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.*

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

Date: Jun 21, 2019
To: "Alisse Hauspurg" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-913

RE: Manuscript Number ONG-19-913

Clinical Course, Predictors and Long-Term Blood Pressure Profile of Delayed-Onset Postpartum Preeclampsia

Dear Dr. Hauspurg:

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 Jul 12, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: This is an interesting manuscript with a stated purpose to "to identify clinical risk factors, describe clinical management, and characterize long-term blood pressure in women readmitted with delayed-onset PPPEC without prior preeclampsia or hypertensive disorders." This is a case control study.

1. The authors note that "Data were collected using chart review and the Magee Obstetric Medical and Infant (MOMI) database." How were the subjects identified in the MOMI database? Did they identify subjects and controls using ICD-9 codes or some other method? Did one of the authors review the entire database by hand and identify subjects and controls?

2. Who enters the data in the MOMI database? Is the MOMI database a research or administrative type of database? What is done to ensure validity of the data entered into the MOMI database?

3. The authors' note that after subjects and controls were identified the "medical record review was performed by a team of physicians." How many physicians were on the team of reviewing physicians? Did each physician review each case and control, or were the cases and controls divided up between the different physicians? Was the data abstracted on to a piloted form? What was done to ensure accuracy of data entry?

4. Was the data transferred to an electronic or other type of database? What was done to ensure accuracy of data transfer to the electronic database?

5. "We conducted a retrospective case-control study of women re-admitted with new delayed onset PPPEC matched to controls with uncomplicated pregnancies without readmissions for postpartum complications. We selected two control subjects with uncomplicated". Why did the authors not match the cases and controls for other variables, than just date of delivery? Why were there fewer than 2 controls per case? Or should this have been 242 controls?

6. The authors note that 8 or 6.6% of subjects had no symptoms. Were they admitted because of isolated high blood pressure? Why did they have their blood pressure checked if they were asymptomatic? They note they had "no cases beyond 19 days post-delivery." After discharge from the hospital what is their standard protocol for having patients return for evaluation?

7. The authors note that "Long-term, affected women demonstrate increased risk of progression to chronic hypertension compared to controls." However, their "median follow-up time of 1.5 years (IQR 0.8-2.8)." Some would argue that 1.5 years is not long-term follow-up especially for cardiovascular disease.

Reviewer #2: The authors performed a case control study to identify risk factors associated with development of delayed onset postpartum preeclampsia (PPPEC), and to characterize clinical management and the risk of future cardiovascular disease.

They identified 121 cases of delayed onset PPPEC between 2014 and 2018. They chose 232 women who had uncomplicated pregnancies, matched by date of delivery within 3 days as controls.

The results showed that non-Hispanic black race, multiparous women, obese patients and cesarean delivery were risk factors for developing PPPEC. The average postpartum day presentation was 7. The most common complaint was headache.

Eighty-six women with PPPEC and 169 controls had long-term information available. The median follow-up time was 1.5 years. Compared to controls, delayed onset PPPEC was associated with higher systolic and diastolic pressures at both the postpartum visit and 3 months postpartum. Delayed onset PPPEC was also associated with odds ratio of 2.83 of developing chronic hypertension after adjusting for BMI and to time postpartum.

This is an important topic and the findings are of interest. The authors should be congratulated for performing a largest case control study on this topic to date. This reviewer has following comments:

1. Because this is a case control study, despite their 2:1 match, their ability to determine risk factors is limited. Unless the patient selection is designed to control for one or two risk factors that are of interest, prospective, randomized studies are needed to determine risk factors. Matching the controls to cases based on the date of delivery is not sufficient to overcome the potential sampling bias. Therefore, their conclusion regarding race, multiparity, obesity and delivery by cesarean section being risk factors for delayed onset PPPED is difficult to accept.

2. Authors should explain why there are 232 control patients since they performed 2:1 match against 121 cases.

3. The data regarding BMI >40 kg/m² being associated with increased risk of delayed onset PPPEC is not presented (i.e. how many patients in each group had BMI >40 kg/m2? Is the adjusted odds ratio of 9.64 different from the odds ratio for obese woman developing antepartum preeclampsia?

