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: Feb 20, 2020
To: "Janet M. Catov" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-120

RE: Manuscript Number ONG-20-120

Early Pregnancy Blood Pressure Elevations and Risk for Maternal and Neonatal Morbidity

Dear Dr. Catov:

Your manuscript has been reviewed by the Editorial Board and by special expert referees. Although it is judged not acceptable for publication in Obstetrics & Gynecology in its present form, we would be willing to give further consideration to a revised version.

If you wish to consider revising your manuscript, you will first need to study carefully the enclosed reports submitted by the referees and editors. Each point raised requires a response, by either revising your manuscript or making a clear and convincing argument as to why no revision is needed. To facilitate our review, we prefer that the cover letter include the comments made by the reviewers and the editor followed by your response. The revised manuscript should indicate the position of all changes made. We suggest that you use the "track changes" feature in your word processing software to do so (rather than strikethrough or underline formatting).

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Mar 12, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: In the manuscript, "Early pregnancy blood pressure elevations and risk for maternal and neonatal morbidity," the authors conducted a clinical cohort study utilizing a large database from a single institution. They applied the AHA/ACC 2017 recommendations for classification of blood pressure and stratified pregnant women by their average systolic blood pressure and average diastolic blood pressure with at least 2 readings prior to 20 weeks' gestation into 4 categories: normal, elevated blood pressure, stage 1 hypertension and stage 2 hypertension. The study included 18,162 women with singleton pregnancies with complete data who delivered at their institution between January 1, 2015 and June 30, 2018. The following are comments regarding their study:

1. In the manuscript, the selection process that resulted in the 18,162 patients that composed the final cohort is well-described. It is not necessary to include both the lengthy description in the text and the flow chart in Figure 1.

2. Table 1 includes characteristic of the 4 groups. Although the difference in the average SBP and average DBP before 20 weeks in the 4 groups is statistically significant, how do you explain the similarity between the elevated, stage 1 and stage 2 hypertension groups. In particular, the average SBP and average DBP in the Stage 1 and Stage 2 groups are both below the cutoff criteria necessary to be included in at least Stage 1 hypertension (Stage 1 SBP 124.8 and DBP 79.7; Stage 2 SBP 128.3 and DBP 77.1).

3. Numerous times in the text, the Elevated Blood Pressure group is stated to have increased overall maternal morbidity. However, in Table 2, the aOR for maternal morbidity is not significant (1.06, CI 0.98, 1.32) and, similarly, maternal morbidity is not significant for either the black or white participants in the elevated blood pressure group. It is correct that the maternal morbidity is significantly increased in the Stage 1 and Stage 2 groups.

Reviewer #2: Single center, retrospective study (large sample, >18,000) from McGhee Womens' MOMI database. Investigate whether women with elevated BP, stage 1, or stage 2 hypertension in early pregnancy exhibit an increased risk for preeclampsia and adverse maternal or neonatal outcomes compared to normotensive women. The primary outcome was preeclampsia, and secondary outcomes included maternal morbidity and neonatal morbidity composite scores

Objective well stated

Methods : Can you explain why previous preeclampsia, renal disease, were not addressed as obstetric risk factors in Table

1. Given that more than half the women were parous, previous preeclampsia would place her at very high risk the next pregnancy. What was your reasoning for not simply using nulliparous women?

Curious why you didn't use all hypertensive diseases of pregnancy as an outcome. Example severe gestational hypertension without proteinuria/ Although I see this in the CPT codes in Supplement I do not see this in the Table. I do think the definition that used for preeclampsia or gestational hypertension should be defined, unless you cant because this is a data base study?? Stage 2 would clearly be superimposed preeclampsia again I see this in the Supplemet but remain confused how this was used in the Tables

Why did you choose these three maternal comorbidities ? What was the reasoning? The maternal composite outcome included placental abruption, gestational diabetes, or severe maternal morbidity. Many of the SMM are related to hemorrhage, embolism, primary heart disease

Why did you choose these neonatal comorbidities ?What was your reasoning as to how they are related to hypertension? The neonatal composite outcome included at least one of the following: intrauterine fetal death after 20 weeks' gestation, neonatal death within 28 days of life, 5-minute Apgar less than 7, neonatal intensive care unit (NICU) admission, small-for-gestational age according to national birth weight standards,or preterm birth (gestational age < 37 weeks at delivery

Discussion about how these comorbidities are related to hypertension example an IUFD >20 weeks could be genetic, birth defects, umbilical cord, infection is needed

Results: Maternal composite morbidity stage 1 hypertension, and stage 2 hypertension were 1.14 [95%CI: 0.98, 1.32), 1.34 [95%CI: 1.09, 1.65], and 2.07 [95%CI: 1.71, 2.49] times higher, respectively, than the risk among women with normal blood pressure/ Clearly Maternal composite morbidity is not increased with elevated as CI crosses 1.0

Discussion
Line 243-244 "Moreover, to our knowledge, this is the largest study on the potential impact of the revised hypertension guidelines in early pregnancy." Dp not make these bold statement like "Largest" unless you specify your search strategy

Reviewer #3:

Abstract
45 - Recommend specifying that the odds are "adjusted odds", since subsequent sentence is using abbreviation of aOR.

53 - The sentence is not accurate because the risk of maternal morbidity in subjects with EBP was not elevated (aOR 1.14, 0.98-1.32). Only black participants had elevated risk (aOR 1.45, 1.08-1.94).

Introduction

Methods
118 - Since blood pressure is the only independent factor analyzed, the authors should describe the blood pressure measurement environment and technique such as: Who took the blood pressure and what level of training and expertise did they possess? What is the cuff size protocol? What was protocol for repeating a blood pressure, and which blood pressure was accepted in the MOMI database if multiple pressures were obtained? Which devices were used and how often calibrated? IF this information is not available, the authors should address this deficiency and the potentials for blood pressure inaccuracy in the discussion section.

132 - How did authors code severe gestational hypertension? As severe preeclampsia or as gestational hypertension?

