OBSTETRICS & GYNECOLOGY

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- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*

**The corresponding author has opted to make this information publicly available.*

Personal or nonessential information may be redacted at the editor's discretion.

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

Date: Apr 07, 2020
To: "Nadine Sauve" em@greenjournal.org
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-282

Please forward this message to
Dr Nadine Sauve

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RE: Manuscript Number ONG-20-282

Evaluation of bleeding complications in postpartum women receiving therapeutic anticoagulation

Dear Dr. Sauve:

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 Mar 27, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: This is a retrospective multi-institutional cohort study of 233 patients who received postpartum therapeutic anticoagulation. The primary objective of the study was to evaluate hemorrhagic and wound complications related to administration of anticoagulation within 96 hours of delivery. The investigators ultimately concluded that composite risk of complications was higher for patients who underwent cesarean section than for vaginal delivery, and that this risk was highest for women who received anticoagulation before 10 hours postpartum for vaginal delivery and before 15 hours for cesarean section. The external validity of this study is presumably good as it includes a moderate sample size of women who received peripartum therapeutic AC (both LMWH and UFH) for a variety of indications (although mechanical valves were under-represented in this cohort). I have a few minimal concerns about the study design, reporting of the analysis and the conclusions drawn from the data (see below). The findings of this study are generalizably important to both general obstetricians and perinatologists as there Is little extant data to guide timing regarding resumption of anticoagulation in the postpartum period.

1) Title: This manuscript focuses on both bleeding AND wound complications and the title should be changed to reflect this.

2) Inclusion criteria
a. It is not mentioned here if these were women who were on therapeutic AC prior to pregnancy or if the study also includes women who were started de novo on therapeutic AC postpartum (e.g. for a newly diagnosed VTE). This should be clarified.
b. It should be mentioned why AC administered within 96 hours of delivery was chosen as an inclusion criterion. If there

are no guidelines for when to resume AC postpartum, why was 4 days selected by the authors? I'm assuming it's because most women go home after a vaginal delivery within 2 days and after a cesarean section within 4 days… if so, this should be stated.
c. Line 129: I have a concern with "fluid resuscitation of 1L or more of crystalloids" as being included as a "major hemorrhagic complication." I see from table 2 that only one patient in the cohort met this definition... how is this possible? Along with crystalloid pre-loading (not evidence-based but routinely practiced) and with normal blood loss during cesarean delivery, it is not uncommon for women to receive 1 L of fluid or more perioperatively.
d. Lines 138-145: It's unclear to me what is meant by "specific risk factors." Do the authors mean to suggest that the listed variables were controlled for in the analysis?
e. Lines 146-149: If these were the time-points (12 -24 hour intervals) used to stratify risk of peripartum complications, how did the authors identify 10 hours for vaginal deliveries and 15 hour for cesarean sections as being significantly increased with composite risk of complication.

3) Results:
a. Line 181: I'm confused as to how risk of major wound complications was 4.8% for women who had cesareans but it's mentioned in line 178-179 that risk of major wound complications was 1.7% in the entire cohort…. Did the study include women with wound complications related to vaginal repairs? If so, this should be mentioned in the inclusion criteria.
b. Line 212-216: I think this is actually a huge deal. 23/197 patients is not a small proportion (~12% of the cohort). Perhaps bleeding complications are related to delayed cessation of antepartum AC, not early resumption of postpartum AC. This should be mentioned in the discussion and study limitations.
c. Figure 1A makes it look like risk of complications was significantly LOWER in women who underwent cesarean section and resumed AC less than 12 hours after delivery compared with between 12-24 hours. This is odd considering that you report (in figure IB and throughout the text) that risk of complications was HIGHER in those who underwent cesarean section and resumed AC less than 15 hours after delivery. This should be addressed in the discussion.

4) Discussion/ conclusions
a. Line 225-227. This conflicts with the statement made in line 179 that "The proportion of major hemorrhagic complications for CS versus VD was 8.4% and 6.0% respectively and was not statistically different (p=0.482)."
b. Line 230-231: This sentence is misleading… it makes it seem like the timing of antepartum AC cessation was not determined to be important (conflicts with lines 212-216). I would rephrase as "when analyzing the 12% of the cohort whose antepartum anticoagulation was stopped < 24 hours prior to delivery, there was no association between timing of postpartum resumption of AC with major postpartum complications."
c. I understand that maximal INR and maximal PTT were included in a multivariate model and determined to be significantly associated with increased composite risk of complications. However, were bleeding complications only increased in patients who had supratherapeutic PTTs or INRs? In other words, is it supratherapeutic anticoagulation rather than early postpartum anticoagulation that's responsible for composite risk of complications? Should be mentioned in the discussion.
d. Lines 271-272: Thank you for including this in your limitations. I think you should specifically mention that women with mechanical heart valves are at the highest risk of thromboembolic complications and are under-represented in this study. Clinicians should weight the benefits of early resumption of AC with the risk of hemorrhagic or wound complications in populations with exceptionally high risk of VTE.

Reviewer #2: Review of Manuscript ONG-20-282 "Evaluation of bleeding complications in postpartum women receiving therapeutic anticoagulation"

Bettache and colleagues have submitted a multicenter (3 centers in Quebec, Canada) retrospective cohort study that attempts to evaluate the potential negative consequences (complications) based on the timing of the resumption, at least one therapeutic dose up to 96 hours following delivery, of therapeutic postpartum anticoagulation therapy. The authors noted that the rate of major complications was similar regardless of route of deliver - vaginal vs. cesarean. As noted by the authors at least some portion, if not all, of this data has been presented as several different meetings. I have the following questions and comments.

Title - No comments

Précis - No comments

Abstract - Consider commenting on your primary outcome of major complications in the abstract conclusions.

