

OBSTETRICS & GYNECOLOGY



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

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obgyn@greenjournal.org.

Date: Mar 08, 2021
To: "Annette K Regan" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-21-241

RE: Manuscript Number ONG-21-241

Adverse birth outcomes associated with preconception and prenatal electronic cigarette use

Dear Dr. Regan:

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 29, 2021, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: This study explores an important question of whether peri-pregnancy use of e-cigarettes is associated with adverse birth outcomes using a large, nationally-representative sample of pregnancies in the US. The analysis seems to be well done and thought out, and identifies an association between low birth weight and e-cigarette use. However to make the study more clinically relevant, I would recommend re-examining the analysis to better clarify the exposure and the influence of combustible cigarettes. My primary concern is the inclusion of smokers of combustible cigarettes with the non-users of e-cigarettes (e.g. the first group in Table 1 and the Overall comparison in Table 2). While I recognize that use of combustible cigarettes has been pulled out as a co-variate in Table 1 and a sub-analysis in Table 2, I do think that combustible cigarette smoking is a unique exposure (as you have it in the supplemental material), and should be handled differently in the analysis. For example, by lumping together smokers and non-smokers into "non-e-cig users," I would assume you are combining two pretty heterogeneous groups, and this limits the utility of the descriptions/comparisons in table 1. I think the most clinically useful comparisons would reflect principles of harm reduction and provide evidence (or not) of what clinicians probably already think: best is not smoking at all, second best is quitting completely prior to pregnancy; this dataset seems to have the ability to answer the more relevant question- if people can't quit completely, then are e-cigarettes during pregnancy safer than continuing to smoke?

Some small suggestions:

-In the title, I would recommend changing "preconception" to "pre-pregnancy," as that is how the question is framed in PRAMS

-Consider gender neutral language. I'm not sure how PRAMS handles transgender or gender non-conforming people, but it would be easy to use "people" instead of "women"

-Again, another important discussion point would be how these results compared to what we know about the harms of cigarette smoking during pregnancy

-With respect to the discussion/conclusions, I would recommend softening the language. All of your significant measures of association are between 1-2, and using observational data like PRAMS that is subject to a variety of potential biases and unmeasured confounding, it would be difficult to call this clearly clinically significant

Reviewer #2: Our knowledge regarding e-cigarette consumption in pregnancy and newborn outcomes is limited. The authors submit a comprehensive study assessing the impact of e-cigarettes in pregnancy and find a significant association with low birthweight. They use a well-established national database which reflects patterns of consumption throughout the country. The results appear indisputable and should serve as a basis for counseling patients against e-cigarette consumption in pregnancy.

The authors describe the findings of their analysis and do not make speculations. They achieve their first aim of describing

the proportion of women using e-cigarettes during pregnancy. The second aim of describing e-cigarette consumption in relation to adverse perinatal outcomes shows a clear association with low birthweight when used during the last three months of pregnancy. More importantly, daily use of e-cigarettes had a stronger association with preterm birth and low birthweight than combined use with combustible cigarettes. E-cigarette consumption may be more efficient in ingestion of nicotine and toxins than smoking combustible cigarettes. Instead of being less harmful, e-cigarettes appear to be more harmful in pregnancy.

Reviewer #3: Regan et al performed a retrospective cohort study using the 2016-2018 Pregnancy Risk Assessment Monitoring System (PRAMS) database. The objective was to evaluate the risk of adverse birth outcomes among women who use electronic cigarettes prior to and during pregnancy.
Abstract: Good.

Introduction:

59-63 Authors should distinguish primary versus secondary objectives here.

Any prespecified hypothesis should be stated here.

Methods: Study design is retrospective cohort using the 2016-2018 Pregnancy Risk Assessment Monitoring System (PRAMS) database to evaluate the risk of adverse birth outcomes among women who use electronic cigarettes prior to and during pregnancy. Excellent description of data source (suggest lines 76-87 be placed in supplemental table for ease of reading). Authors define study population in line 124-127 (recommend moving to initial part of methods section). Definitions of exposures, outcomes and covariates are comprehensive. Recommend stating exclusion criteria in this section.

Results:

187 "Among nonsmokers" in this sentence is confusing.

191 "for women who used e-cigarettes" is redundant.

Discussion:

206-211 Recommend authors discuss why they think the interaction between daily e-cigarettes and combustibles appears to be protective for PTB/LBW versus daily e-cigarette use alone.