136 - The authors should reconsider incorporating gestational diabetes (GDM) into their composite maternal morbidity, or report aOR for severe maternal morbidity (SMM) in Table 2 separately from gestational diabetes, rather than in the supplement. First of all, GDM is not a pathological consequence of preexisting hypertension or vascular dysfunction and its inclusion as a marker of adverse is puzzling. Secondly, the prevalence of GDM is heavily dependent on BMI and weight gain - which are covariates for the variable in study (blood pressure). Thirdly, the diagnosis of GDM is variably defined throughout the US, limiting its generalizability as a marker of adverse outcome for individual centers in US (the authors did not specify their criteria for GDM). Finally, the prevalence of GDM is higher than SMM and will obscure the analysis of other adverse outcomes that are biologically related to maternal hypertension.

Results
168 - "second delivery" is vague. Consider specifying "second delivery during study interval".

169 - Sentence is vague and confusing. Are the authors stating that they found birth records for their subjects in a State of Pennsylvania database that also recorded the gestational age at onset of prenatal care?

180 - This sentence is not correct, given that the frequency of African Amerian race did not increase serially with blood pressure category (28.8%, then 17.8%, then 36.0%). The frequency of African American race was actually lower in the Stage I HTN group than in the Normotensive group.

193 - This sentence is also incorrect. The aOR for Term preeclampsia was not significantly elevated in subjects with Elevated Blood Pressure (EBP).

194 - The authors state there was "…no evidence of effect modification by race…", and yet Table 2 appears to show a pattern of fewer significant associations, and lower aOR associations for African American participants than White participants for many of the outcomes in the study. The authors should consider reporting the multivariate analysis factor parameter and significance for "race" to prove definitively that what readers may see as a trend in Table 2 is not a significant pattern.

Discussion
222 - Again, it is incorrect to state that the EBP category was associated with maternal morbidity (aOR 1.14, 0.98-1.32, Table 2).

226 - It is incorrect to state that the study identified a new population of women at risk for maternal morbidity if their BP was 120-129 - This is the EBP group, and the adjusted risk for composite maternal morbidity on the cohort was not elevated. Furthermore, the only significant risk increase for preeclampsia among women with EBP was for preterm preeclampsia in African Americans (according to Table 2). Within the EBP category, 10 of 15 statistical comparisons were insignificant. By lumping all women with BP from 120-129 into one "at risk group", the authors are unnecessarily pushing the "at risk zone" to such a low blood pressure that providers and women may be overwhelmed with messaging. The authors should consider that because blood pressure is a continuous (albeit highly variable and unreliable) metric, it might theoretically be possible to document elevated risks of preeclampsia in any women with a blood pressure above some absolute lowest level. In this context, the use of categorical cutoffs is arbitrary and selective. Perhaps the authors could consider pointing out that the risk of preeclampsia in women with EBP was only slightly increased (29% above normals), and that the absolute risk remains small.

231 - Replace prophylaxis with prophylactic.

237 - The authors should eliminate the word "gestational" because the sentence reads as if the AHA/ACC Guidelines are intended to reclassify pregnant woment with EBP or Stage I Hypertension as "gestational hypertension". True gestational hypertension is still formally defined by ACOG as per the Practice Bulletin as new onset blood pressure > 140/90.

244 - Again, the study really only documented an elevated aOR for preeclampsia in African American women with preterm preeclampsia.

280 - Is this correct? Are the authors stating that 95% of participants with chronic hypertension had a chart review confirmed clinical diagnosis of preeclampsia? How do they explain that abnormal incidence of preeclampsia?

287 - Can the authors clarify what is meant by "systematically different". It is unclear what assumption about these patients is being made

287 - It is unclear what selection bias effect is being assumed - and what is meant by "more conservative estimate of primary and secondary outcomes." Does this mean a lower or higher aOR for adverse events?

302 - The authors should comment on the origin and especially the relevance of these new blood pressure criteria - considering the population and the outcomes from which they were generated (e.g - from mixed adult men and women with long term cardiovascular endpoints). Did the authors attempt to use their large database to generate their own best pregnancy specific blood pressure cutoffs with ROC and sensitivity analysis?

Figure 1 - Change "improbably" to "improbable".

STATISTICAL EDITOR COMMENTS:

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

General and Fig 1: The exclusion of > 10,000 deliveries due to either no prenatal record or < 2 prenatal visits before 20 wks gestation exlcudes > 1/3 of all eligible visits and is a potential source of bias in the analysis. Needs to be acknowledged as a limitation. Those cohorts should be compared with the others in terms of baseline characteristics and maternal and neonatal outcomes in order to place the potential bias in context.

lines 58-61: The 2017 AHA guidelines also describe in detail the procedure for accurate measurement of BP. Were those

procedures adhered to for all the pregnancies in this study?

All the findings are cited in terms of increased odds and adjusted odds, but this does not give the reader any context for the absolute risks involved. Need to provide a Table showing the absolute proportions of adverse outcomes among the four categories. For example, using the %s from Fig 2 and the totals for each group from Tables 1 or 2, the counts of preeclampsia among the normotensive accounts for about 1/2 of all pre-eclampsia cases. Aggregation of all HTN groups would therefore potentially miss 1/2 of all pre-eclampsia cases.

Table 1: Need to clarify for the reader that the stats used do not identify a specific group, but rather that stats test evaluates whether the allocation of variables among the 4 groups is random. It would be better to have compared each group pairwise with the referent group of normal BP.

Table 2: Need to clarify that all comparisons are vs the referent group with normal BP.

Suppl Table 3 is important enough to include in the main text.

EDITOR'S COMMENTS:

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

Line 35: The objective of the abstract should be a simple “To” statement without background information. Your “to” statement could be edited from the sentence starting on line 37. “To examine whether….”. In your methods section, pleas provide the source of your data. Is this from EMR data at a single institution? Please always spell out abbreviations on first use (BP, AHA, ACC for instance). This is true for the abstract, separate from the manuscript, where the abbreviations need to be spelled out on first use as well.

Line 40: Since some women, potentially those w/ pre-existing hypertension, may have more prenatal visits than those without, is there any bias introduced by averaging BP’s?

Please provide definitions of severe maternal morbidity and neonatal morbidity.

Results section - P Values vs Effect Size and Confidence Intervals:
While P values are a central part of inference testing in statistics, when cited alone, often the strength of the conclusion can be misunderstood. Whenever possible, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.
This is true for the abstract as well as the manuscript, tables and figures.

