

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)*

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obgyn@greenjournal.org.

Date: Jul 19, 2019
To: "Catherine Smith" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-1085

RE: Manuscript Number ONG-19-1085

Maternal and perinatal morbidity and mortality associated with anemia in pregnancy

Dear Dr. Smith:

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 Aug 09, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: Authors used a large, validated Canadian birth registry to evaluate the incidence of anemia in pregnancy and to determine impact of diagnosis of anemia on maternal and neonatal outcomes. Pre delivery anemia occurred in 13% of this population; mild anemia conferred protective effects and moderate to severe anemia predictably were associated with worse peri-natal outcomes.

Good study design and a very well written manuscript.

1. Abstract; lines 53-55 can be re-phrased for clarity; "Women were diagnosed with anemia based on 3rd trimester and or labor & delivery admission hemoglobin values; anemia was categorized into 5 groups...."
2. Materials & methods; lines 110-112: what was the impact of change in coding on the results? A sub analysis comparing results of 2004-2007 to 2009-2016 may clarify this.
3. Lines 113-117; please provide actual definitions of these codes- not all readers will know coding sub classifications..e.g., 50 (iron deficiency anemia) 51 (vitamin B12 deficiency) 52 (folate) etc.
4. Lines 135- 138; please provide definitions for these diagnoses- "birth asphyxia, low APGAR, RDS, fetal asphyxia etc. What is special care unit? ICU equivalent or High Dependency Unit or both?
5. Results; lines 154-155; what is the mean gestational age at diagnosis of anemia (with standard deviations)? It will be useful to also see mean gestational age at diagnosis of antenatal obstetric problems- pre-eclampsia, abnormal placentation etc...this may give insight into any temporal relationship between the diagnosis of anemia and obstetric diagnoses.
6. Do you have data on socio-economic determinants of health? Ethnicity, levels of literacy/education, household incomes? If not, please acknowledge in discussion as a limitation for study generalizability.
7. Line 166; please clarify definition of LOS- is this for antenatal admissions or post partum LOS or both?
8. Since authors have data on types of anemia, it will be very useful to see a sub-analysis of the impact of type of anemia on perinatal outcomes- adjustment for severity of anemia may allow insight into the impact of the underlying disease on perinatal outcomes (e.g., hemolytic anemias)
9. Discussion; lines 206-208 , 213-214 need to be tempered since the data do not demonstrate temporal relationships between anemia and the occurrence of these outcomes.

10. Lines 233-236 need to acknowledge the potential impact of underlying disease state on these outcomes- again, stratifying results based on type of anemia may be helpful here.

Reviewer #2: This is a well-written and researched paper of particular importance with the current focus on maternal mortality and morbidity in addition to perinatal outcomes.

1. The Abstract is clear, concise, and thorough.
2. The Introduction provides a succinct discussion of the rationale for the study: the lack of evidence for deleterious effects of maternal anemia in high-income countries where prenatal care is widely available.
3. Materials and Methods - This is a well-designed retrospective cohort study utilizing a reliable, validated database that included over 99% of births in British Columbia over a 12-year period. Mild, moderate, and severe anemia are clearly defined, although hemoglobin measurements might be better expressed in the more familiar g/dL for American audiences. Statistical methods appear to be appropriate.
4. The Results section is clear, which is especially commendable in light of the multiple parameters that were assessed. (The Tables are also very helpful in this regard.) It is unfortunate that such a small number of women with severe anemia were available for the study and that specific etiologies for the diagnoses of anemia could not be gleaned from more of the records.
5. The Discussion addresses most of the significant issues raised by the study. It reviews the potential role of anemia in adverse pregnancy outcomes, and draws on this background to provide a logical theory for the improved perinatal mortality and morbidity seen in patients with mild anemia. It also addresses the small population attributable fraction found in the Results. However, I would like to see the possible role of socioeconomic status addressed as well. Many of the maternal characteristics found to be associated with anemia (e.g. chronic medical conditions) are known to be more common in socially disadvantaged women, who experience higher rates of maternal and perinatal mortality and morbidity. Although these women may have a higher incidence of anemia, how much is that directly related to their adverse pregnancy outcomes? Finally, the discussion of study limitations is adequate, but it should be broken into a separate paragraph.
6. Tables - I find Table 1 confusing. It's difficult to tell which factors the p values apply to and whether they refer to increased or decreased risk. Some also appear to differ from the results as described in the Results section, e.g. age over 40 and in vitro fertilization are not marked as reaching statistical significance.

