OBSTETRICS & GYNECOLOGY

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

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

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

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

Date: Mar 18, 2020
To: "Matthew J Bicocca" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-351

RE: Manuscript Number ONG-20-351

Maternal Obesity and the Risk of Early and Late Onset Hypertensive Disorders of Pregnancy

Dear Dr. Bicocca:

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 Apr 08, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: The authors present a retrospective study of derived from a United States data base that includes all 50 states about the impact of maternal obesity on hypertensive disorders in pregnancy (HDP).

The introduction provides a good summary of the extensiveness of HDP and the impact on outcome. The authors note the differences in outcome in early versus later onset of disease and the uncertainty regarding the relationship between obesity and early onset HDP. The purpose of the study is clearly stated.

The methodology is appropriate for answering the question.

For the results section you chose to present the results as adjusted relative risk. Include the percentage values for outcomes in each BMI category as well. This can be done in the text. This relates back to the introduction where you start off with the overall risk of HDP as a percentage.

Even though Table 1 is big, include all the variables. For example, in the age category add the row for "18-34 years", for education add in "high school or more", etc.

Reconcile the labeling of the tables in the supplemental digital content. In the text of the article you refer to supplemental tables 2 and 3, yet in the download the tables are labeled 1 and 2.

For the discussion section I would suggest adding some comments. The theme of this study is the impact of obesity on pregnancy outcome and there is a continued rise of obesity in the US. Compare the data from Mbah's article (reference 21) with the current data. Mbah collected data from Missouri (not a thin state) from 1989 to 2005. At that time 78.6% of mothers were normal weight and 21.4% were obese. Your data for the entire US for 2014 to 2017 shows 45.9% non-obese and 54.1% obese. This emphasizes the continued increasing risk of HDP. What is interesting and you point this out, is that you saw about the same rate of early onset HDP and late onset HDP as reported in earlier studies despite the trend of increasing obesity.

This is also an opportunity to reinforce the current recommendation for low dose aspirin for pregnant women with a BMI greater than 30 kg/m2. This may raise the issue of a higher dose requirement for the heavier woman.

Reviewer #2: The authors performed a population based retrospective cohort study utilizing US Vital Statistics period-linked birth and infant death certificates between 2014 and 2017 to examined the relationship between maternal body

mass index and early and late onset hypertensive disorders of pregnancy (HDP).

Their data showed that the risk of early onset HDP was significantly higher in women with class I obesity (aRR 1.13), class II obesity (aRR 1.57) and class III obesity (aRR 2.18) compared to non-obese woman.The risk of late onset HDP was also increased. Class I (aRR 1.71), class II (a RR 2.60) and class III (aRR 3.93) compared to none obese women. In addition, the increase in adjusted relative risk paralleled the increase in maternal BMI.

The study adds to the existing data supporting the relationship between increased BMI and the risk of HDP. It is of particular interest since it is the first large population-based study examining the effect of maternal BMI and early onset HDP. Even though they were unable to distinguish gestational hypertension from preeclampsia in their data set, it is less likely that delivery would occur prematurely for gestational hypertension. Hence their findings on early onset disease is more likely due to preeclampsia rather than gestational hypertension.

This reviewer has two minor questions:

1. Why did they use BMI at delivery instead of pre-pregnancy BMI? It appears that pre-pregnancy BMI was available and other studies they site used pre-pregnancy weight for the analysis.

2. Line 140 to 142: Rates of gestational weight gain above IOM recommendations were lower in the non-obese group (40.2%) 142 compared to all classes of obesity (74.1%, 73.4%, and
68.2% for classes 1,2 and 3, respectively). It would be of interest to examine the correlation between gestational wt gain and the risk of early onset HDP.

The tables and figures appear appropriate as are the references.

Reviewer #3: A population-based, retrospective cohort study using U.S. Vital Statistics period-linked birth and infant death certificates from 2014-2017. Singleton, non anomalous pregnancies delivering between 24-41 completed weeks gestation were included.

Precis: Well stated

Abstract: Objective: To evaluate the relationship of maternal body mass index at delivery on rates of early (<34 weeks) and late onset (>34 weeks) hypertensive disorders of pregnancy (HDP).This is consistent throughout the paper.