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

We ask that you provide crude OR’s followed by adjusted OR’s for all relevant variables. It seems that lines 46 data are “adjusted for covariates” so should be adjusted OR’s. Please clarify, and as noted, provide crude OR’s first.

Please note that effect sizes (RR, OR), other than the aOR of preeclampsia in women w/ stage 2 hypertension, are within the zone of potential bias should be noted as weak. Those effect sizes in the zone of potential interest should be emphasized. (Ref: False alarms and pseudo-epidemics. The limitations of observational epidemiology. Grimes DA, Schulz KF. Ob Gyn 2012;120:920-7). This should be commented upon in your conclusions and the paper.

Line 75: Perhaps a little picky here but I think relevant. Women’s BP hasn’t changed due to these changes, we are just calling it something different. Would you consider a change her “more women will enter pregnancy with the diagnosis of preexisting hypertension”?

Line 87: You’ve already asserted that it is known that women with stage 2 hyperension are at elevated risks, so is it necessary to include this goal in your aims?
Line 92: You’ve indicated earlier that you anticipate a stepwise association (line 91). The last part of this sentence does not seem to indicate the stepwise association. Perhaps on line 93..”will have increasing risk of preeclampsia ….?

Line 96-98 would be a good sentence for your abstract methods.

Line 109: Any gestational age limits? Particularly interested in if there is a lower bound.

If women were on anti-hypertensive meds but didn't have a diagnostic code for hypertension, how did you handle them?

Line 139: How did you define prolonged post partum length of stay?

The use of 3 different definitions of severe maternal morbidity is a bit unusual. Is the composite any finding in any of the 3? Do you report the different components separately?

Line 184: As noted above, provide absolute values and crude OR's, with 95% CI's before providing aOR'

Line 187+ : In the abstract, you report your ORs' to 1 decimals and here, you report them to 2. Please be consistent: I'm agnostic about which you choose but use the same in both places.

Table 2 please define the referent group in the table legend.

Lines 229: What interventions?

Line 230: Is this stage 1 by 2017 definitions?

Line 243. Please edit out the "to our knowledge" or similar wording. As the readers cannot gauge the depth and breadth of your knowledge, this phrase does not add significant meaning. You can either reference your literature search details (database searched and search terms used) that informed your knowledge, or you could say something noting that your cited references provide limited information about this point. As well, this is known as a primacy claim: yours is the first, biggest, best study of its kind. In order to make such a claim, please provide the databases you have searched (PubMED, Google Scholar, EMBASE for example), the date ranges, and the search terms used. If not done, please edit it out of the paper.

Line 250: could you expand here? I'm not sure what you mean by "reassessment", for instance. It seems to me you are talking about preconception or interpregnancy care that is focused on addressing modifiable risk factors for hypertension through lifestyle changes. Most notably, this would likely be obesity.

Line 256: In this paragraph you a mixing non-pregnancy and prenatal care topics. For this sentence, are you referencing the prenatal care time period (noted to begin on line 252) or interventions pre pregnancy)? I really recommend that you separate this whole section by the time period you wish to address rather than mixing them up like this.

Line 265: For clarity, aspirin use is for prevention of preterm preeclampsia.

Line 277: Spell out MOMI throughout your paper.

Line 286: the bias introduced by this definition includes the issue of your transferred patients—many of whom may have been transferred due to hypertensive disease of pregnancy.

Line 297: rather than "clinical translation" perhaps "generalizability"?

Line 298: some of these women likely were on Bp meds so their BP's may have been iatrogenically lowered.

Line 303: It seems from your discussion, much of your findings are replications of prior studies. Do you think further replication is needed to establish the association between early BP measurements and later pregnancy complications? Or is this enough to warrant intervention trials? It seems the rest of your concluding paragraph is suggesting that your paper adds sufficiently to prior work that it's fine to move ahead w/ interventions.

Figure 2: What are the horizontal bars on the graph? Please explain in the legend.

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. Our journal requires that all evidence-based research submissions be accompanied by a transparency declaration statement from the manuscript's lead author. The statement is as follows: "The lead author* affirms 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." *The manuscript's guarantor.

If you are the lead author, please include this statement in your cover letter. If the lead author is a different person, please ask him/her to submit the signed transparency declaration to you. This document may be uploaded with your submission in Editorial Manager.

4. Please submit a completed STROBE checklist.

Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluations of health interventions (ie, CHEERS), quality improvement in health care studies (ie, SQUIRE 2.0), and studies reporting results of Internet e-surveys (CHERRIES). Include the appropriate checklist for your manuscript type upon submission. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at http://ong.editorialmanager.com. In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, CHEERS, SQUIRE 2.0, or CHERRIES guidelines, as appropriate.

5. 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.

6. 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.

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

* All financial support of the study must be acknowledged.
* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.
* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

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

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

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

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

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

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

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

12. Line 243: We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If on the other hand, it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

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

14. 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.

15. Figures 1 and 2 may be resubmitted as-is with the revision.

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

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

17. If you choose to revise your manuscript, please submit your revision through Editorial Manager at http://ong.editorialmanager.com. Your manuscript should be uploaded in a word processing format such as Microsoft Word. Your revision's cover letter should include the following:

* A confirmation that you have read the Instructions for Authors (http://edmgr.ovid.com/ong/accounts/authors.pdf), and
* A point-by-point response to each of the received comments in this letter.

If you submit a revision, we will assume that it has been developed in consultation with your co-authors and that each author has given approval to the final form of the revision.

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Mar 12, 2020, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,
Nancy C. Chescheir, MD

Editor-in-Chief

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

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University of Pittsburgh

SCHOOL OF MEDICINE
Department of Obstetrics, Gynecology and Reproductive Sciences

March 12, 2020

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

Dear Dr. Chescheir:

Enclosed please find our revised manuscript for consideration for publication in *Obstetrics & Gynecology* entitled: "**Early Pregnancy Blood Pressure Elevations and Risk for Maternal and Neonatal Morbidity**". We thank you for the opportunity to improve our manuscript and have addressed each comment in the attached Response to Reviewer document.

Recently, you interviewed the first author of this paper, **Elizabeth F. Sutton, PhD**, for your podcast as an editor's pick for our other publication relevant to this topic. Dr. Sutton mentioned you had expressed an interest in seeing our paper for this submission. We appreciate your interest in our work and the importance of early pregnancy blood pressure for maternal and neonatal health.

