OBSTETRICS & GYNECOLOGY

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Questions about these materials may be directed to the *Obstetrics & Gynecology* editorial office: obgyn@greenjournal.org.

Date: Sep 10, 2020
To: "Alan Thevenet Njie Tita" atita@uab.edu
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-2253

RE: Manuscript Number ONG-20-2253

Maternal and Perinatal Outcomes of Expectant Management of Full-Term Low-Risk Nulliparas

Dear Dr. Tita:

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

REVIEWER COMMENTS:

Reviewer #1:

This is a secondary analysis of a randomized trial of expectant management versus induction at 39 weeks of labor in healthy, nulliparous women, describing the outcomes of expectant management week to week. I thank the authors for their contribution to the literature and the editors for the opportunity to review this manuscript:

Strengths:
* Data collection was via a randomized trial, so was prospective and rigorous
* Outcomes are clinically meaningful and well-defined, and included both a maternal and a neonatal composite outcome
* The population was all women appropriate for this management style (expectant) in that the ARRIVE trial participants were all healthy nulliparous women with singleton, cephalic pregnancies without medical indications for induction or Cesarean delivery at term.
* Large number of women more than adequately powers to see a difference in outcomes.

Limitations
* As expectant management is AFTER randomization, and therefore susceptible to bias of provider preference, there is no way to say if expectant management caused outcomes or if increased likelihood of outcomes (or suspected increased likelihood of outcomes) caused sooner delivery. This is reflected in the fact that hypertensive disorders, which would be an indication for delivery, decreased as weeks of gestation at delivery increased. It would never be inferred from this that longer expectant management decreases the risk of hypertensive disorders; the causality goes the other direction.
* As disclosed in the manuscript, no adjustments were made for multiple comparisons and no imputation for missing data was performed.
* As disclosed in the manuscript, the numbers of participants experiencing placental abruption were too few for multivariable analysis, so the effect of expectant management on this catastrophic outcome cannot be inferred from these results. The same is true for analysis of certain outcomes that are too few for certain analysis, such as stillbirth or neonatal death. The authors acknowledge this in the manuscript.

Comments for authors by section:

Abstract
* Line 46, 57, etc: I believe Cesarean should be capitalized due to the eponymous origins of this term, but I leave that to the copy editors
* Line 57: I would love to see the perinatal composite defined briefly in the abstract, if the editors will permit this due

to abstract word limits.
Introduction
* Line 91: Please present a main hypothesis that was being tested in these analyses.

Methods
* Clearly described outcome in keeping with the parent trial's rigorous methods
* Line 110-111: A better definition of "major anomalies", and what would not constitute a major anomaly, would be helpful here for the reader. As 8 women were excluded for this reason, it is meaningful.
* Good description of statistical methods and, in particular, of the binomial regression and Poisson to compare each subsequent week of gestation to the 39 and 0 to 39 and 6 week interval.
* Factors corrected for in outcomes are reasonable based on the literature. However, based on the differences in higher gestational weeks' insurance status, correcting for this also may have made this even more rigorous.
* Analysis by cervical status is a meaningful and helpful analysis in this study.
* No post-hoc power analysis is presented, which would help to put into context for the reader just how highly powered this large study is to detect small differences in outcomes.

Results
* Line 159-160: That is interesting that insurance differed by gestational age. Would the authors consider correcting for that in a further analysis?

Conclusions
* Line 230-233: I agree with the authors that this is likely confounding of some type; hypertensive disorders or hints that they may arise are more common as the gestational weeks progress, so most women get induced for anything going wrong, and are less likely to therefore get a diagnosis of hypertensive disorders in the subsequent weeks.
* Limitations and the events/outcomes that were too few to analyze well are acknowledged well in this section.

Reviewer #2:

This manuscript represents a secondary analysis over the Maternal-Fetal Medicine Units Network RCT trial comparing labor induction versus expectant management and low risk nulliparous women at term published in 2018 and the NEJM. This study provided more detailed information on the expectantly managed group from 39 weeks onward. It is very well written, clear and concise. The study does provide additional valuable information not included MD 2018 publication. The following not suggested revisions but request which I feel will improve the information provided to clinicians during the counseling process when discussing the options of expectant management versus induction of labor in this cohort of patients:

1. As in the original manuscript I would like to see more detailed reporting in terms of exact numbers regarding birth trauma, intracranial hemorrhage and subgaleal hemorrhage on the perinatal-neonatal portion of table 3 in the 3 gestational age windows. For example a woman may want to know if neonatal injury increases with each gestational age window. This probably is not needed in table 4. since there probably will not enough individual cases to allow statistical comparisons.

2. Do you have shoulder dystocia rates that you can report on in the similar fashion as suggested above?

3. When reporting the rates of blood transfusion in addition to a simple yes or no regarding the utilization of blood transfusions, is there a way of reporting the imbalance of blood transfused on a per week basis?