Introduction - Line 76 - are you referring to prophylactic, therapeutic or both? Please clarify this statement. I think you may be able to combine the first 2 two-sentence paragraphs.

Methods - Line 129 - point of minor clarification was the resuscitation greater than 1L in an episode or in aggregate? Is there perhaps a better way to present the secondary endpoints rather than bulleted as was done? I believe it is Fisher's not Fisher for the exact test.

Results - Line 185 - as data is missing for about ½ of the cohort should you just exclude this? Line 188 - I would delete "Only" as you then subsequently list 6 variables that appear to have an association with the outcomes of interest. In addition, please add the 95% CIs for these variables. For the paragraph starting at Line 195 - you the median time points of resumption of anticoagulation for both delivery groups (Vaginal: 6 vs. 19 hours; CD: 12 vs. 33 hours) associated with and without complications. Yet, in the following paragraph you then evaluated complications in the vaginal delivery group using 12 hours as a cut point and 24 hours in the CD group. While the times in the second paragraph may make more sense from a pragmatic standpoint, did you either evaluate or consider evaluating complication rates above and below the cut point from the preceding paragraph?

Discussion - Line 238/9 - While I think I understand what you are trying to point out here but, in the methods, (lines 121-2) you noted that patients that received only prophylactic doses in the up to 96 hours were excluded and thus I suspect this group of 42% of patients received a varying number of doses of anticoagulation (prophylactic) before starting therapeutic dosing. Do you have information on this for the reader to determine potential applicability of your statement? Line 243-5 would again encourage you to depict the 95% CIs. Line 274-5 - Minor point - Use is common in pregnancy and prescriptions are more commonly written in high risk clinics, as written it sounds like the use is limited to clinic administration which was likely not the point trying to be communicated.

Tables
Table 1 - Is the gestational age which seems similar based on the presented data actually statistically significantly different between the 2 groups? I would delete the row about direct anticoagulants since you note in the manuscript that none were used. Can you add units for Platelets, etc. Does it make sense to include the column data re: the use of instrumentation and perineal trauma when the N in the CD group was 0? Can you just note this data in the manuscript as it relates to the vaginal delivery group?

Table 2 - No comments.

Table 3 - Why is the p value in the first row bolded? Is there a different way to present the additional variables at the bottom of this table for the subgroups? Maybe just refer to in the manuscript? Table 4 can be deleted as it can be completely referenced in the text.

Figures - I think they are okay.

Reviewer #3: The authors present their cohort study regarding use of therapeutic anticoagulation postpartum and complications associated with such use. The analysis evaluated the use of various anticoagulants and the timing of initiation with regards to both predefined major and secondary postpartum complications. The study is overall well written and presents novel data on a relatively common issue. However, I have the following concerns in its present format:

MATERIAL/ METHODS:
-Line 129: "fluid resuscitation of 1 L or more" as part of major hemorrhagic complications- starting at what point? After delivery of the placenta? Or is this for the entire surgery for those undergoing cesarean? The amount seems to be relative low threshold to be included for "major hemorrhagic" complications since 1 L is what most patients undergoing routine cesarean are typically receiving.

-Line 142: can the authors clarify the dose of the concomitant Aspirin use - (I'm assuming low dose 81 mg) and NSAID use?

-Line 146: can the authors clarify the rationale for the various time intervals - I can understand some of the shorter, but don't understand if therapeutic anticoagulation were being started, why waiting 72-96 hr

-Line 149: please expand on how thromboembolic events were diagnosed to be included for analysis

RESULTS:
-What is the ascertainment rate for the patients to assess for wound complications (especially the secondary complications)?

-Table 1 Page 15 - there is an entry for "postpartum thromboprophylaxis" 98 patients out of 233 - please clarify since the objective of the study was to evaluate "early postpartum therapeutic anticoagulation"

STATISTICAL EDITOR COMMENTS:

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

Table 1: The column "Caesarean delivery" has N = 83, so the %s should be rounded to nearest integer %, not to 0.1% precision. The missing data for BMI is such a large proportion of the totals that the estimates may be biased and cannot be reliably generalized.

Table 2: Should include CIs for the estimates of proportions with complications. Eg, for ≥ 1 major complication: 6.0% (CI = 2.7%-11.4%) vs 8.4% (CI = 3.4%-17.4%). In addition, the sample sizes and relative proportions of this adverse event (and others cited in the Table) do not allow sufficient statistical power to generalize the NS finding. For example, based on a vaginal delivery proportion of complications = 6.0%, the C-section cohort would have to have a rate > 18% to achieve 80% power and a difference at the 0.05 level. Put another way, there is < 20% power to discern a difference of 6% vs 8.4% given these sample sizes. Should also include CIs for the rates of recurrent VTE, which were 0.9% (CI= 0.1% - 3.1%) overall.

lines 205-211: Should round the AUC values and CIs to the nearest 0.01, not to 0.001 precision. The optimal cut-off was identified as 15 hrs; Need to cite the CIs for that estimate, so the reader can interpret it with some context.

General: These results compare VD vs CD, where all women received anticoagulation, so what conclusion can be inferred from these data, except that rates of complications (when aggregated to include any complication) are higher in VD than in CD?

lines 163-166: The ROC curves and Youden index were used to identify if a range of delay in resuming anticoagulation was associated with a higher proportion of complications. But to use that threshold to test whether the before vs after had proportions different from random chance is a rigged test. By design, the results are not going to be random. The testing by pre-specified intervals is OK, but not testing intervals which were derived from a test to discern a difference by ROC analysis.

Table 3: These are labelled as univariate associations, yet Table 1 shows multiple differences between the cohorts. Need to also show the multivariable (aORs) for contrast, list the variables included in the final models and justify the use of models with multiple adjustors if the number of adverse outcomes is insufficient (there were only 9+13 = 22 adverse outcomes, per Table 2).