I certify that this manuscript is being submitted only to *Obstetrics & Gynecology*. It will not be submitted elsewhere while under consideration, and it has not been published elsewhere. I further certify that should the manuscript be published in the journal that it will not be published elsewhere in any form without the permission of the editors.

The authors of this manuscript have no conflicts of interest in the subject matter discussed, and all authors have made a substantial contribution to this work. This study was approved by the University of Pittsburgh Institutional Review Board.

As the senior and corresponding author, I affirm that this manuscript is an honest, accurate, and transparent account of the study being reported, and that we have addressed every reviewer and editor comment. No important aspects of the study have been omitted. We have reviewed the Instructions for Authors. A completed STROBE statement is included with the responses to reviewers. We also choose to opt-in to have our point-by-point response to the revisions as supplemental digital content to increase transparency around the peer-review process.

Thank you for your consideration of our manuscript.

Sincerely,

Janet M. Catov, PhD, MS
Associate Professor of Obstetrics, Gynecology and Reproductive Sciences
Associate Professor of Epidemiology & CTSI
Director, Health and Clinical Research Magee-Womens Research Institute
[redacted]

[redacted]

REVIEWER COMMENTS:

Reviewer #1: In the manuscript, "Early pregnancy blood pressure elevations and risk for maternal and neonatal morbidity," the authors conducted a clinical cohort study utilizing a large database from a single institution. They applied the AHA/ACC 2017 recommendations for classification of blood pressure and stratified pregnant women by their average systolic blood pressure and average diastolic blood pressure with at least 2 readings prior to 20 weeks' gestation into 4 categories: normal, elevated blood pressure, stage 1 hypertension and stage 2 hypertension. The study included 18,162 women with singleton pregnancies with complete data who delivered at their institution between January 1, 2015 and June 30, 2018. The following are comments regarding their study:

1. In the manuscript, the selection process that resulted in the 18,162 patients that composed the final cohort is well-described. It is not necessary to include both the lengthy description in the text and the flow chart in Figure 1.

We thank the reviewer for this comment. As other reviewers asked for more details about the methods and the patients who were excluded from the analysis, we have left the text as is. The figure is available for readers who prefer a visual representation of the cohort selection.

2. Table 1 includes characteristic of the 4 groups. Although the difference in the average SBP and average DBP before 20 weeks in the 4 groups is statistically significant, how do you explain the similarity between the elevated, stage 1 and stage 2 hypertension groups. In particular, the average SBP and average DBP in the Stage 1 and Stage 2 groups are both below the cutoff criteria necessary to be included in at least Stage 1 hypertension (Stage 1 SBP 124.8 and DBP 79.7; Stage 2 SBP 128.3 and DBP 77.1).

Thank you for this comment. In the stage 2 hypertension group, the majority of patients were categorized based on diagnostic codes and not by their BP, which we hypothesize is due to a combination of treatment (lifestyle changes or medication) and the physiologic changes of early pregnancy. Additionally, the average BPs in each group are due to the definition of stage 1 and stage 2 hypertension, such that ***either*** the systolic or the diastolic BP criterion needs to be met. To help clarify how women were categorized, we have added a supplemental table (Appendix 4) that shows how women were diagnosed within each category and the mean SBP and DBP for women who were diagnosed by each criterion. We have also addressed this point in the Results and Discussion.

3. Numerous times in the text, the Elevated Blood Pressure group is stated to have increased overall maternal morbidity. However, in Table 2, the aOR for maternal morbidity is not significant (1.06, CI 0.98, 1.32) and, similarly, maternal morbidity is not significant for either the black or white participants in the elevated blood pressure group. It is correct that the maternal morbidity is significantly increased in the Stage 1 and Stage 2 groups.

After reading the comments from all the reviewers, we have chosen to disaggregate our composite maternal outcome in this revised manuscript. Instead, we present severe maternal morbidity, placental abruption, and GDM as individual secondary outcomes, as each is clinically important. We now report that severe maternal morbidity is only increased in the Stage 2 hypertension group.

Reviewer #2: Single center, retrospective study (large sample, >18,000) from McGhee Womens' MOMI database. Investigate whether women with elevated BP, stage 1, or stage 2 hypertension in early pregnancy exhibit an increased risk for preeclampsia and adverse maternal or neonatal outcomes compared to normotensive women. The primary outcome was preeclampsia, and secondary outcomes included maternal morbidity and neonatal morbidity composite scores

Objective well stated

Methods : Can you explain why previous preeclampsia, renal disease, were not addressed as obstetric risk factors in Table 1.

We agree that a history of preeclampsia and renal disease are important variables to consider within this topic, but unfortunately, prior preeclampsia and renal disease history were not available in our database for this study, and thus we are unable to use obstetric history for risk stratification.

[redacted]

Given that more than half the women were parous, previous preeclampsia would place her at very high risk the next pregnancy. What was your reasoning for not simply using nulliparous women?

In regard to using only nulliparous women, Hauspurg et al., 2019 (Hauspurg A, Sutton EF, Catov JM, Caritis SN. Aspirin Effect on Adverse Pregnancy Outcomes Associated With Stage 1 Hypertension in a High-Risk Cohort. Hypertension 2018 Jul;72(1):202-7.) recently demonstrated that elevated BP and stage 1 HTN are associated with an increased risk of preeclampsia among nulliparous women in a research cohort. We included nulliparous and parous women to make our study more generalizable to an overall obstetric population. We did control for parity in our adjusted analyses.

Curious why you didn't use all hypertensive diseases of pregnancy as an outcome. Example severe gestational hypertension without proteinuria/ Although I see this in the CPT codes in Supplement I do not see this in the Table. I do think the definition that used for preeclampsia or gestational hypertension should be defined, unless you cant because this is a data base study?? Stage 2 would clearly be superimposed preeclampsia again I see this in the Supplemet but remain confused how this was used in the Tables

As more women enter pregnancy with chronic hypertension, we anticipate a decrease in the overall incidence of gestational hypertension, as women with chronic hypertension are not given a diagnosis of gestational hypertension. Therefore, we chose to focus on preeclampsia, which generally has more significant clinical implications than gestational hypertension. Additionally, all hypertensive disorders of pregnancy would not have been consistently diagnosed across groups (since GHTN would only be included in the normal, elevated, and stage 1 HTN groups).