Hypothesis is well stated

Results are well presented in Tables and Figures

Excellent discussion of limitations and biologic plausibility

STATISTICAL EDITOR'S COMMENTS:

1. lines 78-80: Should include a reference and concise description of the unified coding and quality control that would ensure that the ascertainment of BMI and HTN (especially those two variables) is accurate. Was the same criteria used for diagnosis of HTN for each of the study years?

2. lines 151, 155, 156: The Supplemental Tables are only labelled as 1 and 2, not as 2 and 3. Need to clarify. Also, the supplemental Table titles "rates of delivery with hypertensive disorder of pregnancy" should be clarified to include "rates of hypertensive disorder per 1,000 live births, with crude and adjusted relative risks using 18.5-29.9 kg/m² cohort as referent"

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:
A. OPT-IN: Yes, please publish my point-by-point response letter.
B. OPT-OUT: No, please do not publish my point-by-point response letter.

2. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will

be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

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

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

4. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric and gynecology data definitions at https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

5. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.

6. 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).

7. Provide a short title of no more than 45 characters (40 characters for case reports), including spaces, for use as a running foot.

8. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

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

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

10. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

11. In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.

If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts.

Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1%").

12. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.
13. The Journal's Production Editor has the following comments on the figures in your manuscript:

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When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint.

When you submit your revision, art saved in a digital format should accompany it. Please upload each figure as a separate file to Editorial Manager (do not embed the figure in your manuscript file).

If the figures were created using a statistical program (eg, STATA, SPSS, SAS), please submit PDF or EPS files generated directly from the statistical program.

Figures should be saved as high-resolution TIFF files. The minimum requirements for resolution are 300 dpi for color or black and white photographs, and 600 dpi for images containing a photograph with text labeling or thin lines.

Art that is low resolution, digitized, adapted from slides, or downloaded from the Internet may not reproduce.

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

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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 Apr 08, 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

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March 19, 2020

Nancy C. Chescheir, MD
The Editor
Obstetrics & Gynecology
409 12th Street, SW
Washington, DC 20024-2188

RE: Manuscript Number ONG-20-351
Maternal Obesity and the Risk of Early and Late Onset Hypertensive Disorders of Pregnancy

Dear Dr. Chescheir:

Thank you kindly for considering the above-titled manuscript for publication in *Obstet Gynecol*.

We appreciate the reviewer's comments and we have extensively revised the manuscript.

For your consideration, we are attaching:

1. Red-ink copy of the manuscript
2. A clean copy of the revised manuscript

Please note that the lines referenced in our responses below pertain to the red-ink copy of the manuscript.

As a lead author, 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 (and, if relevant, registered) have been explained. Additionally, I affirm we followed the STROBE guideline.

[redacted]

Sincerely,

Matthew J. Bicocca, MD
Department of Obstetrics, Gynecology and Reproductive Sciences
McGovern Medical School at The University of Texas Health Science Center at Houston
[redacted]

Reviewer #1

For the results section you chose to present the results as adjusted relative risk. Include the percentage values for outcomes in each BMI category as well. This can be done in the text. This relates back to the introduction where you start off with the overall risk of HDP as a percentage.

We thank the reviewer for this comment and agree with the importance of expressing crude as well as adjusted values. Included in Table 2, along with the adjusted relative risk, are the crude rates with 95% CI. We expressed this rates as per 1,000 lives births due to the rarity of early onset disease.

Even though Table 1 is big, include all the variables. For example, in the age category add the row for "18-34 years", for education add in "high school or more", etc.

We thank the reviewer for their assistance in clarifying the data presented in our large demographics table. We have now included all rows when 3 or more categories are present. Dichotomous variables have been left as a single row.

Reconcile the labeling of the tables in the supplemental digital content. In the text of the article you refer to supplemental tables 2 and 3, yet in the download the tables are labeled 1 and 2.

Thank you for noticing this discrepancy. This has been corrected in the text of the article.

