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RE: Manuscript Number ONG-20-235

Neonatal and Maternal Composite Adverse Outcomes Among Low-Risk Nullipara versus Multipara Women at 39-41 Weeks

Dear Dr. Chauhan:

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 Apr 01, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

Precis - 39-41 weeks nulliparous has significantly higher likelihood of adverse neonatal/ maternal outcome than multiparous

Abstract- Objective - to determine whether frequency of adverse maternal/ neonatal outcome differs between low risk nulliparous and multiparous women between 39-41 weeks
Materials and Methods - secondary analysis - observational obstetrical cohort - low risk women delivering between 39wk 0 d and 41 wk 6d - composite neonatal adverse outcome and maternal adverse outcome

Results - 39,870 women met criteria - 45.8% nullips
composite neonatal adverse outcome - 1.5% for nullips versus 1.0% for multips; maternal adverse outcome - 15.1% nullips versus 3.3% multips; SGA 89% versus 5.8% and risk LGA and Shoulder dystocia lower in nullips

Conclusion - risk of adverse outcomes is higher in nullips

Introduction - risks increase after 39 weeks - uncertain if there is difference between nullips and multips
primary objective - composite adverse neonatal outcome in labor 39wk - 41wk 6 d
secondary purpose - compare maternal outcome

Materials/Methods - secondary analysis APEX - low risk 39wk - 41wk 6d
adverse neonatal outcome or maternal outcome - is there variation by gestational age or parity

Results - 39,870 women - 45.8% nullip and 54.3% multips - neonatal adverse event 1.5% nulliparous and 1% multip - 80% higher risk in nulliparous
decreased risk but still present if c/s
maternal risk is lower in multips (3.3% vewrsus 15.1%)
nullips at greater risk with vaginal delivery and c/s
SGA nullip - 8.9% versus 5.8% in multips - 45% increased in nullips, LGA decreased in nullips and shoulder dystocia decreased in nullips
no variation by gestational week

Discussion - nullips have higher risk of neonatal and maternal adverse events
absolute risk is low - <2% but 80% increased in nullips
Charts reviewed between 2008-2011

Comments -
Interesting display of increased risk of nulliparous women but the conclusion and discussion needs to be revised
The ARRIVE trial shows there is decrease in risk with early delivery after 39 weeks but this study does not appear to have a difference by gestational age - the risk is based on parity

the conclusion discussing the ARRIVE trial and the role of induction does not appear to be relevant to this and the conclusion needs to be revised.

If it is relevant, than clarification of the role of induction in this discussion needs to be made

Reviewer #2: In this manuscript, the authors present a secondary analysis of the APEX cohort comparing neonatal and maternal outcomes from deliveries at or beyond 39 weeks. This is a straightforward analysis and well presented. There are a few questions for the authors.

1. Why was Apgar score <5 chosen as a contributor to the composite? Apgars <3 or <7 have been more commonly reported.

2. The conclusions which state that outcomes are worse for nulliparous women is not necessarily true considering the higher rates of shoulder dystocia in multiparous women. The authors need to be cautious when making overly general statements since their data do show that is higher in multiparous women.

3. Were regional anesthesia rates reported in the cohort?

4. There is a really large difference in cesarean delivery rates between nulliparous and multiparous women that seems larger than expected. The authors should comment on this and if this may have been more of a contributor. They did adjust for it, but the indications for cesarean being more often fetal nonreassurance or dystocia may have played a role in these outcomes.

5. Does this all boil down to longer labor in nulliparous women? Could a factor analysis look at this, because the outcome composites seem to be driven by things stemming from slower labors for nulliparous women, like chorioamnionitis, lacerations, labor augmentation, etc.

6. For the neonatal outcome composite, the difference seems to be driven by higher rates of ventilator support and low apgars- is this more related to the fact that so many of the cesareans in that group were for nonreassuring fetal tracing?

7. The fact that there were more shoulder dystocias and larger babies in the multiparous group is an interesting finding and deserves more discussion.

Reviewer #3: The authors present their secondary analysis of an observational cohort to compare the adverse outcomes of nulliparous and multiparous mothers and newborns in a low risk population delivering at 39-41 weeks. A composite neonatal and maternal outcome were used as outcome measures. There were 18,245 nulliparous and 39,870 multiparous women included in the evaluation. The composite neonatal and maternal outcomes were significantly more frequent in the nulliparous women. The authors conclude that "low-risk" nulliparous women have significantly higher adverse outcomes than multiparous counterparts.

1. The authors categorize the women as "low risk" but women with substance use disorders, tobacco use, prior cesarean, in-vitro conception, maternal age > 45 years, BMI >45 kg/m2, women with ultrasound suspected FGR or oligohydramnios, psychiatric disorders, and immunologic disorders, do not appear to be excluded. Can you comment?

2. When looking at the two groups being compared (Table 1 and 2), there are essentially nothing similar about these groups. Based on this, the expected outcome would be different, as you are not comparing apples to apples. The authors need to evaluate their cohort and match women based on a clinical characteristic deemed appropriate.

3. The shoulder dystocia (line 127) outcome needs a reference for better defining "requiring maneuvers".

4. Why did you include induction of labor and not simply limited to spontaneous labor?

5. Use of the Apgar score <5 at 5 minutes is not an outcome, rather a measure of resuscitation. This should not be considered part of a neonatal composite score.

6. Please define the ventilator support used in the neonatal composite score.
7. Intraamniotic infection, formally chorioamnionitis, has a definition. Explain in the text if antibiotic usage is a surrogate for this definition.

8. In figure 1, there appears to be a low rate of stillbirth (1/68,000). Any thoughts?

9. The operative vaginal delivery rate for the nulliparous women with surprisingly high. Was this vacuum or forceps use? Any particular region of the country different from others?

10. The number of women delivering at 41.0 and 41.6 weeks was also interesting. Was this a regional variation at the delivery centers?

**STATISTICAL EDITOR'S COMMENTS:**

1. Tables 1, 2: As noted by the Authors, the cohorts differed in several ways that could be clinically, as well as statistically important re: risk profile for maternal or neonatal adverse outcomes. Particularly important is the difference in maternal age distributions for the < 20 and ≥ 35 year strata, and for the differences in GA at delivery for the 41.0-41.6 wk group, for the mode of delivery and for proportion of neonates with BW ≥ 4,000 g. The Authors should supplement their analyses with sensitivity analyses to determine how the associations were affected or modified by maternal age, GA at delivery and mode of delivery.

2. Table 3: For example, by what extent is the difference in composite maternal adverse outcomes related to (cesarean rates or rates of BW ≥ 4,000 grams and to what extent is the difference in neonatal adverse outcomes also related to differences in cesarean rates or differences in BW? Also the difference in aRR for shoulder dystocia requiring maneuvers is mirrored by the difference in aRR for LGA among the nulliparous. That is, the association is plausibly related to differences in BW for nulliparous vs multiparous, rather than being directly attributable to parity stratum.

**EDITORIAL OFFICE COMMENTS:**

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

   A. OPT-IN: Yes, please publish my point-by-point response letter.
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   Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page.

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

4. 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.

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* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
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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
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The Editors of Obstetrics & Gynecology

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