4. The clinical course for a few of these women could be of interest and described in greater detail.

5. Three women in the case group presented with eclampsia (2.5%). This is much higher than what is reported in women who develop antepartum preeclampsia. It would be of interest to present additional description of their clinical course including clinical characteristics at the time of presentation and MRI findings.

6. The tables and references are adequate.

I agree with their suggestion that based on their findings, it would be reasonable to extend and increase the frequency of postpartum visits through 12 weeks postpartum.

Reviewer #3: Clinical course, Predictors and long-term Blood Pressure Profile of Delayed -Onset Postpartum Preeclampsia.

This case-control study evaluated a critical obstetric issue i.e., delayed onset or late postpartum preeclampsia, a poorly characterized and understood clinical entity. It remains poorly understood if it is a late manifestation of the same disease process resulting from placental dysfunction and relative ischemia that leads to antepartum and intrapartum preeclampsia. The manuscript is well written. The authors should respond to the following inquiries/suggestions:

1.As with most case-control studies, choosing an appropriate control group is very important. If their goal was to elucidate all potential risk factors completely, why did they exclude any group of patients, including antenatally diagnosed chronic hypertension, preeclampsia, and pregestational diabetes? Pregestational diabetes and chronic hypertension are known risk factors for preeclampsia. Are these clinical entities already well established to be independently associated with delayed onset postpartum preeclampsia?

2.In the precis and conclusion, the authors referred to significant utilization of resources without any prior definition of what constituted significant resource utilization and how utilization of resources was measured (if at all) in their study.

3.The controls were reportedly matched for date of delivery. Among the women who met this criterion, how were controls selected?

4.The authors included 121 cases of PPPEC and reports a ratio of 1 case to two controls. However, they report on 232

controls. What happened to the other ten controls? Why were they excluded?

5.On line 206, they state that the study was among the first examining the long-term cardiovascular risks of delayed-onset PPPEC". Is this the first study to examine this relationship? If it is not, how did this study compare with the previous ones?

6.The multivariable analysis that adjusted for covariates or confounders constitutes the most relevant finding from the study. They should present a table depicting the multivariable logistic regression analysis.

STATISTICAL EDITOR'S COMMENTS:

1. Methods, lines 114-118: This study was from a 4 1/2 year period, from 2014-2018. The reference cited (18) was published in 2018. Were the same criteria used for establishing diagnosis of chronic HTN (and its treatment) throughout the study period?

2. Tables 1, 2, 3, 4: Need to enumerate any missing data.

3. Table 1, 3: Was LOS normally distributed? If not, then should cite as median(IQR) and test non-parametrically.

4. Table 3: Need units for length of hospitalization.

5. Table 4: What is the explanation for the discrepancy in rates of chronic HTN vs rates of anti-hypertensive use at follow-up. For the control group, only 2/27 were treated, while for the delayed onset, only 18/39 were treated. Were the 39 from the PPPEC group among the 69 (Table 2) taking anti hypertensives at discharge? Should include in Table some measure of length of follow-up for the two cohorts. The p-value for comparison of diagnosis of DM2 is incorrect, should use Fisher's test (p = .04, not p = .01).

6. lines 150-154: Need to state the number of women in each cohort with BMI ≥ 40 kg/m². Should include enumeration of all BMI categories in Table 1. It is doubtful that there were sufficient numbers of women in the BMI ≥ 40 kg/m² (per Table 1, values ≥ 40 kg/m² would represent > 2 SD greater than the mean, so if the distributions were normally distributed, < 5 would be in that BMI category for each cohort) to permit adjustment for 3 variables, since there would have to have been ~ 30 such women in the PPPEC group. Probably not enough to adjust for even one variable, so would need to simply state the unadjusted odds.

7. lines 155-163: Since 86/121 (72%) and 169/232 (74%) of the cases and controls had sufficient follow-up, need to compare those cohrts with their larger counterparts in Table 1 to show the reader that follow-up did not result in any potential selection bias.

8. lines 161-163: The number of women requiring anti hypertensive medication was 2 and 18 (table 4). These counts are too few to allow for adjustment of the ORs for two variables, or even for one variable.

9. Should include another Table of all the crude, then adjusted ORs for contrast, but only including the adjusted OR for those in which the adjustment is justified.