4. In table 1 it shows that when you look at the modified Bishop score of less than 5 at the time of randomization there was a significant trend towards a greater gestational age at delivery. We also know that table 3 shows that the cesarean delivery rate increases each gestational age week, also. Therefore, I think it would be clinically valuable to compare the cesarean section rates in women who had modified Bishop scores of less than 5 at the time of randomization in women electively induced at 39 weeks versus the expectantly managed group at each gestational age. If I was counseling a woman with a modified Bishop score less than 5 at 39 weeks I would want this information especially if the analysis shows that the suction rate in this group is lower if induced at 39 weeks

Reviewer #3:

Well written, easy to follow and validates what we already "anecdotally" know. Post dates is associated with increased risk

for cesarean and potentially adverse neonatal outcomes. This study provides relative risks for these outcomes and can be used to guide patient-centered decision making. A couple of questions/comments for the authors that could provide additional information/guidance for clinicians and patients.

1. Exclusion criteria/Figure 1. Understand why fetal anomalies and deliveries <39 weeks were excluded. But not clear who/what "elective delivery" >=39 weeks was, or why they were excluded. Were these elective inductions/elective cesareans? This group should have been kept in the EM arm after randomization and analyzed as intention to treat.

2. Would be helpful if authors provided information re: cesarean delivery based on whether patient went into spontaneous labor or not (i.e. induced). (First and second rows, Table 2).

3. A little misleading to include/focus/emphasize increased risk of medical indication for induction when it includes "post date induction" where the standard of care is to offer induction; and this was the primary reason for induction.

4. Page 10, lines 225-228. Authors note the decrease in the incidence of HDP. They refer to the original ARRIVE study with different incidence rates by gestational age group (9.1% induction group and 12.1% at 40 weeks and 10.8% at 41+weeks in the EM group). If this is a secondary analysis of the ARRIVE study (observational study of patients who were in the EM arm at 39 weeks and beyond), not clear why these numbers/rates are different.

STATISTICAL EDITOR COMMENTS:

lines 56-57, 114, 119-120 and Table 3: There were two primary outcomes. Therefore the inference threshold should be adjusted to a stricter threshold, ie, .025, rather than .05. The primary outcome of CD remains statistically significant, while the difference in rates of perinatal composite does not. If the comparisons were meant to be vs a referent value for CD and for perinatal composite at 39 wks with comparisons for each outcome at 40 and 41-42 wks, then there were 4 comparisons, and the inference threshold should be 0.0125, not .05. This would make the aRR for CD rates significantly higher at 41-42 wks, but not at 40 wks and the 41-42 wk perinatal composite would not be statistically different from its referent. So, need to be clear about defining the primary outcomes and how they are being compared (across the 3 GA strata or using 40 wks as the referent).

Tables 1,2,3: Again, (related to the differences across 3 GA strata vs using one group as a referent), for several variables for which there is a statistically significant p-trend, there appears to be a step-wise difference across 3 strata, while for others, the 41-42 wk GA clearly appears to be the outlier. The trend seems clear for many, e.g., smoking, Bishop score < 5, for induction, CD. However, for baseline BMI, perinatal composite, spontaneous labor, private insurance it appears that the 41-42 wk GA is the outlier. Suggest as supplemental material to compare each GA stratum vs 39 wk to further evaluate these differences.

Table 3: Need to clearly separate the primary from the secondary outcomes. For stillbirth or neonatal death, these are very infrequent events, and by Fisher's test there is no difference among the groups. It seems too few to come to a generalizable conclusion, at least based on these data.

Tables 4 and 5: Should include the unadjusted RRs for contrast with the aRRs.

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:
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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. For studies that report on the topic of race, authors must provide an explanation in the manuscript of who classified individuals' race, ethnicity, or both, the classifications used, and whether the options were defined by the investigator or the participant. In addition, the reasons that race/ethnicity were assessed in the study also should be described (eg, in the Methods section and/or in table footnotes).

Use "Black" and "White" (capitalized) when used to refer to racial categories.

The category of "Other" is a grouping/label that should be avoided, unless it was a prespecified formal category in a database or research instrument. If you use "Other" in your study, please add detail to the manuscript to describe which patients were included in that category.

4. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions and the gynecology data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

5. 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.

6. 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).

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

In addition, the abstract length should follow journal guidelines. The word limit for Original Research articles is 300 words. Please provide a word count.

8. 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.

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"health care professional" if a specific term is not applicable.

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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. 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.

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14. Figure 1: We don’t often see greater than or less than signs in a flow chart. Could you please add an explanation for this to the legend?

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

Sincerely,

John O. Schorge, MD
Associate Editor, Gynecology

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

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