EDITOR'S COMMENTS:

We no longer require that authors adhere to the Green Journal format with the first submission of their papers. However, any revisions must do so. I strongly encourage you to read the instructions for authors (the general bits as well as those specific to the feature-type you are submitting). The instructions provide guidance regarding formatting, word and reference limits, authorship issues, and other things. Adherence to these requirements with your revision will avoid delays during the revision process, as well as avoid re-revisions on your part in order to comply with the formatting.

PRESENTATION OF STATS INFORMATION (P Values vs Effect Size and Confidence Intervals)
While P values are a central part of inference testing in statistics, when cited alone, often the strength of the conclusion can be misunderstood. Whenever possible, 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.
This is true for the abstract as well as the manuscript, tables and figures.

Please provide absolute values for variables, in addition to assessment of statistical significance.

We ask that you provide crude OR’s followed by adjusted OR’s for all relevant variables.

Line 50: Please tell us how patients were identified. Please define the primary outcome a bit more. Is this a composite? How were the complications defined? This is found in part in your results section but should be moved to methods.

Your precis should reflect your primary, not secondary outcomes.

Line 56 and likely in main body of manuscript as well: Please note that your study was conducted from date 1 to date 2, not between those dates. As written, it would exclude the dates given . You could save some word by saying something like “From 2003 to 2015, of 233 consecutive women treated with postpartum therapeutic anti-coagulation, 92 received

unfractionated……"

Throughout, please make sure you are using American-style spelling (example: cesarean rather than caesarean).

Line 62: it is implied but not clearly stated that the total includes the major and minor. These are not proportions (59, 62) but are rates. You could write something like " The composite hemorrhagic and wound complication primary outcome occurred in xx/yy (8,4%) of women who delivered by cesarean and zz/aa(6.0%) who delivered vaginally (p=0.48). Minor wound and bleeding complications occurred in xx/yy(%) and bb/aa (%), respectively . The median interval between delivery and initiating anticoagulation was shorter in women who developed any complication compared to those who did not for cesarean births (12 v 33 hours, p=.) and vaginal births (6 vs 19 hour, p=.)

Line 70 were these in both cesarean and vaginal births?

Line 71: the conclusion should include the primary outcome, not just secondary one.

Line 86: please provide a list of the society's you checked to be able to make this sentence.

Line 105: I don't know what a "delegated consent process" is? Would that be the same as the study being exempt from requiring consent?

Line 109: Who abstracted the charts?

Line 110: Data is plural so this should read that data were extracted

Line 117: as the outcomes in repeat pregnancies may not be independent, it would be ideal to use the first pregnancy outcome only (if there were a complication in pregnancy 1, the patient may have requested delaying initiation of anti-coagulation until later the next time, for instance). At the least, please report a sensitivity analysis of first pregnancy outcomes only.

Line 128: Is this hospital readmission for bleeding complications only or any hospital readmission?
Same query re: ICU admit.

Did you not include episiotomy breakdown or vaginal hematoma?

Line 136 Please report labs with deciliter rather than liter. This would change to 2g/dl.

Line 177+ please note above comments regarding presentation of data.
If you are going to report the components of the primary outcome separately (wound +hemorrhage) do so for all different types—vaginal and cesarean and wound and hemorrhagic.

Line 186: I'm confused by this composite of major + minor. Perhaps just say "Total complications were statistically higher…

Line 188 Please provide 955 CI's and absolute values.

Line 240: This is the first time you've mentioned adding prophylaxis here. Was this all medical or did it include mechanical (compression devices). This, and the data, should be presented in the methods and results section. Line 245: All 3 of these are risk factors for hemorrhage even in non-anticoagulated patients; as well, at least the type of delivery and infection, are risk factors for VTE. Please comment.

Line 248:Provide your search (If not done earlier) for being able to say this is the "largest" and "First". as this constitutes a primacy claim.

Line 274: You haven't really made any comment about this being "common". You don't provide the N for number of deliveries that these 200 odd deliveries were part of. Delete the "common" reference.

Line 276: the benefit outweigh the risks for some indications, not in general.

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.
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. In order for an administrative database study to be considered for publication in Obstetrics & Gynecology, the database used must be shown to be reliable and validated. In your response, please tell us who entered the data and how the accuracy of the database was validated. This same information should be included in the Materials and Methods section of the manuscript.

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 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.

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. Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). Do not structure the title as a declarative statement or a question. Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles. Abbreviations, jargon, trade names, formulas, and obsolete terminology also should not be used in the title. Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," or "A Systematic Review," as appropriate, in a subtitle. Otherwise, do not specify the type of manuscript in the title.

7. 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).

8. 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 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. Line 249-251: We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If on the other hand, it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

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.

14. Figure 1: Please upload as high-res figure files on Editorial Manager (eps, tiff, jpeg, etc).

15. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at http://links.lww.com/LWW-ES/A48. The cost for publishing an article as open access can be found at http://edmgr.ovid.com/acd/accounts/ifauth.htm.

Please note that if your article is accepted, you will receive an email from the editorial office asking you to choose a publication route (traditional or open access). Please keep an eye out for that future email and be sure to respond to it promptly.

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 21 days from the date of this letter. If we have not heard from you by Mar 27, 2020, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,
Nancy C. Chescheir, MD
Editor-in-Chief

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

Sherbrooke, April 21st, 2020

Revised manuscript after reviewers' comments

Manuscript Number ONG-20-282

Dear Dr. Chescheir,

We greatly appreciate the comments provided by the Editor, statistical editor and the reviewers. We have edited our manuscript to address these comments and believe it is improved both in terms of content and clarity. Please find our responses to the comments below, in point form. We have also reviewed the instructions for authors one more time, to ensure we are in full compliance with them.