Associate Editor's Comments:

1) What is the incidence of this entity in your database?;

2) We found it odd that this is a case control study in which ORs and adjusted ORs are not consistently reported;

3) If this entity is as infrequent as your numbers would suggest (~120) out of I would guess 40,000 deliveries, what is actionable about these data given the high prevalence of the conditions which were more frequent among cases (black race, multiparity, cesarean)? That is, how would your data help the practicing obstetrician?

4) Our journal does not recognize dual first authorship so please order authors accordingly;

Thank you for sending your work to Obstetrics & Gynecology. As you might infer from my questions and the reviewers comments, our willingness to move this manuscript forward will depend on the responsiveness of your revision to the substantial issues that have been raised.

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.

Any author agreement forms previously submitted will be superseded by the eCTA. During the resubmission process, you are welcome to remove these PDFs from EM. However, if you prefer, we can remove them for you after submission.

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. 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.

5. 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.

6. 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.

7. 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, tables, boxes, figure legends, and print appendixes) but exclude references.

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

9. 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).

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

11. 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.

12. 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.

13. 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.

14. 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.

15. 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.

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

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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 via Editorial Manager for Obstetrics & Gynecology at http://ong.editorialmanager.com. It is essential that your cover letter list point-by-point the changes made in response to each criticism. Also, please save and submit your manuscript in a word processing format such as Microsoft Word.

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 Jul 12, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

2017 IMPACT FACTOR: 4.982
2017 IMPACT FACTOR RANKING: 5th out of 82 ob/gyn journals

July 26, 2019

Dear Dr. Chescheir,

On behalf of my co-authors, it is my pleasure to submit our revised manuscript entitled “Clinical Course, Predictors and Blood Pressure Profile of Delayed-Onset Postpartum Preeclampsia” for consideration for publication in *Obstetrics and Gynecology*.

Hypertension and preeclampsia are leading causes of maternal morbidity and mortality, particularly in the postpartum period. Delayed-onset postpartum preeclampsia is a poorly understood disease process with current evidence limited to small case series. Finally, while preeclampsia with antepartum onset is associated with an increased risk of hypertension and long-term cardiovascular disease, few studies have characterized these risks after delayed-onset postpartum preeclampsia.

Here we detail a retrospective case-control study of women re-admitted with delayed-onset postpartum preeclampsia matched to controls to identify clinical risk factors, detail clinical management and characterize the risk of progression to hypertension. We show significant overlap in risk factors for antepartum preeclampsia. Additionally, delayed-onset postpartum preeclampsia is associated with extensive resource ultization and substantial maternal morbidity. Finally, we note that delayed-onset postpartum preeclampsia is associated with an increased risk of chronic hypertension and longer term anti-hypertensive medication use.

We appreciate the comments and suggestions raised by our manuscript’s reviewers and editors. In consideration of the proposed changes, we have included their comments followed by our responses:

Reviewer #1: This is an interesting manuscript with a stated purpose to "to identify clinical risk factors, describe clinical management, and characterize long-term blood pressure in women readmitted with delayed-onset PPPEC without prior preeclampsia or hypertensive disorders." This is a case control study.

[redacted] and the Magee Obstetric [redacted] w were the subjects identified in the MOMI [redacted] y subjects and controls using ICD-9 codes or some other method? Did one of the authors review the entire database by hand and identify subjects and controls?

We appreciate these comments asking us to describe how we identified our subjects, and we have updated our Materials and Methods section as follows. The structure of the MOMI database is further outlined in answer to the next comment. The electronic MOMI database has a dedicated research team able to identify subjects and extract their associated clinical data based on specific inquiries.
“Delayed-onset postpartum preeclampsia cases were identified from readmission data, which is tracked prospectively at our institution in compliance with the Centers for Medicare and Medicaid Services (CMS) requirements. Controls were identified from the MOMI database and included women with a term uncomplicated pregnancy without a diagnosis of chronic hypertension, any hypertensive disorder of pregnancy or pre-existing diabetes”

[redacted]

2) Who enters the data in the MOMI database? Is the MOMI database a research or administrative type of database? What is done to ensure validity of the data entered into the MOMI database?

Thank you for asking us to provide more information concerning the MOMI database, we have given more detail on this topic under the Materials and Methods section as follows and added a reference for the validation of the database.

