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: Nov 07, 2019

To: "Robert M Rossi" ████████████████

From: "The Green Journal" em@greenjournal.org

Subject: Your Submission ONG-19-1855

RE: Manuscript Number ONG-19-1855

Risk Calculator to Predict Cesarean Among Women Undergoing Induction of Labor

Dear Dr. Rossi:

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

REVIEWER COMMENTS:

Reviewer #1: Thank you for your submission of "Risk Calculator to Predict Cesarean Among Women Undergoing Induction of Labor". The submission is an examination of a developed risk calculator to calculate likelihood of cesarean delivery after induction of labor for a broad American population. The calculator is developed based on a population-based cohort for all US women who underwent induction of labor between 32w0d and 42w6d and brings together an impressive amount of data regarding these outcomes, with overall good correlation between predicted risk and outcomes and is therefore broadly generalizable. Certainly, this is a strength of the study.

What remains to be elucidated, as the authors aptly mention in their discussion, is the clinical utility of the developed calculator. Specifically, as the authors suggest, the outcomes from the calculated risk 'should not be prescriptive for an elective cesarean delivery'. We fear that with such limited discussion regarding the implications of risk-based counseling of patients, that this calculator will be used precisely for that reason. And no woman independently knows whether she individually will succeed with vaginal delivery or not until a trial of induction is undertaken. This is a weakness of any risk calculator model.   Women and physicians may choose to proceed directly to cesarean delivery based on the risk model, thus turning it into a self-fulfilling prophecy and potentially increasing the cesarean delivery rate even more.

The following needs to be addressed:

1.   Lines 135-138: This rationale seems very weak. How would this actually help in using resources more wisely? This has not been studied and this statement is highly speculative and needs supportive references.

2.   Results: The inclusion of women undergoing induction of labor with prior cesarean is valuable but may be better addressed independently or stratified for analysis. Further, this population was not addressed in the results section. A specific paragraph exploring this population and these data would be welcomed.

3.   Lines 198-210: These findings are well known in other cohorts. What is new in the results?

4.   Lines 198-200: These risks are even more pronounced in an obese cohort where risk of cesarean may be higher but risks associated with cesarean delivery are likewise increased. How much attributable risk does maternal obesity contribute to the model?

5.   Tables 2 & 3: These differences are statistically, but are they clinically relevant? For example, the incidence of no prenatal care was 0.7 % in each group, but the p value was < 0.01? Is this a clinically relevant or important difference?

6.   Lines 262-268: One feature between this model and Grobman's model for risk of CD in VBAC is that this model is

reflective of the entire obstetric community, while Grobman's was primary housed in large academic centers with outstanding resources to allow for more successful VBAC. This is like comparing apples and oranges given the different population characteristics from the perspective of health care capabilities. This is not a surprising finding at all, and reflects the inherent need to validate these tools in prospective studies before being used.

7.   Lines 273-281: It is wishful thinking to believe if the calculator were to be widely adopted that patients and providers would not consciously or subconsciously alter their practices as such. My fear is that these risk calculators come into use without being adequately studied in a prospective fashion to show that outcomes are improved rather than worsened. Otherwise, we stand considerable risk to repeating the errors of electronic fetal monitoring, tocolytics, and other interventions intended to be beneficial that have actually been harmful. A specific strongly worded statement to this effect is in order.

8.   Please describe how use of this model could actually improve clinical outcomes. As written, it is not clear how this actually would make life better for pregnant women, their babies, or their health care providers.

9.   Figures 2, 4, and 5 are very similar. I would merely describe figures 4 and 5 in the results and then include them as an online supplement. Similarly, figure 6 would be best as an online addition.

Reviewer #2: The authors objective was to develop and validate a predictive risk calculator for cesarean delivery among women undergoing induction of labor. To do this they performed a population-based cohort study of all women who had singleton livebirths and underwent an induction of labor (IOL) between 32 0/7 - 42 6/7 weeks of gestation in the United States between 2012-2016. The primary objective was to build a predictive model estimating the probability of cesarean delivery after IOL using antenatal factors obtained from de-identified U.S livebirth records. Multivariable logistic regression estimated the association of these factors on risk of cesarean delivery. External validation was performed using a separate livebirth cohort from 2017. A publicly available online calculator was developed after validation and calibration were performed for individual risk assessment. The 7 variables selected for inclusion in the model by magnitude of influence were prior vaginal delivery, maternal weight at delivery, maternal height, maternal age, prior cesarean delivery, gestational age at induction, and maternal race. The receiver operator characteristic (ROC) curve for the 7 variable model achieved an area under the curve of 0.79 (95% CI 0.78-0.79). External validation demonstrated a consistent measure of discrimination with an AUC of 0.78 (95% CI 0.76-0.80). They conclude that this validated predictive model discriminates between women at increased or decreased risk of cesarean after induction of labor.

