomials instead of the 9th. Again, the figure is for illustration only. For purpose of the manuscript submission only, we have provided the 3rd order polynomial in Figure 2a and the 9th order polynomial in Figure 2b.

Clearly your data exhibit a non-linear relationship of dilation vs time, but I suspect that the improvement in model-fitting would be marginal beyond a cubic term. (eg, using goodness of fit criteria). Or, the data may fit a power or exponential function extremely well, also. Realizing the limitations of a modest size data set to estimate parameters or to build a model, it would be of interest for the reader to state the closeness of fit between observed and model predicted data for each of the cohorts. e.g, what were the R^2 values for the curves and the corresponding p-values?

With our mixed modeling approach we are able to report fit criteria like the AIC or BIC. We note the AIC values in the comment above and will incorporate these values into our results section.

Also, I agree with your response that slope is an imprecise term to use when referring to a non-linear function, since beyond a linear expression, the slope is constantly changing. However, a visual comparison is literally in the eyes of the beholder and imprecise. You could instead simply refer to the average slope in the interval from 6 to 10 cm. That appears to be ~ 1 hr for multiparous and ~ 2 hrs for nulliparous. So, the average slopes were ~ 4 and ~ 2 cm/hr, ie, the nulliparous average rate of dilation was ~ 1/2 as fast. Then leave it to the reader to decide whether those were "comparable".

The slopes of the labor curve are best represented by the traverse times provided for nulliparous and multiparous women in Table 3. We encourage the readers to use this table for estimates of rates of change during the labor course.

Fig 2: I think this figure would be enhanced if data from the nulliparous could be included. Granted that including both cohorts for the <9 hr times would be visually distracting, but you could try including a different symbol for the nulliparous and just showing that data for ≥ 10 hours. This is just a suggestion, but I think it would add to your paper. Otherwise the reader has just the summary from the models to compare, rather than seeing all the data with the models.

The data for the nulliparous women was included, but did not show up well in the uploaded graphic. We have changed the color to red so that it is visible.