"The MOMI database was established in 1995 from all women who have delivered at Magee-Womens Hospital of the University of Pittsburgh Medical Center through the present. It includes information on over 300 variables for maternal, fetal and neonatal characteristics obtained from admitting services, International Classification of Diseases, Ninth Revision (ICD-9) codes, electronic medical record abstraction, electronic birth records and ultrasound. It is populated in real time as a research database, with dedicated data administrators who review, validate and store the data collected."

3) The authors' note that after subjects and controls were identified the "medical record review was performed by a team of physicians." How many physicians were on the team of reviewing physicians? Did each physician review each case and control, or were the cases and controls divided up between the different physicians? Was the data abstracted on to a piloted form? What was done to ensure accuracy of data entry?

We appreciate your inquiry into our record review process and have expanded our Materials and Methods section to include this information as follows.

"The charts for review were randomly distributed to two physician-authors (ER and AH). Each chart was reviewed and data abstracted into pre-specified data collection sheet in REDCAP. Ten percent of the records were randomly selected for re-review by the other physician. If there was any disagreement, then the subject was discussed and adjudicated by the three physician authors (AJ, AH, ER)"

4) Was the data transferred to an electronic or other type of database? What was done to ensure accuracy of data transfer to the electronic database?

Thank you for emphasizing this point. Data was transferred to a RedCap electronic database and information on this database has been added to our Materials [redacted] **oned above, to ensure accuracy of data entry,** [redacted] **the other physician on the** [redacted]

"Each chart was reviewed, and data abstracted into pre-specified data collection forms in REDCAP."

5) "We conducted a retrospective case-control study of women re-admitted with new delayed onset PPPEC matched to controls with uncomplicated pregnancies without readmissions for postpartum complications. We selected two control subjects with uncomplicated". Why did the authors not match the cases and controls for other variables, than just date of delivery? Why were there fewer than 2 controls per case? Or should this have been 242 controls?

Thank you for this comment. Based on reviewer comments, we have revised the design of our study and expanded our control group to include all women with uncomplicated pregnancies who delivered during the study period. We have maintained the 2:1 control to case design for the longer-term follow up analysis and have added the following to clarify the fewer than 2 controls per case point:

[redacted]

"In order to characterize longer-term blood pressure and maternal cardiovascular outcomes following delayed-onset PPPEC, medical record review was performed on a subset of controls (n=232), matched 2:1 by delivery date to cases. If there were more than two control subjects available for inclusion on a given date of delivery, we selected the first two based on delivery time. In the event that we were unable to identify an appropriate control meeting our inclusion criteria on a specific delivery date, there were less than two controls per case (n=10 cases matched to one control)."

6) The authors note that 8 or 6.6% of subjects had no symptoms. Were they admitted because of isolated high blood pressure? Why did they have their blood pressure checked if they were asymptomatic? They note they had "no cases beyond 19 days post-delivery." After discharge from the hospital what is their standard protocol for having patients return for evaluation?

Thank you for this inquiry. We have updated our Results section concerning the reason for presentation for those cases who were asymptomatic as follows. After discharge, standard protocol for women with uncomplicated labor, delivery and immediate postpartum course is for patients to return in 4-6 weeks for a postpartum appointment. For women with hypertensive disorder or hypertension detected antenatally or while in the hospital, BP check within one week and/or home blood pressure monitoring is recommended.

"The 6.6% of women who were asymptomatic had been noted to have incidentally elevated blood pressures, either at home or in another clinical setting, and so had presented to the hospital for further care."

7) The authors note that "Long-term, affected women demonstrate increased risk of progression to chronic hypertension compared to controls." However, their "median follow-up time of 1.5 years (IQR 0.8-2.8)." Some would argue that 1.5 years is not long-term follow-up especially for cardiovascular disease.

We appreciate this point and we agree. Our intentions were to denote the time beyond the standard postpartum period, and so we have updated our lack of clarity by the phrase "long-term" in the revised manuscript.

[redacted] control study to identify risk factors associated with [redacted]C), and to characterize clinical [redacted]ascular disease.

They identified 121 cases of delayed onset PPPEC between 2014 and 2018. They chose 232 women who had uncomplicated pregnancies, matched by date of delivery within as controls.

The results showed that non-Hispanic black race, multiparous women, obese patients and cesarean delivery were risk factors for developing PPPEC. The average postpartum day presentation was 7. The most common complaint was headache.