220-222 Recommend authors highlight the potential for intervention preconceptionally in women using combustible/e-cigarettes based on their work.

275-290 Excellent discussion of limitations.

Figures and Tables: Appropriate

References: Appropriate.

STATISTICAL EDITOR COMMENTS:

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

Table 1: Need to enumerate all missing data. Should also compare statistically the groups, since those using e-cigarettes appear different in several characteristics from the non-users. Note especially the proportion smoking cigarettes among the 3 groups. It will be difficult to separate that influence from the use of e-cigarettes. Missing from these characteristics is any information re: BMI, wgt gain during pregnancy, parity or history of prior PTB.

Table 2: There are many comparisons in this Table, without any adjustment for multiple hypothesis testing. Need to provide the counts for women in the various prevalences cited. In the section "Among women who smoked combustible cigarettes ...", the total is a small proportion of the total and those within each prevalence are small, compared to the overall group. Therefore there is much less power to have discerned any difference. For the last group, that is, those who did not smoke combustible cigarettes during pregnancy, the subsets for e-cigarette use are a subset of all those using e-cigarettes (see Table 1, respectively 73% and 36% during last 3 months of pregnancy).

EDITOR COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:

A. OPT-IN: Yes, please publish my point-by-point response letter.

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2. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA). 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. The following co-authors have not completed their form:

Jennifer M. Bombard (zwf@cdc.gov)
Michelle M. O'Hegarty (izr0@cdc.gov)
Ruben A. Smith (eyb4@cdc.gov)

3. If your study is based on data obtained from the National Center for Health Statistics, please review the Data Use Agreement (DUA) for Vital Statistics Data Files that you or one of your coauthors signed. If your manuscript is accepted for publication and it is subsequently found to have violated any of the terms of the DUA, the journal will retract your article. The National Center for Health Statistics may also terminate your access to any future vital statistics data.

4. For studies that report on the topic of race or include it as a variable, authors must provide an explanation in the manuscript of who classified individuals' race, ethnicity, or both, the classifications used, and whether the options were defined by the investigator or the participant. In addition, the reasons that race/ethnicity were assessed in the study also should be described (eg, in the Methods section and/or in table footnotes). Race/ethnicity must have been collected in a formal or validated way. If it was not, it should be omitted. Authors must enumerate all missing data regarding race and ethnicity as in some cases, missing data may comprise a high enough proportion that it compromises statistical precision and bias of analyses by race.

Use "Black" and "White" (capitalized) when used to refer to racial categories. The nonspecific category of "Other" is a convenience grouping/label that should be avoided, unless it was a prespecified formal category in a database or research instrument. If you use "Other" in your study, please add detail to the manuscript to describe which patients were included in that category.

5. All studies should follow the principles set forth in the Helsinki Declaration of 1975, as revised in 2013, and manuscripts should be approved by the necessary authority before submission. Applicable original research studies should be reviewed by an institutional review board (IRB) or ethics committee. This review should be documented in your cover letter as well in the Methods section of the body text, with an explanation if the study was considered exempt. If your research is based on a publicly available data set approved by your IRB for exemption, please provide documentation of this in your cover letter by submitting the URL of the IRB website outlining the exempt data sets or a letter from a representative of the IRB. In addition, insert a sentence in the Methods section stating that the study was approved or exempt from approval. In all cases, the complete name of the IRB should be provided in the manuscript.

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 data definitions at <https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions> and the gynecology data definitions at <https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions>. 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, references, tables, boxes, figure legends, and print appendixes) but exclude references.

8. 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).

9. 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 limit for Original Research articles is 300 words. Please provide a word count.

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

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

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

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

12. Please review examples of our current reference style at <http://ong.editorialmanager.com> (click on the Home button in the Menu bar and then "Reference Formatting Instructions" document under "Files and Resources"). Include the digital object identifier (DOI) with any journal article references and an accessed date with website references. Unpublished data, in-press items, personal communications, letters to the editor, theses, package inserts, submissions, meeting presentations, and abstracts may be included in the text but not in the reference list.

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

Figure 1: Please upload as a figure file on Editorial Manager. Please update the bars to solid colors.

14. Please change the portion of the acknowledgement thanking the working group members to Appendix 1. ("We thank the Pregnancy Risk Assessment Monitoring System (PRAMS) Working Group members..."). Renumber the subsequent appendixes in the manuscript text and appendixes file.

