OBSTETRICS & GYNECOLOGY

NOTICE: This document contains correspondence generated during peer review and subsequent revisions but before transmittal to production for composition and copyediting:

- 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: Jan 31, 2020
To: "Shravya Govindappagari" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-2366

RE: Manuscript Number ONG-19-2366

Thrombocytopenia and risk of postpartum hemorrhage in nulliparous term singleton vertex deliveries.

Dear Dr. Govindappagari:

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 Feb 21, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

REVIEWER #1:

Govindappagari and colleagues present findings from a retrospective cohort study designed to evaluate whether mild thrombocytopenia (platelet counts 100-149 K/mcLl) were associated with an increased risk for postpartum hemorrhage in women with nulliparous term singleton vertex deliveries. The authors draw their study cohort of 2854 women from a single institution between August 2016-September 2017. The primary study outcome was postpartum hemorrhage as noted from ICD-10 coding and hospital discharge data. Secondary outcomes included EBL >=1000 cc, uterotonic use, and blood transfusion. The authors noted that women with mild thrombocytopenia, when compared to women with normal platelet counts (>=150 K/mcL), were at 2-fold higher risk for postpartum hemorrhage. Overall the paper is well written and addresses an important area of perinatal medicine. A point-by-point critique of the paper follows:

1) There is a major discordance between cases denoted as postpartum hemorrhage (8.5 vs 16.9%) and women with estimated blood loss >=1000 cc (1.7 vs 4.5%). Why was there such a significant discordance in the rates of postpartum hemorrhage? Was there any audit done on the cases that were coded as postpartum hemorrhage to ensure that these cases were actually postpartum hemorrhage cases? Given the inherent concerns with use of coding data, the outcome of estimated blood loss >=1000 cc, would seem to be a more appropriate outcome to correlate with platelet counts.

2) The authors evaluate platelet count and risk for PPH and a number of secondary outcomes. They do not specify when this platelet count was assessed. Was this platelet count at admission for delivery or was it variable? The paper should be revised to more clearly specify when the platelet count was assessed for their analysis.

3) The authors utilized ICD-10 codes for diagnosis of postpartum hemorrhage and maternal fever. What specific codes were used? It would be helpful for reproducibility to include the revised paper? In the case of maternal fever, the authors validated the code with chart review. Was this done for cases where coding denoted postpartum hemorrhage? As noted above the rate of postpartum hemorrhage is significantly higher than the proportion of women with EBL >= 1000cc. It would be useful to include some additional information in the revised paper describing how the women who did not have EBL >= 1000 cc ended up with a diagnosis of postpartum hemorrhage.

4) The authors describe maternal fever in the methods of the paper but no data is presented. If this outcome is not reported in the paper or used in the analysis the description of the diagnosis of maternal fever by ICD-10 code and validation could be removed from the revised paper. Alternatively, the data should be included in the revised paper.

5) The primary outcome of the study is postpartum hemorrhage. Was there a standard approach to risk stratification for

women at risk for postpartum hemorrhage in accordance with the CMQCC or other systems? Were all women managed similarly in the third stage of labor or were these differences in management? Did platelet count alter management for women in the study cohort? The paper currently lacks any specifics regarding management of the third stage and how platelet count may have altered management. The revised paper should include specifics regarding the approach used (standardized or not) for the management of the third stage of labor.

6) The authors only mention use of methergine or hemabate. Were there cases where both agents were used? Was misoprostol or tranexamic acid used at all in these cases? Were there any cases of hysterectomy? Additional specifics would be helpful to aid the reader in understanding the study and use of uterotonics.

7) Tables 1 and 2: It would be helpful to include the n/N with the percentages in the Tables where applicable.

8) Figure 1: For the category of "Admission platelet count missing or erroneous due to platelet clumping" it would be helpful to report the respective n for each separately.

REVIEWER #2:

This is useful retrospective study that attempts to analyze the associations between mild thrombocytopenia and PPH. the major strength is the completeness of the data extracted from the electronic data base and focus of the analysis on PPH. However, the study as currently designed and presented has some flaws:

1) It is not completely clear if the focus of the study is on all thrombocytopenia (severe and mild) or just on mild thrombocytopenia. They report on 2,579 (90.2%) normal platelet count 266 (9.3%) mild thrombocytopenia, and 13 (0.5%)severe thrombocytopenia. They mention a separate analysis of the severe thrombocytopenia cases and ultimately disclose non-significant results due to small numbers. The authors need to reflect on the story they want to tell. It may be a consideration to exclude the severe cases and just report on a comparison of mild thrombocytopenia versus normal platelet count in labor.
2) To reduce confounding variables and provide more meaningful results, cases of cesarean delivery and preeclampsia should be excluded from the primary analysis. Both groups can be analyzed and presented separately
3) Attention is required to important definitions, variables and timelines. For example PPH and EBL process should be defined, Uterine atony, perineal lacerations, DIC should be identified, 1st, 2nd & 3rd stage of labor and blood draw to onset of labor should be included in analysis
4) The Comment section is rambling, speculative and needs to be focused and concise
5) The lack of association with blood transfusion puts this study in perspective and should be highlighted in the discussion section

Specific comments:

1. Line 100:
or with platelet clumping
Comment:
How is this identified in a retrospective study based on data extraction from the electronic medical record?