Reviewer #3: Author comments:

Congratulations to the authors for this large population-based retrospective cohort study comparing outcomes in women with and without anemia over a 12 year epoch.

1. The authors begin by the acknowledging that much of the current literature on anemia in pregnancy is derived from less affluent countries, and contrast this to their work/experience in a more affluent country. While rates of anemia were lower in this study, there is little attention given to other significant contributors of anemia in previously studied populations (ethnic differences, geography, hemoglobinopathies, chronic disease, etc). Furthermore, there was no information regarding treatment available or socioeconomic status of the study groups. How much of an impact do they presume affluence contributes in comparison to these other factors, and what do they use to base their assertion?
2. While the authors commented on perinatal morbidity and mortality, they chose only to report on maternal morbidity. Why was there no discussion or inclusion of maternal mortality data?
3. What do the authors suspect contributes to the increase in antibiotic use, maternal infections, and infant sepsis seen in the study? Any information on mechanisms?
4. There were significantly smaller numbers in 3 of the 4 anemia groups (all except the mild group). What is the significance of this finding?
5. Was there any consideration given to collecting data on chronic diseases? This may have proven helpful and could potentially be a significant confounder in the associations observed.
6. The lack of treatment information prior to admission is significant, as this may reflect the more recalcitrant/severe forms of anemia which were actually responding to therapy, or could have identified those which were recalcitrant to therapy.

7. Racial/ethnic characteristics of the groups would also be of interest, if available. The readers know little of the heterogeneity/homogeneity of the groups, otherwise.

8. In general, the information included in the tables is a bit overwhelming and hard to follow/ read. It may be that you would think of reformatting or presenting the data in a different form.

STATISTICAL EDITOR'S COMMENTS:

General: This study had > 500 K pregnancies over a 12 year period, so likely there were some women represented more than once. Their outcomes are not independent events, but likely correlated, both with respect to anemia and with some of the adverse outcomes. Should either account for the non-independence or chose one pregnancy randomly from those women with more than one pregnancy to preserve independence (which is assumed by the stats methods used.)

Tables 2, 3: Many of the adverse outcomes have relatively small counts, too few to allow for multiple adjustment for 9 variables. All of the aORs for the severe anemia are likely over fitted and should be omitted.

For the moderate anemia cohort, admit to special care, pre-eclampsia, placenta previa with hemorrhage, placental abruption, antepartum transfusion, chorioamnionitis, PP wound infection, PP infection, PP UTI are all likely over fitted.

For the mild anemia cohort, admit to special care, antepartum transfusion, PP UTI are similarly likely over fitted due to small counts of adverse outcomes.

For the unspecified anemia cohort, admit to special care, placenta previa with hemorrhage, antepartum transfusion and post-delivery anemia, chorioamnionitis, PP wound infection, PP infection and PP UTI are all likely over fitted.

Tables 4, 5: Same issue with over fitting (now for 10 variables used as adjustors). All of the aORs for severe anemia should be omitted. Any of the counts < 100 adverse outcomes should also be omitted, which affects some of the moderate or unknown anemia cohorts.

For the no-anemia group, ironically (no pun intended), the antepartum transfusion count is too few for adjustment with 9 variables.

Associate Editor's Comments:

Please throughout report hemoglobin in gm/dL

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.
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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. 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.

7. 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.

8. 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.

9. 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%).

10. 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.

11. 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/ifaauth.htm>.