Each supplemental file in your manuscript should be named an "Appendix," numbered, and ordered in the way they are first cited in the text (do not use wording such as "supplemental Table 1"). Do not order and number supplemental tables, figures, and text separately. References cited in appendixes should be added to a separate References list in the appendixes file.

15. 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 <https://wkauthorservices.editage.com/open-access/hybrid.html>.

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- * 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. Do not omit your responses to the Editorial Office or Editors' comments.

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 29, 2021, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

2019 IMPACT FACTOR: 5.524

2019 IMPACT FACTOR RANKING: 6th out of 82 ob/gyn journals

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: <https://www.editorialmanager.com/ong/login.asp?a=r>). Please contact the publication office if you have any questions.

We would like to thank the Reviewers and Editorial Board members for their thoughtful feedback on the initial draft of our manuscript. We have revised our manuscript based on these comments. Changes are denoted in the manuscript text using track changes. We have additionally provided a response to each reviewer comment below.

RESPONSE TO REVIEWER COMMENTS

Reviewer #1 Comments:

This study explores an important question of whether peri-pregnancy use of e-cigarettes is associated with adverse birth outcomes using a large, nationally-representative sample of pregnancies in the US. The analysis seems to be well done and thought out, and identifies an association between low birth weight and e-cigarette use. However, to make the study more clinically relevant, I would recommend re-examining the analysis to better clarify the exposure and the influence of combustible cigarettes. My primary concern is the inclusion of smokers of combustible cigarettes with the non-users of e-cigarettes (e.g. the first group in Table 1 and the Overall comparison in Table 2). While I recognize that use of combustible cigarettes has been pulled out as a co-variate in Table 1 and a sub-analysis in Table 2, I do think that combustible cigarette smoking is a unique exposure (as you have it in the supplemental material), and should be handled differently in the analysis. For example, by lumping together smokers and non-smokers into "non-e-cig users," I would assume you are combining two pretty heterogeneous groups, and this limits the utility of the descriptions/comparisons in table 1. I think the most clinically useful comparisons would reflect principles of harm reduction and provide evidence (or not) of what clinicians probably already think: best is not smoking at all, second best is quitting completely prior to pregnancy; this dataset seems to have the ability to answer the more relevant question- if people can't quit completely, then are e-cigarettes during pregnancy safer than continuing to smoke?

AUTHOR RESPONSE: Reviewer 1 raises a very important point. Although combustible cigarette smoking has known effects on adverse birth outcomes, the aim of this study was to evaluate whether exposure to e-cigarettes during pregnancy was associated with adverse pregnancy outcomes, and our a priori study design was to evaluate combustible cigarette smoking as an effect modifier. In line with this aim, our analysis considered the entire population of pregnant women – rather than previous smokers (necessary to address ‘harm reduction.’)

Our analysis considers the influence of e-cigarette use separately from combustible cigarette use (analyses for exclusive e-cigarette users), and the results from this analysis show a higher prevalence of adverse birth outcomes was associated with e-cigarette use only. Again, these results align with the aim of our study, and as noted by other reviewers, there are few studies evaluating this question, making these results unique.

We agree with the Reviewer that there remains the question as to whether the prevalence of adverse birth outcomes may be lower among women who cannot quit nicotine entirely and use e-cigarettes instead. Since this is a separate research question and involves consideration of women with a history of tobacco use only, we plan to explore this issue further in a future separate analysis.

1. Some small suggestions:

In the title, I would recommend changing "preconception" to "pre-pregnancy," as that is how the question is framed in PRAMS

AUTHOR RESPONSE: Thank you for this great suggestion. We have rephrased the title as recommended.

2. Consider gender neutral language. I'm not sure how PRAMS handles transgender or gender non-conforming people, but it would be easy to use "people" instead of "women"

AUTHOR RESPONSE: Thank you for the suggestion. We have revised to include gender neutral language throughout the text.

3. Again, another important discussion point would be how these results compared to what we know about the harms of cigarette smoking during pregnancy

AUTHOR RESPONSE: Thank you for this suggestion. In response to Reviewer 3's comment, we have added additional text to include mention of known risks of preterm birth associated with combustible cigarette smoking. The following text has been added at the bottom of page 12:

"Given combustible cigarette smoking can double the risk of preterm birth, combustible cigarette smokers in this sample would have been predisposed to higher rates of preterm birth; prenatal e-cigarette use does not further increase the risk of preterm birth in addition to combustible cigarette use during pregnancy."