Line 105:
Clinical diagnoses and outcomes were extracted from
Comment:
Did you exclude medical disorders such as coagulation disorders, antiphospholipid antibodies syndrome and collagen vascular disease that could affect outcomes

Line 110:
The diagnosis of PPH was identified by ICD10 codes and the hospital discharge
Comment:
Please state the exact definition of PPH that was used for this study

Line 113:
Platelet count (k/µl) and hemoglobin (g/dl) values were abstracted from the first
complete blood count (CBC) following admission for delivery.
Comment:
What was the time interval from blood draw to onset of labor and delivery?

Line 121:
estimated blood loss ≥1000ml
Comment:
Was the estimation of blood loss standard? What method was used for estimation or quantification? What is the reliability of estimated blood loss in this institution?

Line 139:
Length of labor
Comment:
Please analyze 1st 2nd & 3rd stage of labor separately since prolongation of a specific stage of labor may be an important confounding variable

Line 145:
This difference was seen even when excluding women with cesarean delivery (16.0% vs. 7.9%, P<0.001), or exclusion of women with gestational hypertension or preeclampsia (14.1% vs. 8.1%, P=0.002).
Comment:
This is somewhat confusing and a significant study design flaw. Both cesarean section and preeclampsia increase risk of PPH. It is best that these populations are analyzed separately. The primary results should be based on the population in whom thrombocytopenia is the only recognized risk for PPH.

Line 157:
Importantly, the association between mild thrombocytopenia and PPH persisted after multivariable logistic regression (aOR159 2.3, 95% CI 1.6-3.3, P<0.001), with adjustment for BMI, race/ethnicity, gestational hypertension or preeclampsia, and mode of delivery.
Comment:
Duration of labor should be included in this regression analysis.

Line 181:
Such women may benefit from patient and unit readiness, like those with severe thrombocytopenia.
Comment:
This is too powerful a statement based on a retrospective study with significant limitations. This study can only suggest future prospective studies and not dabble into practice guidelines

Line 191-199:
Practice guidelines often focus on platelet count in women with immune mediated thrombocytopenia or preeclampsia, or those undergoing surgery or neuraxial anesthesia. Concern is raised in preeclampsia when the platelet count is <100 k/µl, while concern for epidural hematoma is raised when the platelet count is <70 k/µl. However, the leading cause of PPH is uterine atony, and the mechanisms linking thrombocytopenia to uterine atony is unclear. The platelet count threshold for PPH from uterine atony may differ from the thresholds used to guide bleeding risk in women with medical conditions or those undergoing surgery or neuraxial anesthesia.
Comment:
This segment is rambling, does not contribute much and should be shortened or deleted

Line 200-235
Comment:
This long segment needs to be carefully revised to:
decrease redundancy,
clarify true strengths of this study which are minimal
highlight the limitations which are many
remove speculative statements

Line 200:
The strengths of our study include a large sample size, clear hypothesis and primary outcome, and a well-defined population of women with NSTV pregnancy undergoing labor.
Comment:
This statement may not be completely accurate and is also a perception that some readers may not share. For example, the authors admit that they did not have enough cases of severe thrombocytopenia to be able to draw meaningful results with that group. Also, the above statement should be fundamental for any study design and not a "strength". At the discretion of the authors may consider removing this sentence.

Line 202
By focusing on NTSV pregnancies, we minimized confounding factors such as multiparity, preterm delivery and multifetal gestation, which have an increased risk of PPH regardless of platelet count
Comment:
This has been previously stated line 90-91

Line 212:
Thrombocytopenia may have caused increased PPH through surgical bleeding or perineal lacerations. Yet, our results were unchanged when excluding women with cesarean delivery, and mild thrombocytopenia was associated with use of methergine and hemabate, which are primarily utilized for uterine atony. In addition, thrombocytopenia was associated with EBL ≥1000 ml, which most often reflects uterine atony compared to lower thresholds and is consistent with the new definition of PPH, regardless of mode of delivery. Postpartum hemoglobin was not available in uncomplicated deliveries.
Comment:
This segment raises questions, includes results and identifies some essential methodological concerns. The authors should

include the diagnosis of uterine atony, perineal lacerations and retained placenta in their analysis. How were cases of DIC excluded?

Line 222:
While we continue to support longer labors in the NTSV population to decrease the rate of primary cesarean deliveries , we should also continue to optimize our risk stratification tools to better identify women at high risk for PPH. Risk assessment and preparedness are fundamental to reducing morbidity and mortality related to postpartum hemorrhage, and continuous reassessment of our obstetric toolkits is critical to optimizing patient outcomes.
Comment:
This segment can be deleted without affecting content

Line 231:
Our data suggests that a platelet count threshold of 150 k/µl at the time of delivery, rather than may identify more women at increased risk for postpartum hemorrhage.
Comment:
This is not accurate. You have not done a comparison study between 150 k/µl and 100 k/µl. Your conclusion should be limited to the specific findings of this study and not generalize to current standard of care.

Table 3.
This table shows that mild thrombocytopenia is significantly associated with PPH while severe thrombocytopenia is not. This analysis shows the issue that may arise from inadequate sample size and improper analysis. The authors should discuss with their statistician if this data should be included since this may present an inaccurate clinical derivation regarding severe thrombocytopenia

REVIEWER #3:

This is a well-written manuscript using a single center dataset to examine the association between mild thrombocytopenia (platelet counts of 100-149k) and postpartum hemorrhage (by ICD 10 codes) among women with nulliparous term singleton vertex vaginal or unplanned cesarean deliveries. The rationale for the study is good, given the emphasis by ACOG and CMQCC of using platelet counts of <70k and <100k as risks for PPH. Of note, data similar to that in the authors study have been reported by Carlson et al., utilizing the MFMU dataset with a larger n.