Eighty-six women with PPPEC and 169 controls had long-term information available. The median follow-up time was 1.5 years. Compared to controls, delayed onset PPPEC was associated with higher systolic and diastolic pressures at both the postpartum visit and 3 months postpartum. Delayed onset PPPEC was also associated with odds ratio of 2.83 of developing chronic hypertension after adjusting for BMI and to time postpartum.

This is an important topic and the findings are of interest. The authors should be congratulated for performing a largest case control study on this topic to date. This reviewer has following comments:

1) Because this is a case control study, despite their 2:1 match, their ability to determine risk factors is limited. Unless the patient selection is designed to control for one or two risk factors that are of interest, prospective, randomized studies are needed to determine risk factors. Matching the controls to cases based on the date of delivery is not sufficient to overcome the potential sampling bias. Therefore, their conclusion regarding race, multiparity, obesity and delivery by cesarean section being risk factors for delayed onset PPPEC is difficult to accept.

We appreciate this point, which has been raised by multiple reviewers and we agree. Based on reviewer comments, we have revised the design of our study and expanded our control group to include all women with uncomplicated pregnancies who delivered during the study period to attempt to overcome the potential sampling bias. Please see revised table 1, which now includes N=26,936 women with uncomplicated pregnancies who delivered during the study period. Our findings when we compare our cases to the larger cohort of women who delivered during the study period are consistent, with maternal age, BMI, non-Hispanic black race and cesarean delivery associated with an increased risk of delayed-onset postpartum preeclampsia.

2) Authors should explain why there are 232 control patients since they performed 2:1 match against 121 cases.

As above, we have expanded the control group to include all women with uncomplicated pregnancies who delivered during the study period. We have maintained the 2:1 control:case design for the longer-term follow up analysis due to the feasibility of performing a thorough chart review and have added the following to clarify the fewer than 2 controls per case point:

"In order to characterize follow up blood pressure and maternal cardiovascular outcomes following delayed-onset PPPEC, detailed medical record review was performed on a subset of controls (n=232), matched 2:1 by delivery date to cases. If [redacted]s available for inclusion on a given date of [redacted] the event that we were [redacted] meeting our inclusion criteria on a specific [redacted] less than two controls per case (n=10 cases matched to one control)."

3) The data regarding BMI >40 kg/m² being associated with increased risk of delayed onset PPPEC is not presented (i.e. how many patients in each group had BMI >40 kg/m2)? Is the adjusted odds ratio of 9.64 different from the odds ratio for obese woman developing antepartum preeclampsia?

Thank you for this comment. We have revised the table to include the cases and controls divided up by BMI Category in response to this suggestion and have also included these values in the Results section of the revised manuscript. See below for details on the n for each of the groups (note, that the magnitude of the OR has changed based on the larger control group but the direction of the association is unchanged).

BMI Category†				
Underweight (<18.5 kg/m^2)	**974 (4.0%)**	**0**	**--**	
Normal (18.5-24.9 kg/ m^2)	**12,564 (51.3%)**	**36 (29.8%)**	**Ref.**	
Overweight (25.0-29.9 kg/m^2)	**6,036 (24.6%)**	**37 (30.6%)**	**2.14 (1.35-3.39)**	**<0.001**
Obese Class I (30.0-34.9 kg/m^2)	**2,098 (11.9%)**	**22 (18.2%)**	**2.64 (1.55-4.50)**	
Obese Class II (35.0-39.9 kg/m^2)	**1,302 (5.3%)**	**10 (8.3%)**	**2.68 (1.33-5.41)**	
Obese Class III (≥40.0 kg/m^2)	**723 (3.0%)**	**16 (13.2%)**	**7.72 (4.27-13.98)**	

4) The clinical course for a few of these women could be of interest and described in greater detail.

Thank you for this interesting suggestion, we have revised our manuscript to include more detail concerning the clinical course and work-up of the women with eclampsia as presented in our answer to the subsequent comment.

5) Three women in the case group presented with eclampsia (2.5%). This is much higher than what is reported in women who develop antepartum preeclampsia. It would be of interest to present additional description of their clinical course including clinical characteristics at the time of presentation and MRI findings.