For the discussion section I would suggest adding some comments. The theme of this study is the impact of obesity on pregnancy outcome and there is a continued rise of obesity in the US. Compare the data from Mbah's article (reference 21) with the current data. Mbah collected data from Missouri (not a thin state) from 1989 to 2005. At that time 78.6% of mothers were normal weight and 21.4% were obese. Your data for the entire US for 2014 to 2017 shows 45.9% non-obese and 54.1% obese. This emphasizes the continued increasing risk of HDP. What is interesting and you point this out, is that you saw about the same rate of early onset HDP and late onset HDP as reported in earlier studies despite the trend of increasing obesity.
This is also an opportunity to reinforce the current recommendation for low dose aspirin for pregnant women with a BMI greater than 30 kg/m2. This may raise the issue of a higher dose requirement for the heavier woman.

The above two concerns are appreciated. We have added the below paragraph to our discussion (Lines 202-210) to address the use of aspirin in prevention of HDP, and also to opine on possible reasons for the slow increase in rates of HDP despite the obesity epidemic.

"The increasing prevalence of obesity in the U.S. and worldwide highlights the importance of our findings and underscores the need for prevention of HDP in this population.[28,34] When initiated at < 16 weeks, low-dose aspirin is effective in preventing HDP in high-risk populations, but questions regarding appropriate dosing in the obese population remain unanswered.[35-37] Once at term, induction of labor at 39 weeks prevents development of HDP in low-risk nulliparous women,[38] and there have been progressively fewer late-term and post-term

pregnancies since the 1980's.[39] These interventions, along with changes in diagnostic criteria, may contribute to the relatively slow increase in rates of HDP in the face of the obesity epidemic.[40]"

Reviewer # 2:

Why did they use BMI at delivery instead of pre-pregnancy BMI? It appears that pre-pregnancy BMI was available and other studies they site used pre-pregnancy weight for the analysis.

We appreciate this question as it represents a source of variation in the literature. In our cited studies, maternal BMI is derived either from maternal recall (either at the first prenatal visit or at the time of delivery), from recorded values at the first prenatal visit, or from recorded values during the delivery admission. We chose to use BMI at delivery in order to use a measured value and help minimize recall bias. We have added this to our discussion (Lines 226-228) as shown below:

"Similar to Durst et al., we limited our analysis to maternal BMI at delivery.[19] While pre-pregnancy BMI is available in the U.S. Vital Statistics Database, it is derived from maternal recall during the delivery admission and is therefore subject to recall bias.[41]"

Line 140 to 142: Rates of gestational weight gain above IOM recommendations were lower in the non-obese group (40.2%) 142 compared to all classes of obesity (74.1%, 73.4%, and 68.2% for classes 1,2 and 3, respectively). It would be of interest to examine the correlation between gestational wt gain and the risk of early onset HDP.

We appreciate and agree with the reviewer's comment and would be interested not only in the impact of gestational weight gain on rates of early onset hypertensive disease of pregnancy, but also on the interplay between pre-pregnancy BMI, gestational weight gain, delivery BMI, and HDP. So, while relevant to our topic and of clinical significance, we believe this question is outside the focus of our manuscript and would be better addressed as a separate study.

Statistical Editor's Comments:

lines 78-80: Should include a reference and concise description of the unified coding and quality control that would ensure that the ascertainment of BMI and HTN (especially those two variables) is accurate. Was the same criteria used for diagnosis of HTN for each of the study years?

We appreciate the statistical editor's recommendation and have added two references citing the methodology used by the hospital, CDC, and NCHS for compilation of demographics and outcomes for U.S. Vital Statistics data. Additionally, to minimize variation used for diagnosis of HTN in all study years, we included in our references the 2003 revision of the birth certificate

form (which was used for all study years) as well as a brief discussion on the recently amended definitions to hypertensive disease provided by the ACOG Task Force. These changes can be seen in lines 91-95 and are included below.

“By limiting our analysis to births from 2014-2017 reported using the 2003 revision, we sought to minimize the variations in reported demographics and outcomes,[26] and also to standardize the diagnosis of hypertensive disease following the release of the Hypertension in Pregnancy Task Force Report by the American College of Obstetricians and Gynecologists in November 2013.[27]”

lines 151, 155, 156: The Supplemental Tables are only labelled as 1 and 2, not as 2 and 3. Need to clarify. Also, the supplemental Table titles "rates of delivery with hypertensive disorder of pregnancy" should be clarified to include "rates of hypertensive disorder per 1,000 live births, with crude and adjusted relative risks using 18.5-29.9 kg/m² cohort as referent"

We have amended the labels and titles for the supplemental tables. Thank you for bringing this to our attention.