Please note that there is a slight change in the numbers due to a duplicate that was removed upon our final detailed review of our data (n changed from 233 to 232). All tables and results appearing in this revised manuscript now include the complete and accurate data. This has not impacted our results or conclusions as compared to the previous version.

Thank you again for the opportunity to submit this manuscript to your journal. We are thrilled about this collaboration and hope our revised manuscript will be deemed acceptable for publication in Obstetrics & Gynecology.

With our best regards,

Gabrielle Côté Poirier, MD

Nazila Bettache, MD

Nadine Sauvé, MD

REPLY TO REVIEWER'S COMMENTS:

Reviewer #1: This is a retrospective multi-institutional cohort study of 233 patients who received postpartum therapeutic anticoagulation. The primary objective of the study was to evaluate hemorrhagic and wound complications related to administration of anticoagulation within 96 hours of delivery. The investigators ultimately concluded that composite risk of complications was higher for patients who underwent cesarean section than for vaginal delivery, and that this risk was highest for women who received anticoagulation before 10 hours postpartum for vaginal delivery and before 15 hours for cesarean section. The external validity of this study is presumably good as it includes a moderate sample size of women who received peripartum therapeutic AC (both LMWH and UFH) for a variety of indications (although mechanical valves were under-represented in this cohort). I have a few minimal concerns about the study design, reporting of the analysis and the conclusions drawn from the data (see below). The findings of this study are generalizably important to both general obstetricians and perinatologists as there Is little extant data to guide timing regarding resumption of anticoagulation in the postpartum period.

1) Title: This manuscript focuses on both bleeding AND wound complications and the title should be changed to reflect this.

The title was adapted to fit the maximal number of characters stated in the Instruction for authors (100 characters). By keeping only "complications", we include all complications, hemorrhagic and wound.

2) Inclusion criteria

a. It is not mentioned here if these were women who were on therapeutic AC prior to pregnancy or if the study also includes women who were started de novo on therapeutic AC postpartum (e.g. for a newly diagnosed VTE). This should be clarified.

This has been clarified in the Methods.

b. It should be mentioned why AC administered within 96 hours of delivery was chosen as an inclusion criterion. If there are no guidelines for when to resume AC postpartum, why was 4 days selected by the authors? I'm assuming it's because most women go home after a vaginal delivery within 2 days and after a cesarean section within 4 days… if so, this should be stated.

The reviewer is right that there are no data in pregnancy about the postpartum delay at risk for complication after resuming therapeutic anticoagulation. However, in the non-pregnant peri-operative literature, risks of complications after resumption of anticoagulation is often evaluated for the first 72-96 hours post-surgery, so we used this interval empirically.

c. Line 129: I have a concern with "fluid resuscitation of 1L or more of crystalloids" as being included as a "major hemorrhagic complication." I see from table 2 that only one patient in the

cohort met this definition... how is this possible? Along with crystalloid pre-loading (not evidence-based but routinely practiced) and with normal blood loss during cesarean delivery, it is not uncommon for women to receive 1 L of fluid or more perioperatively.

We appreciate that the reviewer mentioned this point. The criteria was a prescription of at least 1L of crystalloids <u>after</u> the therapeutic anticoagulation was restarted which was always after the immediate intrapartum/postpartum period so it did not include the usual pre-loading and postpartum usual care. These data were extracted manually by chart review, so the researcher was able to make this difference and select only fluid resuscitation for bleeding concern. A comment was added to the manuscript to clarify this issue.

d. Lines 138-145: It's unclear to me what is meant by "specific risk factors." Do the authors mean to suggest that the listed variables were controlled for in the analysis?

As a secondary outcome, we wanted to see if some of the risk factors selected were associated with a higher risk of complications. The covariate analysis was conducted using a univariate and multivariate multiple logistic regression analysis.

e. Lines 146-149: If these were the time-points (12 -24 hour intervals) used to stratify risk of peripartum complications, how did the authors identify 10 hours for vaginal deliveries and 15 hour for cesarean sections as being significantly increased with composite risk of complication.

To try to precisely identify the delay where the risk of complication is higher in order to guide clinical practice, we evaluated the data carefully to provide clinically and statistically meaningful results. As stated in the "statistical analysis section": The association of the delay in resuming postpartum anticoagulation with bleeding complications was first assessed using a Mann-Whitney test using time as a continuous variable. Subsequently, ROC curves and Youden index were used to identify if a range of delay in resuming postpartum anticoagulation was associated with a higher proportion of complications. Finally, Fisher's exact tests were used to compare proportions of complications between prespecified time intervals that are often used clinically by convention (<12h,12h-24h, 24-48, >48h). We believe that our strongest and more useful results are the ROC curve/Youden index and therefore the 9.25 hours vs. 15.1 hours.

3) Results:

a. Line 181: I'm confused as to how risk of major wound complications was 4.8% for women who had cesareans but it's mentioned in line 178-179 that risk of major wound complications was 1.7% in the entire cohort…. Did the study include women with wound complications related to vaginal repairs? If so, this should be mentioned in the inclusion criteria.

We collected major wound complications for both CS and VD, so this is represented by the 1.7% of the entire cohort. However, we did not collect minor vaginal wound

complications since it was not reported in previous studies to be associated with bleeding complication.

b. Line 212-216: I think this is actually a huge deal. 23/197 patients is not a small proportion (~12% of the cohort). Perhaps bleeding complications are related to delayed cessation of antepartum AC, not early resumption of postpartum AC. This should be mentioned in the discussion and study limitations.