Major:

1. Given that this is a study of PPH and the authors took great care to assess group differences (eg. gestational diabetes), why was uterine atony, the leading cause of PPH, not assessed? There is an ICD-10 code for atony.

2. Has ICD-10 been validated for PPH? This should be discussed.

3. The retrospective nature of this study and reliance on codes should be acknowledged as a weakness.

4. The method of calculating EBL in the study Institution should be discussed given its centrality to the primary outcome.

5. As mentioned below (Tables), the n should be shown, not just the percents, particularly given some of the small numbers. For example, only 5 women in the study group had blood transfusion, and this is lost when only the percent is shown. Further, given the small n, Fisher's or McNemar's Exact tests should be used.

6. The discussion mentions that this study was well-powered, yet no power calculation is shown. In fact, some of the outcomes are involve very small numbers, and an N should be shown in addition to the percent.

7. Were women with ITP excluded?

Tables:

1. The n should be shown in addition to percents. This is particularly important given some of the small numbers that are not so apparent when only percents are shown.

2. In tables 1 and 2, Fisher's or McNemar's Exact tests should be used.

Minor:
1. There are words missing in lines 135 and 136

STATISTICAL EDITOR'S COMMENTS:

1. lines 99-102 and Fig 1: Did the n = 3166 represent all NTSV deliveries, or were there some who did not have a CBC or

for whom the data were missing (other than those included in the N = 32 exclusions)?

2. lines 160-161: See later comments re: more exposition of the ORs, but should explicitly state the referent for each OR and aOR. For BMI, I assume the 1.04 is per 1 unit increase in kg/m².

3. Table 2: Since many of the counts among the thrombocytopenia group are few, should format as n(%) for both columns, not just as %s.

4. Table 3: Should include the n(%) for PPH among the severe thrombocytopenia group. From lines 151-154, that is 3 of 13, which should be rounded to 23%, not 23.1%, given the small counts for severe thrombocytopenia. Furthermore, the estimation of that aOR is not justified, since there were only 3 cases and 4 variables were used as adjustors, or even for one variable (BMI), if that was the final model. That is, the Authors are correct that this comparison with the normal platelet count cohort was under powered, but the adjustment was also likely over fitted.

5. Should include (could be on-line material), the unadjusted ORs for PPH vs BMI, race/ethnicity, HTN or pre-eclampsia and mode of delivery? Also, why were mode of delivery and HTN or pre-eclampsia included in the final model, since by Table 1, the direct comparisons were NS and why were HTN and pre-eclampsia aggregated into one category as an adjustor?

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. 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 (40 characters for case reports), including spaces, for use as a running foot.

7. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between

the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Original Research articles, 300 words. Please provide a word count.

8. Only standard abbreviations and acronyms are allowed. A selected list is available online at http://edmgr.ovid.com /ong/accounts/abbreviations.pdf. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

9. 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.

10. 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%").

11. 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.

12. The American College of Obstetricians and Gynecologists' (ACOG) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite ACOG documents in your manuscript, be sure the reference you are citing is still current and available. If the reference you are citing has been updated (ie, replaced by a newer version), please ensure that the new version supports whatever statement you are making in your manuscript and then update your reference list accordingly (exceptions could include manuscripts that address items of historical interest). If the reference you are citing has been withdrawn with no clear replacement, please contact the editorial office for assistance (obgyn@greenjournal.org). In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript (exceptions could include manuscripts that address items of historical interest). All ACOG documents (eg, Committee Opinions and Practice Bulletins) may be found via the Clinical Guidance & Publications page at https://www.acog.org/Clinical-Guidance-and-Publications/Search-Clinical-Guidance.

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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 Feb 21, 2020, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

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

February 28, 2020

Re: ONG-19-2366 - Manuscript Revision- “Mild thrombocytopenia and postpartum hemorrhage in nulliparous term singleton vertex deliveries.”

Attn: Dr. Nancy Chescheir, Editor, Obstetrics & Gynecology

Dear Dr. Chescheir,

Thank you for the opportunity to revise our manuscript ONG 19-2366, “Mild thrombocytopenia and postpartum hemorrhage in nulliparous term singleton vertex deliveries.”

We have carefully reviewed your email dated January 31st, 2020, enclosing your comments and the reviewers’ comments of our manuscript. We have revised the manuscript according to these comments and we have provided our responses in a point-by-point manner. Revisions in the manuscript are updated using Track Changes feature in Microsoft Word. We hope the revised version is now suitable for publication in Obstetrics & Gynecology and we look forward to sharing this work with your readers.

Finally, I affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained."

Sincerely,

Shravya Govindappagari

Cedars-Sinai Medical Center

[redacted]

Reviewer #1

Comment #1. There is a major discordance between cases denoted as postpartum hemorrhage (8.5 vs 16.9%) and women with estimated blood loss >=1000 cc (1.7 vs 4.5%). Why was there such a significant discordance in the rates of postpartum hemorrhage?