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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 Aug 09, 2019, 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

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Maternal and perinatal morbidity and mortality associated with anemia in pregnancy (ONG-19-1085)

Response to Reviewers' and Editor's comments

Reviewer #1:

Comment 1. Abstract; lines 53-55 can be re-phrased for clarity; "Women were diagnosed with anemia based on 3rd trimester and or labor & delivery admission hemoglobin values; anemia was categorized into 5 groups...."

Response: The diagnosis of anemia was based on 3rd trimester hemoglobin values <11 g/dL and the delivery admission diagnosis of anemia recorded in the physician notes that was made before delivery (in order to distinguish this from post-delivery anemia due to hemorrhage during delivery). Although such a diagnosis of anemia was probably made based on hemoglobin values obtained from blood tests done during the delivery admission (but before delivery), our data source did not include these hemoglobin values. This is the reason for the wording used. We have edited the sentence to make this clear both in the Abstract and the Methods section Lines 53-54 and 122-123 respectively. "Women were diagnosed with anemia based on two criteria, namely, 3rd trimester hemoglobin <11 g/dL and/or a delivery admission diagnosis of anemia (made before delivery); anemia was categorized into 5 groups...."

Comment 2. Materials & methods; lines 110-112: what was the impact of change in coding on the results? A sub analysis comparing results of 2004-2007 to 2009-2016 may clarify this.

Response: The addition of a separate mechanism for collecting information on HELLP syndrome, acute fatty liver of pregnancy, admission to a Special Care Nursery, postpartum hemoglobin and several infectious postpartum illnesses was introduced in 2008 as such information was not collected between 2004 and 2007. We did not include the period 2004-2007 in the analysis of these above-mentioned outcomes. We have clarified this in the revised manuscript, line 108-110.

"The information collected by the data registry was expanded in 2008 to specifically include details regarding HELLP syndrome, acute fatty liver of pregnancy, admission to a Special Care Nursery, postpartum hemoglobin and several infectious postpartum illnesses."

Comment 3. Lines 113-117; please provide actual definitions of these codes- not all readers will know coding sub classifications..e.g., 50 (iron deficiency anemia) 51 (vitamin B12 deficiency) 52 (folate) etc.

Response: Each code definition as been added. Please see lines 111-118.

"Cases of anemia in pregnancy were identified using third trimester hemoglobin <11 g/dL, and ICD-10-CA codes for anemia (D50 to D64 and O99.0) including D50 (iron deficiency anemia), D51 (vitamin B12 deficiency anemia), D52 (folate deficiency anemia), D53 (other nutritional anemias), D55 (anemia due to enzyme disorders), D56 (anemia due to thalassaemia), D57 (anemia due to sickle-cell disorders), D58 (other hereditary hemolytic anemias), D59 (acquired hemolytic anemia), D60 (anemia due to acquired pure red cell aplasia), D61 (other aplastic anaemias) D62 (acute post-hemorrhagic anemia), D63 (anemia due to chronic diseases), D64 (other anemias), and O99.0 (anemia complicating pregnancy childbirth and the puerperium)."

Comment 4. Lines 135- 138; please provide definitions for these diagnoses- "birth asphyxia, low APGAR, RDS, fetal asphyxia etc. What is special care unit? ICU equivalent or High Dependency Unit or both?

Response: All diagnoses such as birth asphyxia, respiratory distress syndrome, fetal asphyxia, etc, correspond to diagnoses made by physicians in the medical chart. Low 5-minute Apgar score

has been defined as <7 or <4 in the Methods section (In the Results sections these outcomes are presented separately for 5- minute Apgar <7 and 5-minute Apgar <4). The special care unit included both intensive care units and high dependency units. These points have been clarified in the revised manuscript.

Lines 106-108 “All diagnoses and procedures in the database were based on physician notes regarding diagnoses and interventions as recorded in the medical chart.”

Lines 134-135 “Perinatal outcomes examined included multiple births, preterm birth, low 5-minute Apgar score (<7 or <4), respiratory distress syndrome, fetal asphyxia, birth asphyxia, and perinatal death.”

Lines 392-92 “Special care Unit admissions included admissions to an intensive care unit or high dependency unit.