199 patients over 232 were anticoagulated antepartum (86% of the cohort). Of those, we have data on timing of anticoagulation cessation for 196 and 22/196 patients (11.2%) received their last dose less than 24 hours before delivery. This is 9.5% of the entire cohort. The impact of the delay of stopping anticoagulation before delivery was analysed on the available data and was not statistically significant. However, since number are small, maybe the power was lacking to see any difference that could exist. We corrected the manuscript to make it clearer.

c. Figure 1A makes it look like risk of complications was significantly LOWER in women who underwent cesarean section and resumed AC less than 12 hours after delivery compared with between 12-24 hours. This is odd considering that you report (in figure IB and throughout the text) that risk of complications was HIGHER in those who underwent cesarean section and resumed AC less than 15 hours after delivery. This should be addressed in the discussion.

We believe that these differences are due to chance because the numbers are so small. Therefore, we analysed the data differently with the ROC curve and Youden to pinpoint the inflection point that could orient us better. Those results gave the 9.25 hours for VD and 15.1 hours for CS which we believe are more representative. This was added in the discussion for more clarity.

4) Discussion/ conclusions

a. Line 225-227. This conflicts with the statement made in line 179 that "The proportion of major hemorrhagic complications for CS versus VD was 8.4% and 6.0% respectively and was not statistically different (p=0.482)."

We agree with the reviewer that the definitions of the primary outcome vs. secondary outcomes need to be re-emphasized here. Correction was made for clarity.

b. Line 230-231: This sentence is misleading… it makes it seem like the timing of antepartum AC cessation was not determined to be important (conflicts with lines 212-216). I would rephrase as "when analyzing the 12% of the cohort whose antepartum anticoagulation was stopped < 24 hours prior to delivery, there was no association between timing of postpartum resumption of AC with major postpartum complications."

Thank you, this has been modified with the exact numbers.

c. I understand that maximal INR and maximal PTT were included in a multivariate model and determined to be significantly associated with increased composite risk of complications.

However, were bleeding complications only increased in patients who had supratherapeutic PTTs or INRs? In other words, is it supratherapeutic anticoagulation rather than early postpartum anticoagulation that's responsible for composite risk of complications? Should be mentioned in the discussion.

The analysis was done with supratherapeutic INR but because of small numbers (n=5/213), the confidence interval is extremely wide (OR 15.83, 9%CI 2.38-101.03) so seems to us unreliable. We therefore decided to present the analysis of the continuous variable.

As for aPTT, differences in lab normal values depending of the research site made it impossible to analyze these data. According to your comment, we added some explanations in the discussion about that issue.

d. Lines 271-272: Thank you for including this in your limitations. I think you should specifically mention that women with mechanical heart valves are at the highest risk of thromboembolic complications and are under-represented in this study. Clinicians should weight the benefits of early resumption of AC with the risk of hemorrhagic or wound complications in populations with exceptionally high risk of VTE.

We added some clarifications to make that point clearer. Thank you.

Reviewer #2: Review of Manuscript ONG-20-282 "Evaluation of bleeding complications in postpartum women receiving therapeutic anticoagulation"

Bettache and colleagues have submitted a multicenter (3 centers in Quebec, Canada) retrospective cohort study that attempts to evaluate the potential negative consequences (complications) based on the timing of the resumption, at least one therapeutic dose up to 96 hours following delivery, of therapeutic postpartum anticoagulation therapy. The authors noted that the rate of major complications was similar regardless of route of deliver - vaginal vs. cesarean. As noted by the authors at least some portion, if not all, of this data has been presented as several different meetings. I have the following questions and comments.

Title - No comments

Précis - No comments

Abstract - Consider commenting on your primary outcome of major complications in the abstract conclusions.

Good point, added.

Introduction - Line 76 - are you referring to prophylactic, therapeutic or both? Please clarify this statement. I think you may be able to combine the first 2 two-sentence paragraphs.

Well noted and correction made.

Methods - Line 129 - point of minor clarification was the resuscitation greater than 1L in an episode or in aggregate? Is there perhaps a better way to present the secondary endpoints rather than bulleted as was done? I believe it is Fisher's not Fisher for the exact test.

We clarified the 1L resuscitation endpoint in the text. (Reviewer 1, point 2c)

For the presentation of the secondary endpoints, we tried many ways of presenting the data and thought that this one was the clearest after all. We are open to any other suggestion to present it in a better way.

"Fisher's" corrected throughout manuscript, thank you.

Results - Line 185 - as data is missing for about ½ of the cohort should you just exclude this?

Line 185: We chose to be transparent and explain why we analysed the data without the pre-specified endpoint of hemoglobin drop. Since you believe it creates confusion, we changed it throughout the manuscript and reported only the data without the hemoglobin drop after the initial explanation.

Line 188 - I would delete "Only" as you then subsequently list 6 variables that appear to have an association with the outcomes of interest. In addition, please add the 95% CIs for these variables.

Line 188: Done, thank you.

For the paragraph starting at Line 195 - you the median time points of resumption of anticoagulation for both delivery groups (Vaginal: 6 vs. 19 hours; CD: 12 vs. 33 hours) associated with and without complications. Yet, in the following paragraph you then evaluated complications in the vaginal delivery group using 12 hours as a cut point and 24 hours in the CD group. While the times in the second paragraph may make more sense from a pragmatic standpoint, did you either evaluate or consider evaluating complication rates above and below the cut point from the preceding paragraph?

Line 195: We explored the endpoint "delay of resumption of anticoagulation" in many ways to try to find solid data to guide clinical practice. From all the results available, we believe that the ROC/Youden results (9.25 hours and 15.1 hours) are the more robust cut-off and can help to guide clinical practice (particularly for VD where the CI is narrow). The separation of pragmatic time interval showed significant results for VD but not for CS, although we did not have the power to measure a difference. The median time points with and without complications are not cut-offs, they are the justification to try to establish cut-offs by other means. So, we did not calculate complication rates above and below.