Thank you for this suggestion. We have revised our manuscript to include more detail concerning the women who presented with eclampsia in the Results section as follows.

"Concerning the women with eclampsia, all three experienced new-onset generalized tonic-clonic seizures at home and presented with blood pressures requiring IV anti-hypertensive agents, with one requiring a nicardipine drip, and were admitted to the Intensive Care Unit. The average age was younger than that of the rest of our sample at 20.7 years and the median postpartum day of presentation was 12.0. All had an abnormal brain MRI obtained during their readmission with two demonstrating Posterior Reversible Encephalopathy Syndrome (PRES) and one with a subarachnoid hemorrhage and diffuse white matter hyperintensities."

6) The tables and references are adequate.
I agree with their suggestion that based on their findings, it would be reasonable to extend and increase the frequency of postpartum visits through 12 weeks postpartum.

Thank you for your thorough review of our tables and references, and for sharing [redacted] postpartum care.

Reviewer #3: Clinical course, Predictors and long-term Blood Pressure Profile of Delayed-Onset Postpartum Preeclampsia.

This case-control study evaluated a critical obstetric issue i.e., delayed onset or late postpartum preeclampsia, a poorly characterized and understood clinical entity. It remains poorly understood if it is a late manifestation of the same disease process resulting from placental dysfunction and relative ischemia that leads to antepartum and intrapartum preeclampsia. The manuscript is well written. The authors should respond to the following inquiries/suggestions:

1) As with most case-control studies, choosing an appropriate control group is very important. If their goal was to elucidate all potential risk factors completely, why did they exclude any group of patients, including antenatally diagnosed chronic hypertension, preeclampsia, and

pregestational diabetes? Pregestational diabetes and chronic hypertension are known risk factors for preeclampsia. Are these clinical entities already well established to be independently associated with delayed onset postpartum preeclampsia?

We appreciate your inquiry as to why we excluded women with these antenatal conditions. As you mention, these women are known to be at a higher risk for pregnancy complications, including increased risk of preeclampsia and so are often already followed more closely in the antepartum and postpartum period. These are also already well-established risk factors for future hypertensive disease. Furthermore, as we mention in our Introduction section, most studies published in the literature on delayed-onset postpartum preeclampsia do not exclude women with these conditions and demonstrate them to be at increased risk for this disorder (our references include papers by Al-Safi Z, et al published in *Obstet Gynecol* in 2011, Matthys LA, et al published in *Am J Obstet Gynecol* in 2004, and Yancey LM, et al published in *J Emerg Med* in 2011). Our goal was to examine the clinical course of this disorder for women WITHOUT these pre-identified risk factors.

2) In the precis and conclusion, the authors referred to significant utilization of resources without any prior definition of what constituted significant resource utilization and how utilization of resources was measured (if at all) in their study.

Thank you for making this valid point, we have revised our manuscript to remove the phrase "significant utilization of resources" as rather than attempting to measure this value we offer a description of the frequency of the various radiologic imaging studies performed and the medical treatments given.

3) The controls were reportedly matched for date of delivery. Among the women who met this criterion, how were controls selected?

We appreciate this point, which has been raised by multiple reviewers and we agree. Based on reviewer comments, we have revised the design of our study and expanded our control group to include all women with uncomplicated pregnancies who delivered during the study period to attempt to overcome the potential sampling bias. Please see revised table 1, which now includes N=26,936 women with uncomplicated pregnancies who delivered during the study period.

4) The authors included 121 cases of PPPEC and reports a ratio of 1 case to two controls. [redacted]happened to the other ten controls? Why were they [redacted]

control group to include all women with [redacted]ies who delivered during the study period. We have maintained the 2:1 control:case design for the longer-term follow up analysis and have added the following to clarify the fewer than 2 controls per case point:

"In order to characterize follow up blood pressure and maternal cardiovascular outcomes following delayed-onset PPPEC, detailed medical record review was performed on a subset of controls (n=232), matched 2:1 by delivery date to cases. If there were more than two control subjects available for inclusion on a given date of delivery, we selected the first two based on delivery time. In the event that we were unable to identify an appropriate control meeting our inclusion criteria on a specific delivery date, there were less than two controls per case (n=10 cases matched to one control)."