Although the diagnostic code for severe gestational hypertension was used to identify women with gestational hypertension, the gestational hypertension variable is coded as binary in the database, and we could not disentangle severe gestational hypertension from gestational hypertension. Therefore, severe gestational hypertension is not included in the primary outcome. Superimposed preeclampsia, on the other hand, is coded as preeclampsia and is included in the primary outcome.

The Reviewer is correct that because this is a database study generated from a clinical cohort, we cannot determine exactly what criteria were applied to each patient to provide the diagnosis of a hypertensive disorder. We now state this limitation more directly in the discussion. In general, practitioners at our institution adhere to ACOG guidelines for the diagnosis of hypertensive disorders of pregnancy.

Why did you choose these three maternal comorbidities ? What was the reasoning? The maternal composite outcome included placental abruption, gestational diabetes, or severe maternal morbidity. Many of the SMM are related to hemorrhage, embolism, primary heart disease

We were interested in whether elevated BP and stage 1 hypertension are risk factors for obstetric and maternal morbidity, beyond their effects on preeclampsia risk. Given that the composite maternal outcome generated confusion during peer review, we have eliminated it and now present the maternal complications as separate secondary outcomes. Placental abruption was included because of its association with hypertension. Gestational diabetes was included because of prior work from our group demonstrating in a separate cohort that the risk of gestational diabetes is increased among women with stage 1 hypertension compared to normotensive women (Sutton EF, Hauspurg A, Caritis SN, Powers RW, Catov JM. Maternal Outcomes Associated With Lower Range Stage 1 Hypertension. Obstet Gynecol 2018 Oct;132(4):843-9). Severe maternal morbidity was included to encompass a broad range of complications, many of which are associated with preeclampsia/hypertension (e.g., pulmonary edema, seizure, ICU admission), and others of which are not directly associated with preeclampsia (e.g. sepsis, AFE).

Why did you choose these neonatal comorbidities ?What was your reasoning as to how they are related to hypertension? The neonatal composite outcome included at least one of the following: intrauterine fetal death after 20 weeks' gestation, neonatal death within 28 days of life, 5-minute Apgar less than 7, neonatal intensive care unit (NICU) admission, small-for-gestational age according to national birth weight standards,or preterm birth (gestational age < 37 weeks at delivery

As with maternal morbidity, we were interested in neonatal morbidity in general, as well as morbidity that is associated with preeclampsia and placental insufficiency. (e.g., SGA). We did not have information in our database on ultrasonographic estimated fetal weight data or fluid measurements, so we could not include fetal growth restriction or oligohydramnios in our analysis. Our choice of variables for the composite outcome was partly driven by the information that was available in our database, which is derived from the delivery record. The use of NICU admission as a component should capture specific neonatal complications including respiratory distress syndrome and interventricular hemorrhage, as those conditions are managed in the NICU.

Discussion about how these comorbidities are related to hypertension example an IUFD >20 weeks could be genetic, birth defects, umbilical cord, infection is needed

The reviewer is correct that we cannot determine from our database whether the IUFDs were due to hypertension or to other etiologies. There were only 7 IUFDs in our total cohort.

Results: Maternal composite morbidity stage 1 hypertension, and stage 2 hypertension were 1.14 [95%CI: 0.98, 1.32), 1.34 [95%CI: 1.09, 1.65], and 2.07 [95%CI: 1.71, 2.49] times higher, respectively, than the risk among women with normal blood pressure/ Clearly Maternal composite morbidity is not increased with elevated as CI crosses 1.0

We have revised the text and removed the composite maternal morbidity outcome.

Discussion
Line 243-244 "Moreover, to our knowledge, this is the largest study on the potential impact of the revised hypertension guidelines in early pregnancy." Dp not make these bold statement like "Largest" unless you specify your search strategy

This sentence has been removed from the text.

Reviewer #3:

Abstract
45 - Recommend specifying that the odds are "adjusted odds", since subsequent sentence is using abbreviation of aOR.

This change has been made in the abstract text.

53 - The sentence is not accurate because the risk of maternal morbidity in subjects with EBP was not elevated (aOR 1.14, 0.98-1.32). Only black participants had elevated risk (aOR 1.45, 1.08-1.94).

The text has been removed from the revised manuscript.

Introduction

Methods
118 - Since blood pressure is the only independent factor analyzed, the authors should describe the blood pressure measurement environment and technique such as: Who took the blood pressure and what level of training and expertise did they possess? What is the cuff size protocol? What was protocol for repeating a blood pressure, and which blood pressure was accepted in the MOMI database if multiple pressures were obtained? Which devices were used and how often calibrated? IF this information is not available, the authors should address this deficiency and the potentials for blood pressure inaccuracy in the discussion section.

In the Methods, we have revised the text to more clearly indicate that BP was measured per protocol of each individual clinic and not according to any research protocol. As such, the additional information requested by the reviewer is not available. While this can be viewed as a weakness, BP measurement was performed as is generally done in clinical practice and, therefore, the current study findings have applicability to clinical care. We have also expanded our discussion of this limitation in the Discussion.

[redacted]

Our use of average BP, rather than single highest BP, to classify women should minimize the impact of an erroneous blood pressure measurement.

132 - How did authors code severe gestational hypertension? As severe preeclampsia or as gestational hypertension?

Severe gestational hypertension was coded as gestational hypertension, not as preeclampsia.

136 - The authors should reconsider incorporating gestational diabetes (GDM) into their composite maternal morbidity, or report aOR for severe maternal morbidity (SMM) in Table 2 separately from gestational diabetes, rather than in the supplement. First of all, GDM is not a pathological consequence of preexisting hypertension or vascular dysfunction and its inclusion as a marker of adverse is puzzling. Secondly, the prevalence of GDM is heavily dependent on BMI and weight gain - which are covariates for the variable in study (blood pressure). Thirdly, the diagnosis of GDM is variably defined throughout the US, limiting its generalizability as a marker of adverse outcome for individual centers in US (the authors did not specify their criteria for GDM). Finally, the prevalence of GDM is higher than SMM and will obscure the analysis of other adverse outcomes that are biologically related to maternal hypertension.