Reply 1: Our primary outcome was postpartum hemorrhage, determined by ICD 10 codes and the hospital discharge problem list, among subjects delivered between August 2016 and September 2017. Providers at our institution most often utilized ACOG's 2014 reVITALize Obstetric Data Definitions to diagnose postpartum hemorrhage and this was updated in the Methods section of the revised manuscript:

i) Cumulative blood loss of >=1000ml or
ii) Blood loss accompanied by sign/symptoms of hypovolemia within 24 hours following the birth process (includes intrapartum loss). Signs/symptoms of hypovolemia may include tachycardia, hypotension, tachypnea, oliguria, pallor, dizziness, or altered mental status

However, reVITALize definitions for PPH were not fully incorporated into the ACOG practice Bulletin until October 2017, which is one month after our study period. Thus, some providers may have utilized older definitions for PPH.

Our data shows that the majority of PPH diagnoses were made in women with EBL <1000ml. However, while only 57 women had EBL >=1000ml in our study, we found a significantly higher rate of EBL >=1000ml in those with mild thrombocytopenia compared to those with normal platelet count (Table 2).

Comment #2: Was there any audit done on the cases that were coded as postpartum hemorrhage to ensure that these cases were actually postpartum hemorrhage cases?

Reply 2: The ICD-10 codes utilized for PPH included O72.0, O72.1, O72.2, O72.3 and O75.89. Random chart audit was performed in 10% of cases to validate the ICD-10 diagnosis of PPH. This is explained in the revised manuscript lines 222-226.

Comment #3: Given the inherent concerns with use of coding data, the outcome of estimated blood loss >=1000 cc, would seem to be a more appropriate outcome to correlate with platelet counts.

Reply 3: We agree that EBL >=1000 ml may reflect more significant blood loss and we included it as a secondary outcome. We did not choose to exclude women with EBL <1000ml because, as ACOG notes, women with EBL 500-1000ml can also have hemodynamic changes (hypotension, tachycardia) that

warrant diagnosis and management of PPH. Regardless, we did find that EBL >=1000 ml was increased in women with mild thrombocytopenia compared to those with normal platelet count (Table 2).

Comment #4: The authors evaluate platelet count and risk for PPH and a number of secondary outcomes. They do not specify when this platelet count was assessed. Was this platelet count at admission for delivery or was it variable? The paper should be revised to more clearly specify when the platelet count was assessed for their analysis.

Reply 4: Platelet count (k/µl) and hemoglobin (g/dl) values were abstracted from first complete blood count (CBC) upon admission for labor, and prior to delivery. This information is provided in the revised Methods section, lines 139-141.

Comment #5: The authors utilized ICD-10 codes for diagnosis of postpartum hemorrhage and maternal fever. What specific codes were used? It would be helpful for reproducibility to include the revised paper?

Reply 5: ICD 10 codes used for postpartum hemorrhage were O72.0, O72.1, O72.2, O72.3. The ICD code for chorioamnionitis was O41.1230, but since chorioamnionitis was not the focus of this study, we removed the description of maternal fevers to avoid confusion. We provided the ICD 10 codes for PPH in the Methods section of the revised manuscript lines 222-226.

Comment #6: In the case of maternal fever, the authors validated the code with chart review. Was this done for cases where coding denoted postpartum hemorrhage? As noted above the rate of postpartum hemorrhage is significantly higher than the proportion of women with EBL >= 1000cc. It would be useful to include some additional information in the revised paper describing how the women who did not have EBL >= 1000 cc ended up with a diagnosis of postpartum hemorrhage.

Reply 6: see replies 1-3 above

Comment #7 The authors describe maternal fever in the methods of the paper but no data is presented. If this outcome is not reported in the paper or used in the analysis the description of the diagnosis of maternal fever by ICD-10 code and validation could be removed from the revised paper. Alternatively, the data should be included in the revised paper.

Reply 7: We agree and to avoid confusion we have removed the description of maternal fever in the revised manuscript.

However, since chorioamnionitis increases risk for PPH, we provided data in Table 1 to show that rate of chorioamnionitis was not different in women with mild thrombocytopenia compared to those with normal platelet count.

Comment #8 The primary outcome of the study is postpartum hemorrhage. Was there a standard approach to risk stratification for women at risk for postpartum hemorrhage in accordance with the CMQCC or other systems?

Reply 8: Yes, all women in labor at our institution are risk-stratified for postpartum hemorrhage utilizing CMQCC guidelines. Women with 2 or more medium risk factors, or 1 major risk factor, are classified as high-risk for PPH and managed according to CMQCC guidelines (e.g., T&C, large bore IV, etc.). This was added to the Methods section of the revised manuscript. Lines 231-236.

Comment #9 Were all women managed similarly in the third stage of labor or were these differences in management? Did platelet count alter management for women in the study cohort? The paper currently lacks any specifics regarding management of the third stage and how platelet count may have altered management. The revised paper should include specifics regarding the approach used (standardized or not) for the management of the third stage of labor.

Reply 9: We have numerous provider groups at our institution and management of third stage of labor is not uniform. The most common approach at our institution is oxytocin IV bolus in third stage of labor, followed by maintenance infusion after delivery of the placenta. Women with mild thrombocytopenia were not managed differently because we utilize CMQCC risk stratification for PPH at our institution, and mild thrombocytopenia is not included as a PPH risk factor in the current guidelines. Information on management of third stage of labor, and the effect of mild thrombocytopenia on patient management is provided in the Methods section of the revised manuscript (paragraph 4).