5) On line 206, they state that the study was among the first examining the long-term

cardiovascular risks of delayed-onset PPPEC". Is this the first study to examine this relationship? If it is not, how did this study compare with the previous ones?

Thank you for this comment. Yes, to our knowledge this is the first study specifically examining the relationship between delayed-onset PPPEC in women with no prior hypertensive disorder and longer-term cardiovascular disease risk. However, we have refrained from utilizing this language, per journal guidelines.

6) The multivariable analysis that adjusted for covariates or confounders constitutes the most relevant finding from the study. They should present a table depicting the multivariable logistic regression analysis.

Thank you for this comment. We have added Table 2 that includes our multivariable logistic regression analysis.

Statistical Editor's Comments:

1) Methods, lines 114-118: This study was from a 4 1/2 year period, from 2014-2018. The reference cited (18) was published in 2018. Were the same criteria used for establishing diagnosis of chronic HTN (and its treatment) throughout the study period?
Thank you for this comment. We have updated this reference to reflect the prior guidelines, which were used for the diagnosis of chronic hypertension.

2) Tables 1, 2, 3, 4: Need to enumerate any missing data.
Thank you, we have included this.

3) Table 1, 3: Was LOS normally distributed? If not, then should cite as median(IQR) and test non-parametrically.
It was not normally distributed and we have made this change.

4) Table 3: Need units for length of hospitalization.
Thank you, this has been updated to include days as the unit of measure.

5) Table 4: What is the explanation for the discrepancy in rates of chronic HTN vs rates of anti-hypertensive use at follow-up. For the control group, only 2/27 were treated, while for the delayed onset, only 18/39 were treated. Were the 39 from the PPPEC group among the 69 [redacted]ge? Should include in Table some measure of [redacted]son of diagnosis of DM2 is [redacted] not p = .01).
[redacted]s question. We suspect that the discrepant rates likely reflect the severity of hypertension. Women who have more mild or stage 1 hypertension may not be started on medication, while women with stage 2 or more severe hypertension may be prescribed anti-hypertensive medications. Among the women with PPPEC who were on medication at follow up, 16 of the 20 (80%) were on medication at the time of their postpartum visit. Follow up time (in years) is in the table. Thank you for the comment, we have corrected the p value in the table.

6) lines 150-154: Need to state the number of women in each cohort with BMI ≥ 40 kg/m². Should include enumeration of all BMI categories in Table 1. It is doubtful that there were sufficient numbers of women in the BMI ≥ 40 kg/m² (per Table 1, values ≥ 40 kg/m² would represent > 2 SD greater than the mean, so if the distributions were normally distributed, < 5 would be in that BMI category for each cohort) to permit adjustment for 3 variables, since there would have to have been ~ 30 such women in the PPPEC group. Probably not enough to

adjust for even one variable, so would need to simply state the unadjusted odds.

Thank you for this comment, Table 1 has been updated to detail BMI categorically.

7) lines 155-163: Since 86/121 (72%) and 169/232 (74%) of the cases and controls had sufficient follow-up, need to compare those cohrts with their larger counterparts in Table 1 to show the reader that follow-up did not result in any potential selection bias.

Thank you, we have included 3 supplemental tables stratified by availability of follow up data (Supplemental tables 1-3). As Supplemental Table 3 demonstrates, there were no significant differences in baseline characteristics between women with and without follow up available. We have included language in the text to reflect this: "Women with follow up data available did not significantly differ in demographic or delivery characteristics from women without available follow up data (Supplemental Tables 2 and 3)."

8) lines 161-163: The number of women requiring anti hypertensive medication was 2 and 18 (table 4). These counts are too few to allow for adjustment of the ORs for two variables, or even for one variable.

Thank you, we have removed this analysis.

9) Should include another Table of all the crude, then adjusted ORs for contrast, but only including the adjusted OR for those in which the adjustment is justified.

Thank you, we have included this on Table 1 and added Table 2 with adjusted ORs.

Associate Editor's Comments:

1) What is the incidence of this entity in your database?

We had 31,399 term, singleton deliveries during this time period. The overall incidence of re-admission due to delayed-onset postpartum preeclampsia is 0.4%. We are unable to comment on the overall incidence of the disease as there are likely women seen in an outpatient office or in the Emergency Room who were not readmitted. As mentioned in our discussion, by limiting our cohort to women who were re-admitted postpartum, we are likely missing less severe cases.

