OBSTETRICS & GYNECOLOGY

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

Date: May 24, 2021
To: "Michelle Yee Lu" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-21-1021

RE: Manuscript Number ONG-21-1021

Safety and efficacy of risk-stratified heparin-based thromboprophylaxis in obstetric patients

Dear Dr. Lu:

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, 2021, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: Safety and efficacy of risk-stratified heparin-based thromboprophylaxis in obstetric Patients

Considering the venous thromboembolism (VTE) is the leading cause of maternal mortality, interventions to mitigated the risks of the complications are warranted. Risk stratification and heparin-based thromboprophylaxis (HBT) is one such strategy. But before the intervention trial is recommended by national guidelines, there ought to be objective evidence about it's safety and efficacy. The investigators are to be congratulated for undertaking this pre- and post-intervention trial to assess the clinical utility of HBT.

While revising the manuscript, please address the following:
1. Since both the primary and secondary outcomes could occur up to 6 weeks after delivery, please provide data on: i) how was the follow-up done (i.e. chart review, phone call, social media); ii) what proportion of individuals had a follow-up to 6 weeks (i.e. not lost to follow-up)?
2. What was the protocol for the diagnosis of VTE and was it similar / same during the pre- and post-intervention periods?
3. This seems like a quality improvement project. Hence, please consider using SQUIRE guideline (Ogrinc G, et al. SQUIRE 2.0 (Standards for QUality Improvement Reporting Excellence): revised publication guidelines from a detailed consensus process. BMJ Qual Saf. 2016;25:986-992). If SQUIRE guideline is not applicable to their undertaking, please opine why.
4. After (or before) the results of the analysis, at their institution have the researchers stopped using risk stratified HBT? If so, please state so in the Discussion.
5. The maternal mortality during the study period was 49 / 100,000 births (12/24,149). Understandably this high maternal mortality is due to the high-risk individuals they manage. Nonetheless, in a supplement Table please provide details about the 12 maternal deaths. Such a table should include details like time interval from delivery to death, the cause of death, whether they received HBT.
6. Perhaps as a separate manuscript, please consider a predictive model (calculator) to identify which individuals are likely to be harmed with HBT. Alternatively, if it is not possible to identify individuals with predictive models, that is knowledge worth publishing.

Reviewer #2: The authors have performed a large single-center study of the impact of adopting a risk-based protocol for pharmacologic thromboprophylaxis when compared to a pre-protocol comparable time period and numbers of patients studied.
Their primary endpoints were occurrence of VTE and post-drug bleeding complications.

After appropriate corrections, they found that risk-based use of unfractionated or LMWH heparins resulted in no significant reductions in VTE incidence and an increase in bleeding-related complications.
The study appears to be appropriately conducted and its data subjected to appropriate statistical analysis.
Questions:
1. While the numbers might be too small, could the authors drill down into the specific risk factors in the one-factor and two-factor stratification groups to see if there were specific subgroups that seemed to benefit or at least had fewer harms?
2. One of the confounding factors between the control and study populations is the considerable increase in aspirin use in the latter. Would it be possible to isolate the aspirin-exposed group for risk of bleeding disorders, particularly if this drug were taken near the time of delivery?
3. How many patients in the control and study groups received mechanical thrombophylaxis even though it was recommended in both time frames for all antepartum patients and postoperative patients?

Reviewer #3: ONG 21-1021

In the manuscript under review, Lu et al present the results of their retrospective cohort study evaluating the safety and efficacy of a risk stratified heparin-based thromboprophylaxis protocol in obstetric patients. Analyzing over 24,000 deliveries, the authors found no difference in the rate of VTE however the patients exposed to the intervention were more likely to develop hematomas and require blood transfusions.

A few comments on the manuscript are as follows:

ABSTRACT
1. A clear objective is stated. The last sentence of the results section is confusing and should be re-phrased.

INTRODUCTION
2. A clear argument is made for the need for such analysis. A hypothesis and a clear objective are both presented here.

METHODS
3. Line 84-85 Was any "washout" period considered in this analysis?
4. Line 88 - how was the protocol implemented and how was compliance tracked? Was this added as a care bundle to the EMR? How were providers introduced to the new protocol? How long was this introduction in place for? What educational strategies were implemented to help with the roll out of the new protocol?
5. Line 96 - how were hematomas defined? Same for wound infections? What constituted a positive case? Was this classification left to the treating provider?
6. Did wound complications include perineal lacerations or were they limited to cesarean incisions?
7. Was there any change to the follow-up practice for patients having undergone cesarean section pre and post protocol implementation? This is especially important since some of the secondary outcomes would increase in frequency if follow-up rates increased postpartum.
8. The authors should add a line stating that the STROBE guidelines were followed in this manuscript.

RESULTS
9. Table 2 - some abbreviations should be explained in the footnote
10. Since there is a statistically significant difference in the rate of cesarean delivery between the 2 groups (30.6% versus 32.1%), shouldn't mode of delivery be a covariate adjusted for when evaluating all wound complications (specifically wound dehiscence and superficial wound hematoma)?
11. Do the authors have any data on the rate of routine postpartum visits/wound checks? IF so, this data should be added to the postpartum resource utilization section.

DISCUSSION
12. Line 245-257 I would suggest adding, as a limitation, the possibility of type I error since the rate of the primary outcome was half of what the authors had intended.

STATISTICAL EDITOR COMMENTS:

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

Table 2: Although the samples are large, the counts for VTE are small and the study is underpowered to generalize the NS conclusions re: efficacy. Based on the usual criteria of 80% power, alpha = .05, the samples given and a control group rate of VTE of 0.13%, the RR would have to exceed 2.4 or be less than 0.17. (At these incidence rates, RR and OR have essentially the same values.) The power is even less favorable for subsets of VTE. Also, the aORs are likely over fitted, based on the counts of VTEs for a multivariable model. The safety outcomes have sufficient power and of course, were statistically significant for any and for superficial wound hematomas.

Table 3: Based on the counts of VTEs, likely the comparison of times from delivery to VTE are underpowered and thus the NS finding cannot be generalized. The study is underpowered to evaluate differences in maternal death rates.

General: Underpowered for efficacy, would require much larger sample to verify.

EDITOR COMMENTS:

1. We are very happy to have received this manuscript and look forward to a revised version. Additional point. I don't see you can calculate a NNT or NNH when there is no effect of the heparin?

2. 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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The following authors need to complete the agreement, and the email with the link the form was sent to them on May 24, 2021:

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4. For studies that report on the topic of race or include it as a variable, 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). Race/ethnicity must have been collected in a formal or validated way. If it was not, it should be omitted. Authors must enumerate all missing data regarding race and ethnicity as in some cases, missing data may comprise a high enough proportion that it compromises statistical precision and bias of analyses by race.

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5. Please add the name of the IRB mentioned on line 81.

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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, RECORD, CHEERS, SQUIRE 2.0, or CHERRIES guidelines, as appropriate.

7. 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.

8. 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 5,500 words. Stated word limits include the title page, précis, abstract, text, tables, boxes, and figure legends, but exclude references.

9. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

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Please add text to describe how Hannah Howard and Maahum Z Kamal participated in your study.

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

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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%").

13. 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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* A point-by-point response to each of the received comments in this letter. Do not omit your responses to the Editorial Office or Editors' comments.

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, 2021, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

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