Comment 10: The authors only mention use of methergine or hemabate. Were there cases where both agents were used? Was misoprostol or tranexamic acid used at all in these cases? Were there any cases of hysterectomy? Additional specifics would be helpful to aid the reader in understanding the study and use of uterotonics.

Reply 10: There were 35 cases in which both methergine and hemabate were utilized for PPH. Women with mild thrombocytopenia were more likely to receive both agents compared to those with normal platelet count, and this information was added to Table 2. At our institution, methergine and hemabate are consistently utilized as first line agents for PPH and thus data was abstracted for these agents. Because misoprostol use is variable at our institution, and some

providers use it prophylactically, data on misoprostol was not collected. Recently, tranexamic acid has been used as a 2nd or 3rd line agent for PPH, but its use was rare during the study time period (2016-2017) and such data was not collected. There were no cases of cesarean hysterectomy in this study cohort, emphasizing the overall low risk nature of our NTSV study population.

The Methods section was updated in the revised manuscript to note that methergine and hemabate were first line agents for PPH at our institution (Lines 242-245). Table 2 was updated to provide data on combined use of both Methergine and Hemabate after delivery.

Comment #11: Tables 1 and 2: It would be helpful to include the n/N with the percentages in the Tables where applicable.

Reply 11: Tables 1 and 2 were updated to include n (%) in the revised manuscript. The total N is included in the column header.

Comment # 12: Figure 1: For the category of "Admission platelet count missing or erroneous due to platelet clumping" it would be helpful to report the respective n for each separately.

Reply 12: This is reported in the revised version of Figure 1

Reviewer #2

Comment #1 It is not completely clear if the focus of the study is on all thrombocytopenia (severe and mild) or just on mild thrombocytopenia. They report on 2,579 (90.2%) normal platelet count 266 (9.3%) mild thrombocytopenia, and 13 (0.5%) severe thrombocytopenia. They mention a separate analysis of the severe thrombocytopenia cases and ultimately disclose non-significant results due to small numbers. The authors need to reflect on the story they want to tell. It may be a consideration to exclude the severe cases and just report on a comparison of mild thrombocytopenia versus normal platelet count in labor.

Reply: Thank you for this comment. We agree that the primary study group is mild thrombocytopenia, since there is already a known association between severe thrombocytopenia and PPH. Thus, to avoid confusion and because of the small numbers of patients with severe thrombocytopenia, we have chosen to remove the severe thrombocytopenia group from all analyses and Table 3. We provide some description of the 13 NTSV pregnancies with severe thrombocytopenia that were excluded from analysis (6 gestational thrombocytopenia, 4 preeclampsia with severe features, 2 ITP, 1 SLE) Lines 359-362..

Comment #2 To reduce confounding variables and provide more meaningful results, cases of cesarean delivery and preeclampsia should be excluded from the primary analysis. Both groups can be analyzed and presented separately

Reply 2: We understand the reviewers' concern, but our primary study group was NTSV pregnancies undergoing labor, which does include some women with term preeclampsia or those who ended up with cesarean delivery. However, women with preeclampsia and platelet count <100k/ul were excluded from analyses. To address the reviewers' concern we performed sensitivity analyses, by independently evaluating the association between mild thrombocytopenia and PPH after exclusion of cesarean delivery cases, and then additional exclusion of gestational hypertension and preeclampsia cases, and the significant association between mild thrombocytopenia and PPH persisted (Results Pargraph 4, Supplemental Tables 1 and 2). After removal of cesarean deliveries, the association between mild thrombocytopenia and PPH was lost, and we noted in this in the revised Methods section (lines 379-387). We also performed multivariable logistic regression to adjust for confounders, including preeclampsia and cesarean delivery, and the association also persisted. Thus, we believe that our findings are robust.

Comment #3 Attention is required to important definitions, variables and timelines. For example PPH and EBL process should be defined, Uterine atony, perineal lacerations, DIC should be identified.

Reply 3: For clarity we provided additional information regarding EBL and the diagnosis of PPH in the revised manuscript. For additional details, please see replies 1-3 to reviewer 1 above.
ICD 10 codes used to screen for postpartum hemorrhage were O72.0, O72.1, O72.2, O72.3 and O75.89 lines 222-226.

The diagnosis of 3rd and 4th degree perineal lacerations were coded separately (O70.20-23) from PPH status. We provided data on rates of 3rd and 4th degree lacerations between study groups, and the rate of 3rd and 4th degree laceration was no different in women with mild thrombocytopenia or normal platelet count. This is described in Table 1 in the revised manuscript.

We did not identify any women with DIC in our study, but in our EMR it is coded as D65, and listed separate from PPH.

We agree that PPH is a broad diagnosis and reflects a variety of underlying etiologies. To better capture cases with uterine atony, we evaluated subjects receiving methergine or hemabate, because these are first line agents for treatment of uterine atony at our center. They don't have another clear indication since they are not used routinely for perineal lacerations in the absence of

uterine atony. Thus, we considered uterotonic use as surrogate measures of uterine atony.