The authors should be commended on tackling this important dimension of clinical care. I have a few questions and comments:

1. The cohort is quite heterogeneous (nullips, multips, prior cesarean). While this may enhance the generalizability of the model, it does raise the concern for its applicability to the various sub-groups in this very broad cohort. K-fold cross validation was performed but I believe this issue should be more thoroughly elaborated on in the methods and results for the purposes of clarity and completeness.

2. This also raises the concern around the 7 variables chosen by magnitude of influence, and their sustained influence contextualized to a more focused cohort analysis. As above more elaboration on this dimension would be helpful to the reader.

3. An AUC of 0.79-0.78 can be categorized as acceptable--the authors should more clearly define the threshold level definitions for AUCs, and comment on this broadly.

4. The authors correctly note the significant limitations to this study: retrospective, administrative data; practice pattern heterogeneity; unknown indication for cesarean delivery. There is no way around these limitations given the data set, but it does limit the strength of the study.

5. The authors should clearly state that Bishop score was not available in the dataset.

6. The authors should make clearer the details of 2017 U.S. livebirth dataset on which the model was externally validated (inclusion and exclusion).

Reviewer #3: The authors present a reasonably well done study of factors which predict cesarean section in a large cohort of women. This is an important topic to help predict which women who undergo induction of labor will ultimately require a C-section. Overall I thought this was a reasonably well done paper that doesn't seem broadly overreaching.

Specific comments:

Lines 127-129; I think that you need more sources to support this statement that C-section rates are up to 27%. While this is likely true I think you need more citations.

Lines 157-159: I am unsure if you should include failed OVD in this data set. Is this truly a failed induction of labor in the global sense? Given that a failed OVD is likely the result of CPD or fetal intolerance, I think that this is prejudicing your data set.

Lines 208-210: I think this is a very interesting part of your data set and should be expounded upon in the discussion more. What are the reasons for this? Are they obvious or is their something else going on here?

Lines 220-225: The ROC curves for this study are decent with a AUC of .78. However, the NPV for this data set is not superb as for most clinical tests an NPV of >95% is required. How do you account for this and does this decrease the validity of your test?

The limitations section of this manuscript is weak and should be expanded upon.

STATISTICAL EDITOR COMMENTS:

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

Figs 2, 4, 5: Should round the AUC to nearest 0.001 in the figures and consistently use 3 significant for the AUC and its CIs in the figure legends.

The Authors should emulate the TRIPOD article (ref). Note especially the nomogram (fig 7 in the reference), which is a useful visual aid for showing the various model inputs, but we
also encourage use of a visual display of a calibration curve (fig 8). This figure allows the reader to see the relationship of observed vs predicted probabilities along the spectrum of
probabilities from the data, along with confidence intervals for those prediction estimates. The advantage to this level of detail is that it would convey to the reader the strength of
association at various model scores, along with their relative uncertainty, reflecting how many data were available at various cut-points.

Ref:
"Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): Explanation and Elaboration" by K.G.M. Moons, D.G. Altman, J.B.
Reitsma, J.P.A. Ionnidis, P. Macaskill, E.W. Steyerberg, A.J. Vickers, D. F. Ransohoff and G. S. Collins, Annals of Internal Medicine 2015:162:W1-W73.

Fig 3, lines 175-179, Table 5: The 10 increments are equally spaced along the probability axis, but do not have equal sample sizes, since the mean CD rate was 19%. Fig 3 needs to include CIs for each 10% increment. The analysis should also conform to the TRIPOD guidelines, that is, the final scores should be divided into deciles (or, given the sample sizes, could use 20 ~ equal cohorts, if desired). The observed vs predicted probabilities should then be plotted (with CIs for each subset) and the Hosmer-Lemeshow GOF analysis compared the observed vs predicted. The current Fig 3 would have unequal representation, since the lower deciles would have many more examples than the upper deciles.

Table 5: The sens, spec should include CIs. The PPV and NPV are dependent on the prevalence of CD in the population. A better metric should be to include the LR(+) and LR(-), each with CIs, since those are independent on the population prevalence of CD.

Fig 6: Should round the risk estimate to the nearest 0.1% and should incorporate the CIs from the decile (as outlined in TRIPOD guidelines) for that cohort, to give more context for the estimate, lest an individual woman's risk be interpreted at the precision level implied by the on-line calculator.

EDITOR 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.
B.   OPT-OUT: No, please do not publish my point-by-point response letter.

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.

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.

5. 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).

6. Provide a short title of no more than 45 characters, including spaces, for use as a running foot.

7. Provide a précis on the second page, for use in the Table of Contents. The précis is a single sentence of no more than 25 words that states the conclusion(s) of the report (ie, the bottom line). The précis should be similar to the abstract's conclusion. Do not use commercial names, abbreviations, or acronyms in the précis. Please avoid phrases like "This paper presents" or "This case presents."

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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. 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. Figures 1–6: Current figure files may be resubmitted as-is.

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16. 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 14 days from the date of this letter. If we have not heard from you by Nov 21, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Dwight J. Rouse, MD, MSPH
Associate Editor for OB

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

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