Comment 5. Results; lines 154-155; what is the mean gestational age at diagnosis of anemia (with standard deviations)? It will be useful to also see mean gestational age at diagnosis of antenatal obstetric problems- pre-eclampsia, abnormal placentation etc...this may give insight into any temporal relationship between the diagnosis of anemia and obstetric diagnoses.

Response: We agree that such information would have provided insight into the relationships between anemia and subsequent obstetric problems. Unfortunately, the database does not record the gestational age at different points during pregnancy when specific diagnoses were made and only provides the best obstetric estimate of gestational age at delivery. In fact, we had mentioned in the original manuscript that reverse causality was a potential limitation of the study as we could not exclude a presumably small effect of antepartum hemorrhage on third trimester hemoglobin or pre-delivery diagnosis of anemia. We have expanded on this and acknowledged that information on gestational age at diagnosis of anemia and gestational age at diagnosis of placental complications would have provided better insight into the relationships.

Lines 288-290 “Information on gestational age at diagnosis of anemia and gestational age at diagnosis of placental complications would have provided better insight into potential cause-effect relationships.”

Comment 6. Do you have data on socio-economic determinants of health? Ethnicity, levels of literacy/education, household incomes? If not, please acknowledge in discussion as a limitation for study generalizability.

Response: Unfortunately, the BC Perinatal Database Registry does not contain individual-level information on ethnicity, education or household income. We have listed this as a limitation in the Discussion section.

Lines 282-291 “Other limitations included the potential for reverse causality (e.g., some of the association between anemia and placenta previa/abruption may have been because of antepartum hemorrhage leading to anemia) and the lack of individual-level information on maternal ethnicity, education and household income. Several of the maternal characteristics associated with anemia in our study (e.g., age <20 years, and chronic medical conditions) are also associated with socioeconomic deprivation. Information on gestational age at diagnosis of anemia and gestational age at diagnosis of placental complications would have provided better insight into potential cause-effect relationships and information on socioeconomic status would have provided insight into the social determinants of perinatal health.”

Comment 7. Line 166; please clarify definition of LOS- is this for antenatal admissions or post partum LOS or both?

Response: The LOS is referring to the LOS postpartum. We have clarified as below.

Line 174. “The mean length of postpartum stay was 2.6 days for women without anemia...”

Comment 8. Since authors have data on types of anemia, it will be very useful to see a sub-analysis of the impact of type of anemia on perinatal outcomes- adjustment for severity of anemia may allow insight into the impact of the underlying disease on perinatal outcomes (e.g., hemolytic anemias)

Response: Unfortunately, most of the anemia cases in the study did not have an etiologically specific diagnosis. Appendix Table S2 shows the breakdown of anemias based on etiologic type and reveals that there were very few hemolytic or aplastic anemias identified. This number limits the value of an additional analysis by type as there is too little data to analyze in order to obtain precise and meaningful estimates. We have mentioned this in the revised manuscript Lines 279-281 “Another limitation was our inability to analyze the data by type of anemia due to the rarity of some anemias (Appendix Table S2); differences in anemia types may have resulted in different maternal and fetal responses. ”

Comment 9. Discussion; lines 206-208 , 213-214 need to be tempered since the data do not demonstrate temporal relationships between anemia and the occurrence of these outcomes.

Response: We have revised the wording

Lines 225-26 “In addition to a higher burden of illness, anemic women had higher rates of placentally- mediated antepartum morbidity such as pre-eclampsia.”

Lines 231-232 “Maternal anemia may lead to compensatory physiologic changes in the placenta which predispose to placental dysfunction.”

Comment 10. Lines 233-236 need to acknowledge the potential impact of underlying disease state on these outcomes- again, stratifying results based on type of anemia may be helpful here.

Response: As mentioned, we have added in a comment to our limitations section to address this issue.

Lines 279-81 “Another limitation was our inability to analyze the data by type of anemia due to the rarity of some anemias (Appendix Table S2); differences in anemia types may have resulted in different maternal and fetal responses.”

Reviewer #2:

Comment 1. The Abstract is clear, concise, and thorough.