Comment #4:
1st, 2nd & 3rd stage of labor and blood draw to onset of labor should be included in analysis

Reply 4: In our study, length of labor was defined as the time interval between admission and delivery. We do not have the exact time of blood draw for study subjects, but at our institution most women admitted for labor have an initial line placed for IV access and blood drawn for CBC.

We do not have separate data for length of 1st stage or 3rd stage of labor. However, we do have additional data on the length of the 2nd stage of labor and this was in included in the revised manuscript (Table 1). Neither total length of labor, or length of 2nd stage of labor, were different between study groups.

Comment #5 The Comment section is rambling, speculative and needs to be focused and concise

Reply 5: The wording in the comment section has been revised significantly.

Comment #6 The lack of association with blood transfusion puts this study in perspective and should be highlighted in the discussion section

Reply 6: We agree with the reviewer that the overall rate of blood transfusion was low, and there was no difference in blood transfusion between groups. The low rate of blood transfusion may reflect the overall healthy nature of our NTSV population and average starting hemoglobin 12.4-12.6 g/dl among study subjects. We did find higher rates of PPH and EBL >1000ml in women with mild thrombocytopenia, but this did not translate to blood transfusion, possibly due to small numbers. Increased uterotonic use in the mild thrombocytopenia group may have also reduced blood loss and need for blood transfusion. Given the overall low number of women with blood transfusion, detailed analysis was not possible. We have acknowledged this as a limitation in the revised manuscript.

Comment #7: Platelet clumping. How is this identified in a retrospective study based on data extraction from the electronic medical record?

Reply 7: Platelet count was abstracted from the electronic medical record, and platelet clumping was reported by the lab through written text, in lieu of a numerical value.

Comment #8 Did you exclude medical disorders such as coagulation disorders, antiphospholipid antibodies syndrome and collagen vascular disease that could affect outcomes

Reply 8: The study population included NTSV pregnancies undergoing labor, and all subjects meeting that criteria were included. In the revised manuscript, we excluded all women with platelet count <100 k/ul from analysis. This removed 13 cases (6 gestational thrombocytopenia, 4 preeclampsia with severe features, 2 ITP, 1 SLE).

Comment #9 Please state the exact definition of PPH that was used for this study

Reply 9: Please see Reply 1 to Reviewer 1 above. In the revised manuscript we have updated the definition of PPH used at our institution.

Comment #10 What was the time interval from blood draw to onset of labor and delivery?

Reply 10: See Reply 4 above.

Comment: 11
Was the estimation of blood loss standard? What method was used for estimation or quantification? What is the reliability of estimated blood loss in this institution?

Reply 11: We utilized estimated blood loss as documented by the provider at delivery, and there was no standardized method of quantification. Partly for that reason we utilized PPH as our primary outcome, which is a diagnosis made by the delivery provider, and not based on EBL alone. Our providers utilize ACOG's reVITALize definition for PPH, put forth in 2014, which allows PPH to be diagnosed in the setting of any blood loss accompanied by signs or symptoms of hypovolemia. Understanding that this definition may be subjective, we also included data on uterotonic agents to support the provider diagnosis of PPH This has been described in the Methods section of the revised manuscript.

Comment # 12
Please analyze 1st 2nd & 3rd stage of labor separately since prolongation of a specific stage of labor may be an important confounding variable

Reply 12:
See Reply 4 above.

Comment #13
This difference was seen even when excluding women with cesarean delivery (16.0% vs. 7.9%, P<0.001), or exclusion of women with gestational hypertension or preeclampsia (14.1% vs. 8.1%, P=0.002). This is somewhat confusing and a

significant study design flaw. Both cesarean section and preeclampsia increase risk of PPH. It is best that these populations are analyzed separately.

Reply 13: **See Reply 2 above**

Comment # 14: The primary results should be based on the population in whom thrombocytopenia is the only recognized risk for PPH.

Reply 14: At our institution, we utilize CMQCC risk assessment for PPH. Recognized risk factors for PPH include obesity, fibroids, anemia, preeclampsia, chorioamnionitis, and prolonged labor, among others. Unfortunately, our study was not powered to assess the association between mild thrombocytopenia and PPH in women with NTSV pregnancy and no recognized risk factors. However, we will pursue this as an area for future study.

Comment #15 Importantly, the association between mild thrombocytopenia and PPH persisted after multivariable logistic regression (aOR159 2.3, 95% CI 1.6-3.3, P<0.001), with adjustment for BMI, race/ethnicity, gestational hypertension or preeclampsia, and mode of delivery. Duration of labor should be included in this regression analysis.

Reply 15: We agree with reviewers' concern that length of labor may confound the association between platelet count and PPH. We did not initially include it in our regression analysis because length of labor was no different between platelet count study groups. However, we performed additional univariable analysis for factors associated with PPH (supplemental Table 3). Length of labor was associated with PPH and thus we included it as an intrapartum confounder in our stepwise regression (Table 3).

Comment #16 Such women may benefit from patient and unit readiness, like those with severe thrombocytopenia. This is too powerful a statement based on a retrospective study with significant limitations. This study can only suggest future prospective studies and not dabble into practice guidelines

Reply 16: This statement has been modified lines 445-446.

