NOTICE: This document contains comments from the reviewers and editors generated during peer review of the initial manuscript submission and sent to the author via email.

Questions about these materials may be directed to the Obstetrics & Gynecology editorial office: obgyn@greenjournal.org.
Date: 01/06/2023
To: "Vivienne Louise Souter"
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-22-2013

RE: Manuscript Number ONG-22-2013

Impact of the ARRIVE Trial on Elective Induction and Outcomes in Term Nulliparas

Dear Dr. Souter:

Thank you for sending us your work for consideration for publication in Obstetrics & Gynecology. Your manuscript has been reviewed by the Editorial Board and by special expert referees. The Editors would like to invite you to submit a revised version for further consideration.

If you wish to revise your manuscript, please read the following comments submitted by the reviewers and Editors. Each point raised requires a response, by either revising your manuscript or making a clear argument as to why no revision is needed in the cover letter.

To facilitate our review, we prefer that the cover letter you submit with your revised manuscript include each reviewer and Editor comment below, followed by your response. That is, a point-by-point response is required to each of the EDITOR COMMENTS (if applicable), REVIEWER COMMENTS, and STATISTICAL EDITOR COMMENTS (if applicable) below.

The revised manuscript should indicate the position of all changes made. Please use the "track changes" feature in your document (do not use strikethrough or underline formatting).

Your submission will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by 01/27/2023, we will assume you wish to withdraw the manuscript from further consideration.

EDITOR COMMENTS:

After peer review and discussion among the Editorial Board, the journal is willing to reconsider a revised manuscript that addresses the following points below and those points raised by the reviewers:

1) Please justify the time analysis windows selected for the pre- and post-period. Longer follow-up periods can ultimately introduce bias in an interrupted time series analysis as they increase the likelihood of non-policy-related influences on the outcomes of interest. A sensitivity analysis that demonstrates the robustness of the findings with varied follow-up windows would provide stronger evidence in support of your findings.

2) The use of a linear counterfactual in the post-ARRIVE period for the perinatal composite is problematic as it ultimately projects a negative rate of the outcomes. In reality, the relationship likely takes a different shape (for example, appears more exponential) as it would expect to level off at or above 0. This makes the results, particularly the change in slope estimates, unreliable. Please address by considering alternative modeling approaches for this outcome and/or remove the perinatal composite as an outcome of interest.

3) Please provide a hypothesis or explanation for why there was a decreasing trend in the perinatal composite and NICU admission in the pre-ARRIVE period. Similarly, please discuss why the NICU admission rate for term newborns was up to 10% in some months where the perinatal composite was closer to 3%. The rates of NICU admission appear higher than commonly reported for term neonates. Is there information on indication for NICU admission? Please address.

4) Were standard errors adjusted for heteroskedasticity? If not, does using robust standard errors change the findings?

5) There are several comments about the appropriateness of including "high risk" patients in a study that seeks to examine the effects of the ARRIVE trial. In addition to the points below, please describe why high-risk patients were included in the primary analysis as it appears many conditions as "high risk" would not be eligible for elective induction of labor and very dissimilar similar to the ARRIVE cohort.

6) Please add that no simulation studies or power estimations were performed, thus it remains possible that there may not be adequate power to detect small differences, including those subgroup analyses, in the outcomes that had a non-
significant result.

Please also note the following:

* Help us reduce the number of queries we add to your manuscript after it is revised by reading the Revision Checklist at https://journals.lww.com/greenjournal/Documents/RevisionChecklist_Authors.pdf and making the applicable edits to your manuscript.

* Figure 1: Please upload as a figure file on Editorial Manager. Please remove ARRIVE text from the figure. This will be added back per journal style.

REVIEWER COMMENTS:

Reviewer #1:

Overall: This is an observational study using an interrupted time series design to evaluate the real world effects of the ARRIVE trial on elective induction of labor and maternal and neonatal outcomes. The manuscript is well-written and clear and offers compelling interpretation of the author's data.

Major
1. Line 151-153 - It seems notable that the overall likelihood of induction of labor (medical and elective) increased by more than the increase in elective induction would have accounted for alone. I appreciate the pre-post numbers are not as robust as result from the model, but I wonder if the authors ensured other indications for induction were stable throughout the study period. It may not matter as the outcomes remain what they are, but could be indicative of other underlying and confounding changes in care.

2. Lines 68-79 - very nice explanation of ITS design.

3. Line 128 - It seems like a sensitivity analysis is needed to ensure that EARLIER timepoints as well as later would not have been more important implementation inflection points. The authors do actually do this with the second washout analysis, so they just need to reword to indicate.

4. Line 158 - As many health systems were implementing hypertensive management bundles around this timeframe, did the authors ensure the definition of hypertension remained constant?

5. Table 3 and throughout - while the results are not statistically significant, there is a trend toward a very small decrease in cesarean birth and hypertensive disorders. Just not reaching statistical significance of p<0.05. I think the author's current conservative description of results is good, and recognize a power calculation doesn't make sense for this study AND should not be done post-hoc. But, perhaps the trends should be acknowledged as justification for an even larger study?

6. Another framing issue is that this research provides some reassurance that the ARRIVE trial did not INCREASE the rate of cesarean. Given the common misconception in the world and among obstetricians that induction increases risk of cesarean (despite good evidence suggesting it does not), it seems like this might be a salient point.

Minor
1. Line 20- final sentence of the results could use some wordsmithing for clarity.

2. Line 51 - It seems like a sensitivity analysis removing 2020 births might offer further reassurance.

3. Line 55 - "where possible electronic uploading..." I think the authors mean that electronic abstracting was used where possible but a trained abstractor would have to abstract all the information, otherwise. Please clarify. Current wording suggests some data elements might be missing if not "possible."