2) We found it odd that this is a case control study in which ORs and adjusted ORs are not [redacted] **odds ratios and adjusted ORs** [redacted] **and 2.**

3) If this entity is as infrequent as your numbers would suggest (~120) out of I would guess 40,000 deliveries, what is actionable about these data given the high prevalence of the conditions which were more frequent among cases (black race, multiparity, cesarean)? That is, how would your data help the practicing obstetrician?

Thank you for this comment. While the incidence of this condition may be low, both in our study and in prior publications, our data is likely influenced by the fact that we are only capturing women who are readmitted, and we have added some language to this effect into the discussion section. Importantly, we and others (Friedman *ObGyn* 2019) show significant morbidity associated with this condition with very little understanding of the underlying pathophysiology. Further, we feel it is important for the practicing obstetrician to be aware that preeclampsia can develop postpartum and perhaps to identify risk factors that may warrant strict precautions and closer follow up postpartum.

4) Our journal does not recognize dual first authorship so please order authors accordingly;

We appreciate you making us aware of this policy, we have updated the authorship order to reflect Dr. Emily K. Redman as first author.

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.

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.

Thank you for making us aware of this process.

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. [redacted]

[redacted]**I will upload the Transparency Declaration Statement signed by Dr. Emily Redman and submit it along with the revised manuscript in Editorial Manager.**

[redacted]

4) 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.

Thank you for asking us to provide more information concerning the MOMI database, we have given more detail on this topic under the Materials and Methods section as follows.

“Data were collected using hospital readmission data, the Magee Obstetric Maternal and Infant (MOMI) database and chart review. The MOMI database was established in 1995 from all women who have delivered at Magee-Womens Hospital through the present. It includes information on over 300 variables for maternal, fetal and neonatal characteristics obtained from admitting services, International Classification of Diseases, Ninth Revision (ICD-9) codes, electronic medical record abstraction, electronic birth

records and ultrasound. It is populated in real time as a research database, with dedicated data administrators who review, validate and store the data collected. Delayed-onset PPPEC cases were identified from readmission data, which is tracked prospectively at our institution in compliance with the Centers for Medicare and Medicaid Services (CMS) requirements. Controls were identified from the MOMI database and included women with a term, uncomplicated pregnancy without a diagnosis of chronic hypertension, any hypertensive disorder of pregnancy or pre-existing diabetes. After identification of cases and controls, a thorough chart review of the cases and a subset of the controls was performed.

The charts for review were randomly distributed to two physician-authors (ER and AH). Each chart was reviewed and data abstracted into pre-specified data collection sheet in REDCAP. Ten percent of the records were randomly selected for re-review by the other physician. If there was any disagreement, then the subject was discussed and adjudicated by the three physician authors (AJ, AH, ER)."

5) 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. 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.

Thank you for this information, we acknowledge these specific guidelines and associated checklists however they do not apply to our study type.

6) 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.

[redacted]**with this reference.**

7) 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, tables, boxes, figure legends, and print appendixes) but exclude references.

We have ensured that our manuscript conforms to the required length limits.

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

manuscript in the title.

The title has been updated to "Clinical course, predictors and blood pressure profile of delayed-onset postpartum preeclampsia" and meets the character requirement.

9) Specific rules govern the use of acknowledgments in the journal.

Thank you for detailing the guidelines for use of acknowledgments in the journal.

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

The short title has been updated to "Clinical course of postpartum preeclampsia" and meets the character requirement.

11) 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.

We have reviewed the revised Abstract and ensured that its word count meets requirements, and we have provided a word count within the updated manuscript.

12) 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.

We appreciate you providing us with this reference and guidelines.

13) 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.

Thank you for making us aware of this, we have updated the text to remove this symbol where necessary.

14) 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.

Thank you, we have removed this statement.

15) 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.

We appreciate you providing us with this resource to ensure that our tables conform.

16) 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.

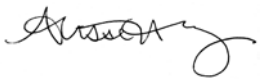
Thank you for providing us with this information concerning appropriate citation of ACOG documents in our manuscript.

17) 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.

We appreciate you making us aware of this process.

Thank you in advance for consideration of our revised manuscript for publication.

Sincerely,



Alisse Hauspurg, MD

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