Comment # 17 Practice guidelines often focus on platelet count in women with immune mediated thrombocytopenia or preeclampsia, or those undergoing surgery or neuraxial anesthesia. Concern is raised in preeclampsia when the platelet count is <100 k/µl, while concern for epidural hematoma is raised when the platelet count is <70 k/µl. However, the leading cause of PPH is uterine atony, and the mechanisms linking thrombocytopenia to uterine atony is unclear. The platelet count threshold for PPH from uterine atony may differ from the thresholds used to guide bleeding risk in women with medical conditions or those

undergoing surgery or neuraxial anesthesia. This segment is rambling, does not contribute much and should be shortened or deleted.

Reply 17: This paragraph has been modified and shortened lines 455-458.

Comment #18 This long segment needs to be carefully revised to: decrease redundancy, clarify true strengths of this study which are minimal highlight the limitations which are many remove speculative statements.

Reply 18: We have modified the strengths and limitations discussion in the revised manuscript. Lines 511-519.

Comment # 19 The strengths of our study include a large sample size, clear hypothesis and primary outcome, and a well-defined population of women with NSTV pregnancy undergoing labor. This statement may not be completely accurate and is also a perception that some readers may not share. For example, the authors admit that they did not have enough cases of severe thrombocytopenia to be able to draw meaningful results with that group. Also, the above statement should be fundamental for any study design and not a "strength". At the discretion of the authors may consider removing this sentence.

Reply 19: We have modified the strengths and limitations discussion in the revised manuscript lines 511-535.

Comment #20 By focusing on NTSV pregnancies, we minimized confounding factors such as multiparity, preterm delivery and multifetal gestation, which have an increased risk of PPH regardless of platelet count
Comment: This has been previously stated line 90-91

Reply 20: This has been modified to reduce redundancy.

Comment #21 Thrombocytopenia may have caused increased PPH through surgical bleeding or perineal lacerations. Yet, our results were unchanged when excluding women with cesarean delivery, and mild thrombocytopenia was associated with use of methergine and hemabate, which are primarily utilized for uterine atony. In addition, thrombocytopenia was associated with EBL ≥1000 ml, which most often reflects uterine atony compared to lower thresholds and is consistent with the new definition of PPH, regardless of mode of delivery. Postpartum hemoglobin was not available in uncomplicated deliveries. This segment raises questions, includes results and identifies some essential methodological concerns. The authors should include the diagnosis of uterine atony, perineal lacerations and retained placenta in their analysis. How were cases of DIC excluded?

Reply 21: **See Reply 3 above**.

Comment #22 While we continue to support longer labors in the NTSV population to decrease the rate of primary cesarean deliveries, we should also continue to optimize our risk stratification tools to better identify women at high risk for PPH. Risk assessment and preparedness are fundamental to reducing morbidity and mortality related to postpartum hemorrhage, and continuous reassessment of our obstetric toolkits is critical to optimizing patient outcomes. This segment can be deleted without affecting content

Reply 22: This segment has been modified lines 537-541.

Comment # 23 Our data suggests that a platelet count threshold of 150 k/µl at the time of delivery, rather than may identify more women at increased risk for postpartum hemorrhage. This is not accurate. You have not done a comparison study between 150 k/µl and 100 k/µl. Your conclusion should be limited to the specific findings of this study and not generalize to current standard of care.

Reply 23: The statement was modified. Lines 545-548.

Comment # 24 This table shows that mild thrombocytopenia is significantly associated with PPH while severe thrombocytopenia is not. This analysis shows the issue that may arise from inadequate sample size and improper analysis. The authors should discuss with their statistician if this data should be included since this may present an inaccurate clinical derivation regarding severe thrombocytopenia

Reply 24: We agree that the study was designed to evaluate mild thrombocytopenia and not severe thrombocytopenia. To maintain study emphasis on mild thrombocytopenia, we have removed the severe thrombocytopenia group from the analyses and Tables.

Reviewer #3

Comment #1. Given that this is a study of PPH and the authors took great care to assess group differences (eg. gestational diabetes), why was uterine atony, the leading cause of PPH, not assessed? There is an ICD-10 code for atony.

Reply 1: We utilized PPH as the primary outcome, which we agree has a variety of underlying etiologies including uterine atony. Unfortunately, uterine atony was not consistently coded by the delivery provider thus we assessed administration of methergine or hemabate as secondary outcomes, and these measures may serve as surrogate markers of uterine atony. We believe that our findings were robust since mild thrombocytopenia was associated with PPH, but was also associated with uterotonic use and EBL >1000ml. To evaluate other factors that may be associated with vaginal bleeding after delivery, we also evaluated third and fourth degree perineal lacerations in the revised manuscript, and the rate of

these complications were not different between the study groups (Table 1). Moreover, 3rd and 4th degree lacerations were not associated with PPH in univariable analysis (Supplemental Table 3).

Comment #2. Has ICD-10 been validated for PPH? This should be discussed.

Reply 2: Use of ICD-9 codes for PPH have been validated by Butwick et al. in 2018, who found 97% specificity but only 28% sensitivity. While ICD-10 codes may be more accurate than ICD-9 codes, a validation study has not been performed. We added this statement and reference to the revised manuscript (Ref #23, Lines 520-523). For our study, 10% of charts were randomly selected for chart audit and PPH was confirmed in all cases. This is described in the methods section and discussion in revised manuscript.

Comment # 3. The retrospective nature of this study and reliance on codes should be acknowledged as a weakness.

Reply 3: We agree with the reviewer. While we assessed secondary outcomes such as administration of methergine or hemabate, or EBL >1000ml, to support our primary outcome of PPH, the limitations of ICD-10 coding remain a weakness of the study design and we have acknowledged this in the discussion.