Comment 2. The Introduction provides a succinct discussion of the rationale for the study: the lack of evidence for deleterious effects of maternal anemia in high-income countries where prenatal care is widely available.

Response: Thank you.

Comment 3. Materials and Methods - This is a well-designed retrospective cohort study utilizing a reliable, validated database that included over 99% of births in British Columbia over a 12-year period. Mild, moderate, and severe anemia are clearly defined, although hemoglobin measurements might be better expressed in the more familiar g/dL for American audiences. Statistical methods appear to be appropriate.

Response: The units for hemoglobin have been changed for the manuscript, Tables and Figure.

Comment 4. The Results section is clear, which is especially commendable in light of the multiple parameters that were assessed. (The Tables are also very helpful in this regard.) It is unfortunate that such a small number of women with severe anemia were available for the study and that specific etiologies for the diagnoses of anemia could not be gleaned from more of the records.

Response: Thank you. Yes, despite the large study size, we were unable to obtain sufficient precision with regard to estimates for women with severe anemia and acknowledge this in the Limitations section.

Comment 5. The Discussion addresses most of the significant issues raised by the study. It reviews the potential role of anemia in adverse pregnancy outcomes, and draws on this background to provide a logical theory for the improved perinatal mortality and morbidity seen in patients with mild anemia. It also addresses the small population attributable fraction found in the Results. However, I would like to see the possible role of socioeconomic status addressed as well. Many of the maternal characteristics found to be associated with anemia (e.g. chronic medical conditions) are known to be more common in socially disadvantaged women, who experience higher rates of maternal and perinatal mortality and morbidity. Although these women may have a higher incidence of anemia, how much is that directly related to their adverse pregnancy outcomes? Finally, the discussion of study limitations is adequate, but it should be broken into a separate paragraph

Response: We agree that risk factors for anemia such as chronic medical conditions could have been more common among women of low socioeconomic status. Unfortunately, our data source, the British Columbia Perinatal Database Registry, did not include any socioeconomic information. We have mentioned this issue in the limitations section. Additionally, the limitations section now appears as a separate paragraph.

Lines 282-291 “Other limitations includedand the lack of individual-level information on maternal ethnicity, education and household income. Several of the maternal characteristics associated with anemia in our study (e.g., age <20 years, and chronic medical conditions) are also associated with socioeconomic deprivation.”

Comment 6. Tables - I find Table 1 confusing. It's difficult to tell which factors the p values apply to and whether they refer to increased or decreased risk. Some also appear to differ from the results as described in the Results section, e.g. age over 40 and in vitro fertilization are not marked as reaching statistical significance.

Response to reviewer: We have added horizontal lines in Table 1 to clarify this. The P value for in vitro fertilization has also been provided.

Reviewer #3:

Comment 1. The authors begin by the acknowledging that much of the current literature on anemia in pregnancy is derived from less affluent countries, and contrast this to their work/experience in a more affluent country. While rates of anemia were lower in this study, there is little attention given to other significant contributors of anemia in previously studied populations (ethnic differences, geography, hemoglobinopathies, chronic disease, etc). Furthermore, there was no information regarding treatment available or socioeconomic status of the study groups. How much of an impact do they presume affluence contributes in comparison to these other factors, and what do they use to base their assertion?

Response: Our study provides information on some aspects of anemia. This include associations between various risk factors (such as maternal age, pre-pregnancy weight, chronic medical conditions and in vitro fertilization) and anemia and associations between anemia and various maternal and perinatal outcomes. Unfortunately, our data source lacked information on some upstream risk factors such low socioeconomic status and ethnicity. This limitation has been acknowledged in the Discussion/Limitations section. Similarly, we did not have information on treatments provided, which is also acknowledged in the limitations section.

Lines 291-293 “.... we did not have access to treatments that may have been provided when anemia was diagnosed; specifically, mild anemia identified by the third trimester hemoglobin may have been treated by the time of delivery.”

Comment 2. While the authors commented on perinatal morbidity and mortality, they chose only to report on maternal morbidity. Why was there no discussion or inclusion of maternal mortality data?