4. Line 143- this could be better worded "Patients self-reported..."

5. (multiple lines) Could the authors provide data on what the expected distribution would be with the distressed communities index? It strikes me that this population is relatively affluent and thus may not be representative of the Pacific NW or US as a whole.

Reviewer #2:
The authors use an interrupted time series analysis to evaluate the facts of publication of the arrive trial on both elective inductions and obstetric outcomes using a large available data set. The overall methodology seems appropriate but justification of certain choices regarding inclusion and exclusion criteria are needed.

1. Methods, line 48: I question the inclusion of all risk levels of term births in this analysis. Can you justify why you included high-risk individuals as well? Given that ARRIVE specifically only includes low risk individuals, this is somewhat inconsistent with the aims of the analysis. My understanding of your data source is that it does include information that would allow you to exclude high-risk individuals.

2. Methods, line 50: given that many other articles have found an increase in neonatal complications within the COVID-19 pandemic, could you consider a sensitivity analysis without inclusion of births after March or April 2020?

3. Methods, line 97: I question the classification of inductions for advanced maternal age as elective. Given the increasing risk of stillbirth after 39 weeks pregnant people over 40 years old, an induction at 39 weeks in this population would not be considered elective. Perhaps you could refine this to indication of advanced maternal age and less than 40 years old.

4. Methods, line 114: I also question the exclusion of individuals with antepartum stillbirth. If you have already limited the population to those delivering at 39 weeks or beyond, any stillbirth is likely to have occurred at 39 weeks or beyond and thus would have had an improved outcome had they been induced at 39 weeks, prior to the stillbirth. Although it is impossible to power to this outcome, it is never the less important. This is an outcome, not an exposure.

5. Results: can you report the breakdown of type of hospital and delivery volume included?

6. Results, lines 175 to 179: based on your definition of high risk, it seems that he’s inductions would not be elective. Perhaps the definition of your high risk group requires more clarity.

Reviewer #3:

Thank you for the opportunity to review this manuscript.

Please see my comments below:

1. Lines 26-29: secondary outcome from ARRIVE trial was hypertensive disorders of pregnancy which included either gestational hypertension or preeclampsia, not just preeclampsia

2. Lines 45-47: what are the characteristics of these hospitals? tertiary? community-based?

3. Lines 53-59: how is gestational age determined in this database? dating based on LMP? ultrasound? what is the latest gestational age for dating included?

4. Line 97: suspected macrosomia in the absence of diabetes?

5. Lines 109-117: I am not sure I understand the rationale here. If the objective was to evaluate the impact of the ARRIVE trial publication on perinatal outcomes in singleton term nulliparas, and the authors’ hypothesis was that this would result in a population-level decrease in cesarean birth and HDP, the authors should only report outcomes related to the study population of interest i.e. low-risk patients; evaluating the impact of the ARRIVE trial on outcomes in ‘higher risk’ patients (alone or included as part of the total study population) would be a separate objective and lacks some validity because those inductions would no longer be considered ‘elective’ and such patients were not included in the ARRIVE trial

6. Lines 109-117: why were IVF patients excluded?

7. Line 124: what were the potential confounders?

8. Was there enough power to detect significant differences in cesarean births and hypertensive disorders?

9. What were the percentages of these outcomes (cesarean births and hypertensive disorders) in the low-risk group alone?

10. The authors should report differences in rates of cesarean births and hypertensives compared between their study and the ARRIVE trial and provide reasoning that may explain such differences, if such exists.

11. Lines 221-227: There is a flaw here. First, on the basis of stating that a younger mean population may not be generalizable. This concern misunderstands the basis of generalizability. Full replicability of characteristics among populations is not essential as long as differences in the means or proportions of these characteristics do not impact the magnitude of association between the exposure and outcome (sometimes power may be an issue, however). Second,
findings from the 35/39 trial cannot be compared to populations that included patients who were younger than 35.

12. What about the rationale that induction did not result in an increase in risk of cesarean births or hypertensive disorders or adverse neonatal outcomes? Would more 'elective' inductions be considered a bad thing as a result?

13. Is using the term elective correct here? There is level 1 evidence to suggest benefit associated with induction of labor in low-risk nulliparas at 39 weeks; 'elective' does not imply that 1 choice has more value or benefit over the other

STATISTICAL EDITOR COMMENTS:

- Lines 18-20: Should change this sentence to more accurately reflect the difference. That is, "After ARRIVE, models showed a slight, but statistically significant increase in rates of adverse perinatal events (1.03; 95% CI 1.01,1.04) when compared with the previous declining rates observed in the Pre-ARRIVE time period." Similarly, in Table 4, among the higher risk, a slight, but statistically significant, increase in the rate of NICU admits.

- Fig 1: Suggest using a different format for the CIs. Rather than showing in grey, which seems hard to see, suggest using dashed or otherwise interrupted lines of a different color to contrast with the other lines. Also, suggest changing the scale for the y-axes for HTN disorders, perinatal adverse outcomes and NICU admits, for easier readability for the reader.

- General and lines 175-191: The problem with analysis of subsets by risk group or by exclusion of some hospitals is a decrease in stats power that limits generalization of any NS findings. This is especially problematic for those outcomes which were less common, ie, HTN disorders, perinatal adverse events or NICU admits. Would have to note limitation in acceptance of any of those NS findings as generalizable.

--

Sincerely,
Mark A. Clapp, MD, MPH
Editorial Fellow

The Editors of Obstetrics & Gynecology

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