Thank you for this comment. As suggested, we have reconsidered and eliminated our maternal morbidity composite, and we present our GDM results independently. We included GDM in our initial analysis because of our prior research demonstrating an association between stage 1 hypertension and GDM (Sutton EF, Hauspurg A, Caritis SN, Powers RW, Catov JM. Maternal Outcomes Associated With Lower Range Stage 1 Hypertension. Obstet Gynecol 2018 Oct;132(4):843-9.). We also added information in the Methods regarding the GDM diagnostic criteria that are used at our institution.

Results
168 - "second delivery" is vague. Consider specifying "second delivery during study interval".

This change has been made in the text.

169 - Sentence is vague and confusing. Are the authors stating that they found birth records for their subjects in a State of Pennsylvania database that also recorded the gestational age at onset of prenatal care?

Yes, our database is linked to a state database that contains all information that is collected from birth certificates. We did pull that information from the state birth records of the women in our initial cohort without prenatal care in our hospital system and determined that per their report, they received prenatal care. Thus, we concluded that they received their prenatal care outside of our system. This explanation has been clarified in the text.

180 - This sentence is not correct, given that the frequency of African Amerian race did not increase serially with blood pressure category (28.8%, then 17.8%, then 36.0%). The frequency of African American race was actually lower in the Stage I HTN group than in the Normotensive group.

The text has been corrected.

193 - This sentence is also incorrect. The aOR for Term preeclampsia was not significantly elevated in subjects with Elevated Blood Pressure (EBP).

The text has been corrected.

194 - The authors state there was "…no evidence of effect modification by race…", and yet Table 2 appears to show a pattern of fewer significant associations, and lower aOR associations for African American participants than White participants for many of the outcomes in the study. The authors should consider reporting the multivariate analysis factor parameter and significance for "race" to prove definitively that what readers may see as a trend in Table 2 is not a significant pattern.

We now include the p-value for the interaction term and the multivariate model parameter for race in the Results, as requested. While race is a significant covariate in the model, there is no evidence that the association between early BP and preeclampsia varies by maternal race.

[redacted]

Discussion
222 - Again, it is incorrect to state that the EBP category was associated with maternal morbidity (aOR 1.14, 0.98-1.32, Table 2).

We now conclude that only stage 2 hypertension is associated with severe maternal morbidity.

226 - It is incorrect to state that the study identified a new population of women at risk for maternal morbidity if their BP was 120-129 - This is the EBP group, and the adjusted risk for composite maternal morbidity on the cohort was not elevated. Furthermore, the only significant risk increase for preeclampsia among women with EBP was for preterm preeclampsia in African Americans (according to Table 2). Within the EBP category, 10 of 15 statistical comparisons were insignificant. By lumping all women with BP from 120-129 into one "at risk group", the authors are unnecessarily pushing the "at risk zone" to such a low blood pressure that providers and women may be overwhelmed with messaging. The authors should consider that because blood pressure is a continuous (albeit highly variable and unreliable) metric, it might theoretically be possible to document elevated risks of preeclampsia in any women with a blood pressure above some absolute lowest level. In this context, the use of categorical cutoffs is arbitrary and selective. Perhaps the authors could consider pointing out that the risk of preeclampsia in women with EBP was only slightly increased (29% above normals), and that the absolute risk remains small.

Thank you for this comment. In the revised manuscript, we have been more cautious in regard to our conclusion that there is a modest increase in preeclampsia risk among women with elevated BP. There have been other studies demonstrating excess risk in this group, thus we do feel it is important to add to that existing evidence. We recognize that BP is a continuous variable, and the categorical cutoffs are somewhat arbitrary. Given that the categories are what are now being recommended clinically, we want to determine what impact that categorization would have on our patient population.

231 - Replace prophylaxis with prophylactic.

This change has been made.

237 - The authors should eliminate the word "gestational" because the sentence reads as if the AHA/ACC Guidelines are intended to reclassify pregnant woment with EBP or Stage I Hypertension as "gestational hypertension". True gestational hypertension is still formally defined by ACOG as per the Practice Bulletin as new onset blood pressure > 140/90.

We have removed our reference to the Hu et al. paper in our revised manuscript as that paper reported results of a different clinical question.

244 - Again, the study really only documented an elevated aOR for preeclampsia in African American women with preterm preeclampsia.

We have modified our discussion of the race-stratified analysis.
280 - Is this correct? Are the authors stating that 95% of participants with chronic hypertension had a chart review confirmed clinical diagnosis of preeclampsia? How do they explain that abnormal incidence of preeclampsia?

This explanation was misworded and has been corrected in the revised manuscript. Of the women who were identified by diagnostic codes to have superimposed preeclampsia, 95% actually had a clinical diagnosis of superimposed preeclampsia on chart review. We did this chart review to validate our dataset.

287 - Can the authors clarify what is meant by "systematically different". It is unclear what assumption about these patients is being made

This phrase has been removed from the revised manuscript. We compared women who were included and excluded from the cohort and concluded that they were overall similar in baseline demographics (Appendix 1).

[redacted]

287 - It is unclear what selection bias effect is being assumed - and what is meant by "more conservative estimate of primary and secondary outcomes." Does this mean a lower or higher aOR for adverse events?

This section of the Discussion has also been revised, and that phrase was removed after we conducted the analysis now presented in Appendix 1.

302 - The authors should comment on the origin and especially the relevance of these new blood pressure criteria - considering the population and the outcomes from which they were generated (e.g - from mixed adult men and women with long term cardiovascular endpoints). Did the authors attempt to use their large database to generate their own best pregnancy specific blood pressure cutoffs with ROC and sensitivity analysis?

We clarified the wording in the Introduction to indicate that the data behind the new criteria are from an older adult population of both men and women. We reference the study by Yano et al (Yano Y, Reis JP, Colangelo LA, Shimbo D, Viera AJ, Allen NB, et al. Association of Blood Pressure Classification in Young Adults Using the 2017 American College of Cardiology/American Heart Association Blood Pressure Guideline With Cardiovascular Events Later in Life. JAMA 2018 Nov 6;320(17):1774-82.) that demonstrated that among young adults (a mixed population of men and women and black and white race), these new blood pressure criteria identify a population at risk for later-life cardiovascular disease. Our analysis was conducted to determine the relevance of the new criteria to reproductive-aged women/pregnancy. A sensitivity analysis to determine pregnancy-specific blood pressure criteria was beyond the scope of this manuscript.