Response: Maternal mortality was not included in this study due to the rarity of this event in the British Columbia Perinatal Data Registry. The numbers were too small to provide meaningful associations with anemia (see also Statistical Editors comments) and also would have required suppression in order to prevent potential identification of individual women.

Comment 3. What do the authors suspect contributes to the increase in antibiotic use, maternal infections, and infant sepsis seen in the study? Any information on mechanisms?

Response: There has not been a clear physiologic explanation in the literature regarding the link between anemia and infectious morbidity, although this has been found in post-operative patients as well (mentioned in the Discussion section).

Lines 242-243 “Both anemia and receipt of allogenic blood transfusions have been associated with higher rates of infection in trauma as well as non-cardiac and gynecologic surgical patients.”²⁷⁻²⁹

Comment 4. There were significantly smaller numbers in 3 of the 4 anemia groups (all except the mild group). What is the significance of this finding?

Response: In general, few women were found to have the more severe anemia. This may reflect a) a healthy population typical of a high-income country where severe anemia is not common or b) effective treatment and management of anemia including early treatment of iron deficiency anemia detected in the first trimester and also use of antepartum blood transfusion.

Comment 5. Was there any consideration given to collecting data on chronic diseases? This may have proven helpful and could potentially be a significant confounder in the associations observed.

Response to reviewer: Yes, we agree that data on chronic diseases is relevant to this study. We did adjust for chronic diseases and pre-existing hypertension. Chronic disease included pre-existing diabetes, chronic renal disease due to hypertension, liver disease, other renal disease and disease of the circulatory system. Note: This was a database study using information from a perinatal database registry. The authors had no role in collecting information nor in determining what information to collect.

Comment 6. The lack of treatment information prior to admission is significant, as this may reflect the more recalcitrant/severe forms of anemia which were actually responding to therapy, or could have identified those which were recalcitrant to therapy.

Response: Yes we agree. However, as mentioned such information was not available in the data source and we have acknowledged this as a limitation of the study.

Lines 291-292 “Finally, we did not have access to treatments that may have been provided when anemia was diagnosed;”

Comment 7. Racial/ethnic characteristics of the groups would also be of interest, if available. The readers know little of the heterogeneity/homogeneity of the groups, otherwise.

Response: Yes, we agree. However, as mentioned such information was not available in the data source and we have acknowledged this as a limitation of the study.

Lines 282-286 “Other limitations included.....and the lack of individual-level information on maternal ethnicity, education and household income.”

Comment 8. In general, the information included in the tables is a bit overwhelming and hard to follow/ read. It may be that you would think of reformatting or presenting the data in a different form.

Response: We have tried to present a study which comprehensively examines the risk factors and outcomes associated with anemia. Readers not interested in the details will skip through the extensive information but hopefully this paper will be useful as a detailed study on the risk factors and consequences of anemia.

Statistical Editor’s Comments:

Comment General: This study had > 500 K pregnancies over a 12 year period, so likely there were some women represented more than once. Their outcomes are not independent events, but likely correlated, both with respect to anemia and with some of the adverse outcomes. Should either account for the non-independence or chose one pregnancy randomly from those women with more than one pregnancy to preserve independence (which is assumed by the stats methods used.)

Response: We agree that over the course of the study period, a significant fraction of women would have had more than 1 delivery recorded in the database. This would have affected the variance estimates depending on the tracking of outcome between pregnancies. Unfortunately, we did not have information to identify and link women who had more than 1 delivery during the study period. As an alternative option, we carried out sensitivity analyses restricted to nulliparous women having their first baby during the study period. This is not ideal since restriction to nulliparous women reduced the study size by some 40-45%. Nevertheless, the results with regard to variance estimates were essentially comparable. We present the original analysis in Table 3, mention the results of the analysis restricted to nulliparous women in the Results section, and present the detailed results of the analysis of nulliparous women in the Online Appendix. In the Limitations section, we discuss the non-independence issue as affecting the variance of the estimates of effect. We did have information on twin and triplet sets and used this information to correct the variance for the non-independence of outcomes to babies born following multi-fetal gestation. We also presented the results for fetuses and infants after restricting to nulliparous women (and adjusting the variance for non-independence of twin and triplet babies) in the Online Appendix.