Discussion - Line 238/9 - While I think I understand what you are trying to point out here but, in the methods, (lines 121-2) you noted that patients that received only prophylactic doses in the up to 96 hours were excluded and thus I suspect this group of 42% of patients received a varying number of doses of anticoagulation (prophylactic) before starting therapeutic dosing. Do you have information on this for the reader to determine potential applicability of your statement?

Exactly: in the first 96 hours after delivery, 42.2% of women received prophylactic anticoagulation BEFORE the dose was increased to therapeutic when deemed safe and/or absolutely indicated by clinicians. Minor changes were done in the manuscript for clarity.

Line 243-5 would again encourage you to depict the 95% CIs.

Done, thank you.

Line 274-5 - Minor point - Use is common in pregnancy and prescriptions are more commonly written in high risk clinics, as written it sounds like the use is limited to clinic administration which was likely not the point trying to be communicated.

You are right, modification made.

Tables

Table 1 - Is the gestational age which seems similar based on the presented data actually statistically significantly different between the 2 groups?

Although the medians are the same, Mann-Whitney are rank sum test and not median-based test, which explains the significant p value.

I would delete the row about direct anticoagulants since you note in the manuscript that none were used.

Done.

Can you add units for Platelets, etc.

Done.

Does it make sense to include the column data re: the use of instrumentation and perineal trauma when the N in the CD group was 0? Can you just note this data in the manuscript as it relates to the vaginal delivery group?

We elected to present all the baseline data in the same table so that the reader can get all the answers he is looking for at the same place.

Table 2 - No comments.

Table 3 - Why is the p value in the first row bolded?

This was an error. With all the suggested corrections, we removed all p values from the table 3 to include confidence intervals and aORs instead.

Is there a different way to present the additional variables at the bottom of this table for the subgroups? Maybe just refer to in the manuscript?

We agree with that comment and changed the bottom part of the table 3 to include the information in the manuscript.

Table 4 can be deleted as it can be completely referenced in the text.

Done.

Figures - I think they are okay.

Reviewer #3: The authors present their cohort study regarding use of therapeutic anticoagulation postpartum and complications associated with such use. The analysis evaluated the use of various anticoagulants and the timing of initiation with regards to both predefined major and secondary postpartum complications. The study is overall well written and presents novel data on a relatively common issue. However, I have the following concerns in its present format:

MATERIAL/ METHODS:

-Line 129: "fluid resuscitation of 1 L or more" as part of major hemorrhagic complications- starting at what point? After delivery of the placenta? Or is this for the entire surgery for those undergoing cesarean? The amount seems to be relative low threshold to be included for "major hemorrhagic" complications since 1 L is what most patients undergoing routine cesarean are typically receiving.

Clarification was made in the manuscript: only fluid resuscitation of more than 1L AFTER the resumption of therapeutic anticoagulation was considered. It does not include fluid received in the intrapartum/immediate postpartum period. This is a standard endpoint in similar studies. (Reviewer 1, point 2c)

-Line 142: can the authors clarify the dose of the concomitant Aspirin use - (I'm assuming low dose 81 mg) and NSAID use?

Good point: detail provided in Table 1 for both ASA and NSAIDs.

-Line 146: can the authors clarify the rationale for the various time intervals - I can understand some of the shorter, but don't understand if therapeutic anticoagulation were being started, why waiting 72-96 hr

It happened 1) when thromboembolic disease was diagnosed at that moment in the postpartum period or 2) if a complication occurred during delivery/postpartum that made the risk of bleeding higher while the indication for therapeutic anticoagulation was considered at low risk for thrombosis by the physician (for example, a woman anticoagulated on the long term for multiple previous thrombosis but last episode over one year ago: there is no emergency after delivery to restart the therapeutic anticoagulation 24 hours after; sometimes, 48-72 hours is soon enough if bleeding risk is high).

-Line 149: please expand on how thromboembolic events were diagnosed to be included for analysis

Diagnosis of a postpartum thromboembolic event had to be confirmed by standard diagnostic tools including leg ultrasonography (whole or proximal depending on the site), V/Q scan and pulmonary angio-CT. Charts were reviewed during the hospitalization for delivery and all inpatients or outpatients/emergency visits for 6 weeks postpartum. This was specified in the manuscript. One of our limitation, as stated

in the discussion, is that if a thromboembolic event would occur in another hospital (since all participating centers were tertiary care center), we could have missed it.

RESULTS:

-What is the ascertainment rate for the patients to assess for wound complications (especially the secondary complications)?

All wound complications were pre-specified in the protocol. Only two researchers reviewed all the charts. Any mention of one of those in the notes or summary sheet was reported on the database. In case of uncertainty, the situation was discussed between the two researchers and a consensus was obtained.

-Table 1 Page 15 - there is an entry for "postpartum thromboprophylaxis" 98 patients out of 233 - please clarify since the objective of the study was to evaluate "early postpartum therapeutic anticoagulation"

Awaiting the resumption of the therapeutic anticoagulation, 98 women received prophylactic anticoagulation as a bridge to minimize bleeding and thrombosis risks. A clarification was added in the manuscript.

STATISTICAL EDITOR COMMENTS:

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

Table 1: The column "Caesarean delivery" has N = 83, so the %s should be rounded to nearest integer %, not to 0.1% precision. The missing data for BMI is such a large proportion of the totals that the estimates may be biased and cannot be reliably generalized.

% have been changed, thank you.

As for BMI, we elected to keep it in the Table 1 as an exploratory information, understanding that it might be biased, but added a note at the bottom of the table to reflect that.