Figure 1 - Change "improbably" to "improbable".

This change has been made in Figure 1.

STATISTICAL EDITOR COMMENTS:

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

General and Fig 1: The exclusion of > 10,000 deliveries due to either no prenatal record or < 2 prenatal visits before 20 wks gestation exlcudes > 1/3 of all eligible visits and is a potential source of bias in the analysis. Needs to be acknowledged as a limitation. Those cohorts should be compared with the others in terms of baseline characteristics and maternal and neonatal outcomes in order to place the potential bias in context.

Thank you for this suggestion. We now present the requested data for women who were excluded from the final cohort in Appendix 1, and we discuss the exclusion of patients in our discussion.

lines 58-61: The 2017 AHA guidelines also describe in detail the procedure for accurate measurement of BP. Were those procedures adhered to for all the pregnancies in this study?

We are unable to describe the protocols followed for BP measurement. We have clarified this in the Methods, and we have addressed its implications in our Discussion. (See also Review #3 comment).

All the findings are cited in terms of increased odds and adjusted odds, but this does not give the reader any context for the absolute risks involved. Need to provide a Table showing the absolute proportions of adverse outcomes among the four categories. For example, using the %s from Fig 2 and the totals for each group from Tables 1 or 2, the counts of preeclampsia among the normotensive accounts for about 1/2 of all pre-eclampsia cases. Aggregation of all HTN groups would therefore potentially miss 1/2 of all pre-eclampsia cases.

We have added the incidence and frequencies of our outcomes to Tables 1 and 2 and have included the referent group.

[redacted]

Table 1: Need to clarify for the reader that the stats used do not identify a specific group, but rather that stats test evaluates whether the allocation of variables among the 4 groups is random. It would be better to have compared each group pairwise with the referent group of normal BP.

We have added the pairwise comparisons with the referent group, in addition to reporting the p-value for the allocation of variables among the 4 groups.

Table 2: Need to clarify that all comparisons are vs the referent group with normal BP.

The table has been edited to make this clarification.

Suppl Table 3 is important enough to include in the main text.

Thank you for this suggestion. We have moved the maternal morbidity, gestational diabetes, and placental abruption data to the main text. As the neonatal composite score was only significant for the stage 2 hypertension group, we still report the individual components of the neonatal composite in the Supplemental material.

EDITOR'S COMMENTS:

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

Line 35: The objective of the abstract should be a simple “To” statement without background information. Your “to” statement could be edited from the sentence starting on line 37. “To examine whether….”. In your methods section, pleas provide the source of your data. Is this from EMR data at a single institution? Please always spell out abbreviations on first use (BP, AHA, ACC for instance). This is true for the abstract, separate from the manuscript, where the abbreviations need to be spelled out on first use as well.

We have revised our objective, clarified our source of data, and ensured all abbreviations are spelled out on first use.

Line 40: Since some women, potentially those w/ pre-existing hypertension, may have more prenatal visits than those without, is there any bias introduced by averaging BP’s?

Women in the stage 2 group did have slightly more visits than women in other BP groups (3.3 vs 2.8-3.0). We controlled for number of prenatal visits in our adjusted analysis. We used average BP both because that is how the ACC/AHA guidelines recommend determining HTN diagnosis and because it minimized the impact of an erroneous BP measurement, since BP was not measured according to a research protocol in our study.

Please provide definitions of severe maternal morbidity and neonatal morbidity.

Do to word limit restrictions, we are unable to provide these definitions within the abstract.

Results section - P Values vs Effect Size and Confidence Intervals:
While P values are a central part of inference testing in statistics, when cited alone, often the strength of the conclusion can be misunderstood. Whenever possible, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.
This is true for the abstract as well as the manuscript, tables and figures.

[redacted]

We have reported odds ratios with confidence intervals where ever possible. We do use p-values to compare baseline demographics of our cohort.

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

We have added the incidence and frequency of each outcome to Tables 2 and 3.

We ask that you provide crude OR's followed by adjusted OR's for all relevant variables. It seems that lines 46 data are "adjusted for covariates" so should be adjusted OR's. Please clarify, and as noted, provide crude OR's first.

Due to word count limitations in the abstract, we only report adjusted ORs, but we provide the crude and adjusted ORs in the Results and Tables.

Please note that effect sizes (RR, OR), other than the aOR of preeclampsia in women w/ stage 2 hypertension, are within the zone of potential bias should be noted as weak. Those effect sizes in the zone of potential interest should be emphasized. (Ref: False alarms and pseudo-epidemics. The limitations of observational epidemiology. Grimes DA, Schulz KF. Ob Gyn 2012;120:920-7). This should be commented upon in your conclusions and the paper.

We acknowledge that some of the increased risk reported in our study, particularly for the elevated BP group, is modest. That being said, we see a "dose-response" effect with increasing odds ratios by BP category, which adds credibility to our findings. Moreover, there are now several studies reporting similar findings in research cohorts, thus we do think that our reported observations are real. We have addressed this limitation in our revised Discussion. We note that several aspects of Hill's criteria of causality (as described in the Grimes, et al paper noted by the reviewer) are achieved in our study: strength of association (most OR >2 in a cohort study); consistency of observation (elevated BP associated with preeclampsia in our cohort and in other cohorts); dose response (as noted); temporality (all BP measured prior to preeclampsia diagnosis); and coherence (BP is continuous and thus risk of preeclampsia is plausibly related to women with modest elevations.

Line 75: Perhaps a little picky here but I think relevant. Women's BP hasn't changed due to these changes, we are just calling it something different. Would you consider a change her "more women will enter pregnancy with the diagnosis of preexisting hypertension"?

This change has been made in the text.

Line 87: You've already asserted that it is known that women with stage 2 hyperension are at elevated risks, so is it necessary to include this goal in your aims?

We removed stage 2 hypertension from our aims. We included it in our analysis so that we could compare the level of risk across BP categories.

Line 92: You've indicated earlier that you anticipate a stepwise association (line 91). The last part of this sentence does not seem to indicate the stepwise association. Perhaps on line 93.."will have increasing risk of preeclampsia ….?