Comment # 4. The method of calculating EBL in the study Institution should be discussed given its centrality to the primary outcome.

Reply 4: We utilized estimated blood loss as documented by the provider at delivery, and there was no standardized method of quantification. Partly for that reason we utilized PPH as our primary outcome, which is a diagnosis made by the delivery provider, and not based on EBL alone. Our providers utilize ACOG's reVITALize definition for PPH, put forth in 2014, which allows PPH to be diagnosed in the setting of any blood loss accompanied by signs or symptoms of hypovolemia. Understanding that this definition may be subjective, we also included data on uterotonic agents to support the provider diagnosis of PPH. An improved description of EBL and PPH definition was provided in the Methods section of the revised manuscript. Lines 237-243.

Comment 5. As mentioned below (Tables), the n should be shown, not just the percents, particularly given some of the small numbers. For example, only 5 women in the study group had blood transfusion, and this is lost when only the percent is shown. Further, given the small n, Fisher's or McNemar's Exact tests should be used.

Reply 5: We revised the tables to present data as n (%), with total N in the column header. For data in the table with n ≤5 we utilized Fisher's exact test and this footnote was provided.

Comment 6. The discussion mentions that this study was well-powered, yet no power calculation is shown. In fact, some of the outcomes are involve very small numbers, and an N should be shown in addition to the percent

Reply 6: We have removed this line from the discussion to avoid any misunderstanding. We meant to say that we were well powered for our primary outcome of PPH, and we added power calculation in the last paragraph of the revised Methods section. We agree that the study was not specifically powered for secondary outcomes that occurred with lower frequency. We utilized P<0.01 for secondary outcomes to avoid Type 1 error, and all secondary outcomes were significant at this level except blood transfusion. It is possible that the null result for blood transfusion was a Type 2 error, but given the similar rate of blood transfusion in both groups (1.5 vs 1.9%), a much larger study would be needed. We provided n (%) in the revised tables.

Comment 7. Were women with ITP excluded?

Reply 7: All women with platelet count <100 k/ul were excluded, including those with ITP. We identified 2 women with ITP and Plt <100k who were excluded from analyses. We did not identify any women with ITP in our group of subjects with mild thrombocytopenia 100-149 k/ul.

STATISTICAL EDITOR'S COMMENTS:

Comment 1. lines 99-102 and Fig 1: Did the n = 3166 represent all NTSV deliveries, or were there some who did not have a CBC or for whom the data were missing (other than those included in the N = 32 exclusions)?

Reply 1: Yes 3166 are all NTSV deliveries. We modified Figure 1 to make it clear that the 79 precipitous deliveries were excluded because they did not have platelet count resulted prior to delivery. An additional 32 patients had CBC resulted before delivery, but had no result for platelet count due to platelet clumping.

Comment 2. lines 160-161: See later comments re: more exposition of the ORs, but should explicitly state the referent for each OR and aOR. For BMI, I assume the 1.04 is per 1 unit increase in kg/m^2.

Reply 2: Yes. This has been updated in Table 3 and Supplemental Table 3 of the revised manuscript.

Comment 3. Table 2: Since many of the counts among the thrombocytopenia group are few, should format as n(%) for both columns, not just as %s.

Reply 3: We provided n (%) for column data in the revised Tables. Total N is listed in the column header.

Comment 4. Table 3: Should include the n(%) for PPH among the severe thrombocytopenia group. From lines 151-154, that is 3 of 13, which should be rounded to 23%, not 23.1%, given the small counts for severe thrombocytopenia. Furthermore, the estimation of that aOR is not justified, since there were only 3 cases and 4 variables were used as adjustors, or even for one variable (BMI), if that was the final model. That is, the Authors are correct that this comparison with the normal platelet count cohort was under powered, but the adjustment was also likely over fitted.

Reply 4: Since the focus of the manuscript was mild thrombocytopenia, and because we had so few cases with severe thrombocytopenia, we decided to remove the severe thrombocytopenia group from all analyses.

Comment 5. Should include (could be on-line material), the unadjusted ORs for PPH vs BMI, race/ethnicity, HTN or pre-eclampsia and mode of delivery?

Reply 5: We included this data as Supplemental Table 3

Comment 6. Also, why were mode of delivery and HTN or pre-eclampsia included in the final model, since by Table 1, the direct comparisons were NS and why were HTN and pre-eclampsia aggregated into one category as an adjustor?

Reply 6: While gestational HTN or preeclampsia and mode of delivery were not different in women with mild thrombocytopenia compared to those with normal platelet count, the two variables were associated with PPH in univariable analysis (as shown in Supplemental Table 3 of Revised manuscript). Thus, in the Revised Table 3, we performed a stepwise regression, first adjusting for antepartum risk factors and then intrapartum risk factors associated with PPH.

We aggregated gestational hypertension and preeclampsia because both are associated with an increased risk for thrombocytopenia. We evaluated magnesium sulfate use separately, as a proxy for those with preeclampsia with severe features. In Supplemental Table 3 of the revised manuscript we found that the aggregate of GHTN or preeclampsia was associated with PPH, and thus it was included as an adjustor. Magnesium sulfate use was no different between groups and its association with PPH in our study was limited by small numbers, thus it was not utilized as an adjustor.