Table 2: Should include CIs for the estimates of proportions with complications. Eg, for ≥ 1 major complication: 6.0% (CI = 2.7%-11.4%) vs 8.4% (CI = 3.4%-17.4%). In addition, the sample sizes and relative proportions of this adverse event (and others cited in the Table) do not allow sufficient statistical power to generalize the NS finding. For example, based on a vaginal delivery proportion of complications = 6.0%, the C-section cohort would have to have a rate > 18% to achieve 80% power and a difference at the 0.05 level. Put another way, there is < 20% power to discern a difference of 6% vs 8.4% given these sample sizes. Should also include CIs for the rates of recurrent VTE, which were 0.9% (CI= 0.1% - 3.1%) overall.

Confidence intervals were added for each sub-group (CD and VD). The CIs for the entire cohort are available if judged essentials but we felt they were not useful and made the Table 2 too busy.

lines 205-211: Should round the AUC values and CIs to the nearest 0.01, not to 0.001 precision. The optimal cut-off was identified as 15 hrs; Need to cite the CIs for that estimate, so the reader can interpret it with some context.

Confidence intervals were added for the two cut-off points, 9.25 (95%C.I. = 6.17-9.5) for the vaginal group and 15.1 (95%C.I. = 6.33-56.88) for the cesarean group. It shows how uncertain the best cut-off is for the cesarean group, but it does not change our choice for our optimal cut-off point maximizing the Youden's index. Bootstraps methods (n=2000) were used to calculate confidence intervals around our best threshold.

General: These results compare VD vs CD, where all women received anticoagulation, so what conclusion can be inferred from these data, except that rates of complications (when aggregated to include any complication) are higher in VD than in CD?

These data are mainly exploratory. Those numbers can however be used when discussing with patients about starting therapeutic anticoagulation postpartum to better inform them about the risks or in the discussion with the obstetrician when

deciding on the mode of delivery for a woman who needs postpartum therapeutic anticoagulation.

lines 163-166: The ROC curves and Youden index were used to identify if a range of delay in resuming anticoagulation was associated with a higher proportion of complications. But to use that threshold to test whether the before vs after had proportions different from random chance is a rigged test. By design, the results are not going to be random. The testing by pre-specified intervals is OK, but not testing intervals which were derived from a test to discern a difference by ROC analysis.

We agree with that comment. Modifications were made in the manuscript accordingly.

Table 3: These are labelled as univariate associations, yet Table 1 shows multiple differences between the cohorts. Need to also show the multivariable (aORs) for contrast, list the variables included in the final models and justify the use of models with multiple adjustors if the number of adverse outcomes is insufficient (there were only 9+13 = 22 adverse outcomes, per Table 2).

We changed Table 3 to report the aORs included in the multiple regression model.

EDITOR'S COMMENTS:

We no longer require that authors adhere to the Green Journal format with the first submission of their papers. However, any revisions must do so. I strongly encourage you to read the instructions for authors (the general bits as well as those specific to the feature-type you are submitting). The instructions provide guidance regarding formatting, word and reference limits, authorship issues, and other things. Adherence to these requirements with your revision will avoid delays during the revision process, as well as avoid re-revisions on your part in order to comply with the formatting.

All requirements were respected.

PRESENTATION OF STATS INFORMATION (P Values vs Effect Size and Confidence Intervals)

While P values are a central part of inference testing in statistics, when cited alone, often the strength of the conclusion can be misunderstood. Whenever possible, 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.

This is true for the abstract as well as the manuscript, tables and figures.

Since our data is retrospective, mainly descriptive, and with a relatively small number of women, we consider most of the results exploratory. In that perspective, we elected to report the crude % in Table 1 and 2, to better inform the clinicians. The difference between the 2 groups VD vs. CS is not so important, but the absolute numbers are to make clinical decision about timing of anticoagulation resumption depending on the mode of delivery.

Please provide absolute values for variables, in addition to assessment of statistical significance.

In Table 3, we elected to provide only the ORs and aORs with the 95%CI and not the absolute values to simplify the presentation of an already busy table.

We ask that you provide crude OR's followed by adjusted OR's for all relevant variables.

Table 3 was corrected accordingly.

Line 50: Please tell us how patients were identified. Please define the primary outcome a bit more. Is this a composite? How were the complications defined? This is found in part in your results section but should be moved to methods.

Line 50 is the abstract and information there is greatly limited by the allowed number of words. The method section was revised to ensure clarity according to your comments.

Your precis should reflect your primary, not secondary outcomes.

The change was made, thank you.

Line 56 and likely in main body of manuscript as well: Please note that your study was conducted from date 1 to date 2, not between those dates. As written, it would exclude the dates given . You could save some word by saying something like "From 2003 to 2015, of 233 consecutive women treated with postpartum therapeutic anti-coagulation, 92 received unfractionated……"

All changes done throughout manuscript.

Throughout, please make sure you are using American-style spelling (example: cesarean rather than caesarean).

Done.

Line 62: it is implied but not clearly stated that the total includes the major and minor. These are not proportions (59, 62) but are rates. You could write something like " The composite hemorrhagic and wound complication primary outcome occurred in xx/yy (8,4%) of women who delivered by cesarean and zz/aa(6.0%) who delivered vaginally (p=0.48). Minor wound and bleeding complications occurred in xx/yy(%) and bb/aa (%), respectively . The median interval between delivery and initiating anticoagulation was shorter in women who developed any complication compared to those who did not for cesarean births (12 v 33 hours, p=.) and vaginal births (6 vs 19 hour, p=.)

We corrected the formulation of the outcomes throughout the manuscript, thank you.

Line 70 were these in both cesarean and vaginal births?

Described later in the text (Results, section "Thromboembolic events"). Not enough space due to limit of words to include it in the abstract.

Line 71: the conclusion should include the primary outcome, not just secondary one.

You are definitively right, this was corrected.

Line 86: please provide a list of the society's you checked to be able to make this sentence.