This change has been made in the text.

Line 96-98 would be a good sentence for your abstract methods.

Thank you for this suggestion. We have rewritten the methods section of the abstract.

Line 109: Any gestational age limits? Particularly interested in if there is a lower bound.

The lower gestational age limit was 20 weeks' gestation, and this limit has been added to the description of the database in the Methods.

[redacted]

If women were on anti-hypertensive meds but didn't have a diagnostic code for hypertension, how did you handle them?

Our database does not include information on patient medications. If women with chronic hypertension did not have a diagnostic code for hypertension and did not meet BP criteria for hypertension, then they were not identified as hypertensive. They would have been classified according to their early pregnancy blood pressure. The limitations of the database are discussed in more detail in the revised discussion.

Line 139: How did you define prolonged post partum length of stay?

This definition was previously provided in our supplemental information but is now also stated in the Methods. As recommended by Main et al. (Main EK, Abreo A, McNulty J, Gilbert W, McNally C, Poeltler D, et al. Measuring severe maternal morbidity: validation of potential measures. Am J Obstet Gynecol 2016 May;214(5):643.e1-.e10), we determined the mean and SD postpartum LOS for women at our hospital during the study time period, stratified by mode of delivery (vaginal or Cesarean). Women with a LOS more than 3 SD above the mean for their particular mode of delivery were considered to have a prolonged LOS.

The use of 3 different definitions of severe maternal morbidity is a bit unusual. Is the composite any finding in any of the 3? Do you report the different components separately?

There is no universal screening definition of severe maternal morbidity, and gold standard diagnosis requires detailed chart review. Thus, we chose the most expansive screening definition, outlined by Main et al (Main EK, Abreo A, McNulty J, Gilbert W, McNally C, Poeltler D, et al. Measuring severe maternal morbidity: validation of potential measures. Am J Obstet Gynecol 2016 May;214(5):643.e1-.e10), for our analysis. Patients were considered to have the outcome if they met any one of the three criteria.

Line 184: As noted above, provide absolute values and crude OR's, with 95% CI's before providing aOR'

Crude ORs have been added throughout the manuscript.

Line 187+ : In the abstract, you report your ORs' to 1 decimals and here, you report them to 2. Please be consistent: I'm agnostic about which you choose but use the same in both places.

The Abstract was revised so that we use two decimal places throughout the manuscript.

Table 2 please define the referent group in the table legend.

The table has been edited to include the referent group for each row.

Lines 229: What interventions?

We have changed the wording to indicate that women might benefit from increased surveillance from preeclampsia. We are not recommending specific interventions (antenatal surveillance, ldASA)

Line 230: Is this stage 1 by 2017 definitions?

Yes, and this sentence has been clarified in the manuscript.

Line 243. Please edit out the "to our knowledge" or similar wording. As the readers cannot gauge the depth and breadth of your knowledge, this phrase does not add significant meaning. You can either reference your literature search details (database searched and search terms used) that informed your knowledge, or you could say something noting that your cited references provide limited information about this point. As well, this is known as a primacy claim: yours is the first, biggest, best study of its kind. In order to make such a claim, please provide the databases you have searched (PubMED, Google Scholar, EMBASE for example), the date ranges, and the search terms used. If not done, please edit it out of the paper.

This sentence has been removed from the manuscript.

[redacted]

Line 250: could you expand here? I'm not sure what you mean by "reassessment", for instance. It seems to me you are talking about preconception or interpregnancy care that is focused on addressing modifiable risk factors for hypertension through lifestyle changes. Most notably, this would likely be obesity.

We are referring to optimization of modifiable cardiovascular risk factors, and we have clarified this text.

Line 256: In this paragraph you a mixing non-pregnancy and prenatal care topics. For this sentence, are you referencing the prenatal care time period (noted to begin on line 252) or interventions pre pregnancy)? I really recommend that you separate this whole section by the time period you wish to address rather than mixing them up like this.

Thank you for the suggestion. We have split this section into two separate paragraphs to address preconception and prenatal care separately.

Line 265: For clarity, aspirin use is for prevention of preterm preeclampsia.

We have specified that aspirin use is for prevention of preterm preeclampsia among high-risk women.

Line 277: Spell out MOMI throughout your paper.

This change has been made throughout the text.

Line 286: the bias introduced by this definition includes the issue of your transferred patients—many of whom may have been transferred due to hypertensive disease of pregnancy.

We conducted an additional analysis and compared outcomes of patients included vs. excluded from the cohort (Appendix 1) to address this potential bias. The overall rate of preeclampsia was similar between these two groups (6.9 % among included patients, 7.3% among excluded patients).

Line 297: rather than "clinical translation" perhaps "generalizability"?

This change has been made in the text.

Line 298: some of these women likely were on Bp meds so their BP's may have been iatrogenically lowered.

Yes, we hypothesize that many of these women were on treatment of hypertension and yet still had the highest degree of risk. We address this issue in the Discussion.

Line 303: It seems from your discussion, much of your findings are replications of prior studies. Do you think further replication is needed to establish the association between early BP measurements and later pregnancy complications? Or is this enough to warrant intervention trials? It seems the rest of your concluding paragraph is suggesting that your paper adds sufficiently to prior work that it's fine to move ahead w/ interventions.

We conclude that there is now sufficient observational evidence demonstrating an increased risk of preeclampsia, and intervention trials are warranted. We are not proposing that interventions be implemented without demonstrating their efficacy. We have revised the text of this paragraph to clarify our recommendation.

Figure 2: What are the horizontal bars on the graph? Please explain in the legend.

The figure legend has been revised to indicate that the bars indicate statistical comparison with the reference (normal BP) group.

[redacted]

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	7 9-10 16
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	8-9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	9 Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each	 9-10

[redacted]

			variable of interest (c) Summarise follow-up time (eg, average and total amount)	
Outcome data		15*	Report numbers of outcome events or summary measures over time	10
Main results	16		(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-12
Other analyses	17		Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
Discussion				
Key results	18		Summarise key results with reference to study objectives	13
Limitations	19		Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-17
Interpretation	20		Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17-18
Generalisability	21		Discuss the generalisability (external validity) of the study results	17-18
Other information				
Funding	22		Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	6

*Give information separately for exposed and unexposed groups.