Lines 146-153 “Some women contributed more than one delivery to the study population and such deliveries (which represented non-independent observations because of potential correlation in maternal/perinatal outcome rates) would have affected the precision of the estimates of effect. We were unable to address this problem directly as our data did not include identifiers permitting linkage of women across deliveries, and hence we carried out additional analyses restricted to nulliparous women. This non-independence of observations issue also affected analyses of perinatal outcomes involving twins and triplets and this problem was addressed by using generalized estimating equations and cluster-specific regression models.^{19,20}”

Lines 210-216 “Results of analyses restricted to nulliparous women, which were based in 239,315 women, showed that variance estimates were generally similar to those from results of analyses based on all women with some notable differences (Appendix Tables S3-S6). For instance, the aOR for mild anemia and prolonged hospital stay was 1.45 (95% CI 1.34-1.57) among deliveries to nulliparous women and 1.66 (95% CI 1.57-1.75) among all deliveries, while

the aOR for multiple birth was 1.65 (95% 1.52-1.80) among deliveries to nulliparous women and 1.69 (95% CI 1.59-1.79) among all deliveries.”

See also Online Appendix Tables 3-6.

Comment: Tables 2, 3: Many of the adverse outcomes have relatively small counts, too few to allow for multiple adjustment for 9 variables. All of the aORs for the severe anemia are likely over fitted and should be omitted. For the moderate anemia cohort, admit to special care, pre-eclampsia, placenta previa with hemorrhage, placental abruption, antepartum transfusion, chorioamnionitis, PP wound infection, PP infection, PP UTI are all likely over fitted. For the mild anemia cohort, admit to special care, antepartum transfusion, PP UTI are similarly likely over fitted due to small counts of adverse outcomes. For the unspecified anemia cohort, admit to special care, placenta previa with hemorrhage, antepartum transfusion and post-delivery anemia, chorioamnionitis, PP wound infection, PP infection and PP UTI are all likely over fitted.

Tables 4, 5: Same issue with over fitting (now for 10 variables used as adjustors). All of the aORs for severe anemia should be omitted. Any of the counts < 100 adverse outcomes should also be omitted, which affects some of the moderate or unknown anemia cohorts.

For the no-anemia group, ironically (no pun intended), the antepartum transfusion count is too few for adjustment with 9 variables.

Response: We agree that there some underestimation or overestimation of variance would have occurred in regression models where several variables were adjusted (because of the small numbers of events in some anemia categories). In the revised manuscript, we have omitted the regression results wherever the number of events per variable in any category was <100. This approximately follows that event per variable rule of 1:10 for logistic regression. We have mentioned this in the Methods section and provide a reference justifying this.

Lines 143-145 “Event frequencies in some categories of anemia were too small to permit fitting regression models with the covariates mentioned above.¹⁸ Therefore, adjusted models were only estimated if the anemia severity category included at least 100 women with the event of interest.”

Associate Editors comments:

Please throughout report hemoglobin in gm/dL.

Response: The units for hemoglobin have been changed for the manuscript, Tables and Figure.

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.**
- 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.

Response: Confirmed.

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.

Response: Not applicable.

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.

Response: The manuscript is 22 pages excluding references and the online Appendix.

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).

Response: Acknowledged or not applicable.

6. 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.

Response: Abstract has been checked. The word count available on title page (297).

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.

7. 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.

Response: Only standard abbreviations were used.

8. 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.

Response: Virgule symbol not used.

9. 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.

Response: P values not provided in the Abstract or Tables.

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.

Response: Not applicable.

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%).

Response: Done.

10. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.

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We thank the Editors and Reviewers for their helpful comments.



Catherine Smith, BSc, MD



Cc: Dr K.S. Joseph, Dr. Flora Teng, Emma Branch and Scally Chu