American Society of Hematology, Society of Obstetrics and Gynecology Canada, American College of Chest physicians, American College of Obstetrics & Gynecology, Royal College of Obstetrics & Gynecology, Society of Obstetric Medicine of Australia and New Zealand. Since there are many, we elected not to name them all in the paper and changed the manuscript to say a more general sentence: "There are no guidelines…".

Line 105: I don't know what a "delegated consent process" is? Would that be the same as the study being exempt from requiring consent?

Yes. According to Dre Cumyn, who is a co-author and the Chair of our ethics-IRB, this is the appropriate way to say that this study did not require individual consent but

resorted to a delegated consent process to meet Quebec legislation (no exemptions from consent).

Line 109: Who abstracted the charts?

Gabrielle Côté-Poirier and Nazila Bettache. This was added in the manuscript.

Line 110: Data is plural so this should read that data were extracted

Thank you for notifying us, the correction was made.

Line 117: as the outcomes in repeat pregnancies may not be independent, it would be ideal to use the first pregnancy outcome only (if there were a complication in pregnancy 1, the patient may have requested delaying initiation of anti-coagulation until later the next time, for instance). At the least, please report a sensitivity analysis of first pregnancy outcomes only.

There was 24/232 (10.3%) repeated pregnancies. The sensitivity analysis was done and did not change the results and conclusions. These results are available on request.

Line 128: Is this hospital readmission for bleeding complications only or any hospital readmission?

Same query re: ICU admit.

Readmission or ICU admission were considered only when related to a bleeding or wound complication after the initiation of therapeutic anticoagulation. Clarification was made in the manuscript.

Did you not include episiotomy breakdown or vaginal hematoma?

We included major vaginal wound complication defined as wound complication requiring a surgery. We elected NOT to include minor vaginal wound complication since it was not reported in previous studies to be associated with bleeding complications.

Line 136 Please report labs with deciliter rather than liter. This would change to 2g/dl.

Modification done, thank you.

Line 177+ please note above comments regarding presentation of data.

Corrected in all manuscript.

If you are going to report the components of the primary outcome separately (wound +hemorrhage) do so for all different types—vaginal and cesarean and wound and hemorrhagic.

See Table 2 for all details. Only minor vaginal wound complications were not recorded.

Line 186: I'm confused by this composite of major + minor. Perhaps just say "Total complications were statistically higher…

Correction made.

Line 188 Please provide 955 CI's and absolute values.

All 95%CI added. Absolute values were not judged useful since the effect size is privileged and made the Table 3 overloaded.

Line 240: This is the first time you've mentioned adding prophylaxis here. Was this all medical or did it include mechanical (compression devices). This, and the data, should be presented in the methods and results section.

The use of thromboprophylaxis is mentioned in Table 1 in baseline characteristics and Table 3 as an analyzed risk factor. We added it to the explicit risk factor analyzed as secondary endpoints in the methods.

Line 245: All 3 of these are risk factors for hemorrhage even in non-anticoagulated patients; as well, at least the type of delivery and infection, are risk factors for VTE. Please comment.

We recognized that, so these results are not surprising. Therefore, the causal relationship cannot be established with our study. This was added in the discussion.

Line 248: Provide your search (If not done earlier) for being able to say this is the "largest" and "First". as this constitutes a primacy claim.

Since we did not do a systematic review to ascertain this but only a literature search, we changed the sentence.

Line 274: You haven't really made any comment about this being "common". You don't provide the N for number of deliveries that these 200 odd deliveries were part of. Delete the "common" reference.

We would argue here that as full-time clinicians working with high-risk pregnancies, we see these many times per month. To us, this is common to all general obstetricians. This was also acknowledged by reviewer #3 "The study is overall well written and presents novel data on a relatively common issue". And reviewer #1 "The findings of this study are generalizably important to both general obstetricians and perinatologists as there is little existent data to guide timing regarding resumption of anticoagulation in the postpartum period". Of course, this is more a general statement than a fact documented in this particular study.

Line 276: the benefit outweighs the risks for some indications, not in general.

You are right, we added the precision.

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.

Yes, we agree with the publication of the point-by-point response.

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.

Well noted.

Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page.

Done.

3. In order for an administrative database study to be considered for publication in Obstetrics & Gynecology, the database used must be shown to be reliable and validated. In your response, please tell us who entered the data and how the accuracy of the database was validated. This same information should be included in the Materials and Methods section of the manuscript.

N/A

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 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.

Done.

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.

22 pages, 4226 mots.

6. Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). Do not structure the title as a declarative statement or a question. Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles. Abbreviations, jargon, trade names, formulas, and obsolete terminology also should not be used in the title. Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," or "A Systematic Review," as appropriate, in a subtitle. Otherwise, do not specify the type of manuscript in the title.

OK

7. 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).

OK

8. 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 limits for different article types are as follows: Original Research articles, 300 words. Please provide a word count.

293 words.

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.

OK.

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.

All checked and removed.

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.

N/A

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%").

VERIFIED.

12. Line 249-251: We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If on the other hand, it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

Removed.

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.

14. Figure 1: Please upload as high-res figure files on Editorial Manager (eps, tiff, jpeg, etc).

Done.

15. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at http://links.lww.com/LWW-ES/A48. The cost for publishing an article as open access can be found at http://edmgr.ovid.com/acd/accounts/ifauth.htm.

OK.

Please note that if your article is accepted, you will receive an email from the editorial office asking you to choose a publication route (traditional or open access). Please keep an eye out for that future email and be sure to respond to it promptly.

OK.

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). ***DONE.***

* A point-by-point response to each of the received comments in this letter. ***DONE.***

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.

Each author revised the revised manuscript.

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 Mar 27, 2020, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy C. Chescheir, MD

Editor-in-Chief

2018 IMPACT FACTOR: 4.965

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

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