4. With respect to the discussion/conclusions, I would recommend softening the language. All of your significant measures of association are between 1-2, and using observational data like PRAMS that is subject to a variety of potential biases and unmeasured confounding, it would be difficult to call this clearly clinically significant

AUTHOR RESPONSE: Thank you for this comment. We have reviewed the content of the Discussion to confirm we use language consistent with measured associations. We believe the reviewer may be referring to the final statement in our conclusions "E-cigarettes are not safe to use during pregnancy." This statement comes from currently approved language in CDC communication materials: <https://www.cdc.gov/reproductivehealth/maternalinfanthealth/substance-abuse/e-cigarettes-pregnancy.htm#safer>. However, we appreciate the need to soften conclusions based on the results of this study alone. We have therefore adjusted the final sentence in the conclusion to read:

"Results from this study further support guidance by the CDC, stating that e-cigarettes are not safe to use during pregnancy."

Reviewer #2 Comments:

Our knowledge regarding e-cigarette consumption in pregnancy and newborn outcomes is limited. The authors submit a comprehensive study assessing the impact of e-cigarettes in pregnancy and find a significant association with low birthweight. They use a well-established national database which reflects patterns of consumption throughout the country. The results appear indisputable and should serve as a basis for counselling patients against e-cigarette consumption in pregnancy.

The authors describe the findings of their analysis and do not make speculations. They achieve their first aim of describing the proportion of women using e-cigarettes during pregnancy. The second aim of describing e-cigarette consumption in relation to adverse perinatal outcomes shows a clear association with low birthweight when used during the last three months of pregnancy. More importantly, daily use of e-cigarettes had a stronger association with preterm birth and low birthweight than combined use with combustible cigarettes. E-cigarette consumption may be more efficient in ingestion of nicotine and toxins than smoking combustible cigarettes. Instead of being less harmful, e-cigarettes appear to be more harmful in pregnancy.

AUTHOR RESPONSE: Thank you for your review of our paper. We agree this is an area of research where further evidence is needed.

Reviewer #3 Comments:

Regan et al performed a retrospective cohort study using the 2016-2018 Pregnancy Risk Assessment Monitoring System (PRAMS) database. The objective was to evaluate the risk of adverse birth outcomes among women who use electronic cigarettes prior to and during pregnancy.

1. Introduction:

59-63 Authors should distinguish primary versus secondary objectives here.
Any prespecified hypothesis should be stated here.

AUTHOR RESPONSE: Thank you for this suggestion. We have clarified that evaluation of frequency of use was a secondary aim. This section of the introduction now reads:

“The primary aims of the present study were to assess a) the proportion of adults who used e-cigarettes before and during pregnancy, b) whether e-cigarette use during pregnancy, either exclusively or in combination with combustible cigarette smoking, was associated with increased prevalence of adverse birth outcomes including preterm birth, small-for-gestational age (SGA), and low birthweight (LBW). A secondary aim of the study was to evaluate whether this association varied by frequency of e-cigarette use during pregnancy.”

2. Methods: Study design is retrospective cohort using the 2016-2018 Pregnancy Risk Assessment Monitoring System (PRAMS) database to evaluate the risk of adverse birth

outcomes among women who use electronic cigarettes prior to and during pregnancy. Excellent description of data source (suggest lines 76-87 be placed in supplemental table for ease of reading). Authors define study population in line 124-127 (recommend moving to initial part of methods section). Definitions of exposures, outcomes and covariates are comprehensive. Recommend stating exclusion criteria in this section.

AUTHOR RESPONSE: Thank you for these suggestions. We have re-organized the methods section as recommended. Exclusion criteria are outlined in lines 77-78 of the revised manuscript:

“The study sample was restricted to singleton pregnancies with birthweight ≥ 400 grams and with information on e-cigarette use and all covariates.”

3. Results: 187 "Among nonsmokers" in this sentence is confusing.

AUTHOR RESPONSE: We have revised this sentence for clarity. This now reads:

“Among nonsmokers, use of e-cigarettes exclusively during the last 3 months of pregnancy was associated with a higher prevalence of preterm birth (aPR 1.69; 95% CI 1.20, 2.39) and LBW (aPR 1.88; 95% CI 1.38, 2.57).”

4. 191 "for women who used e-cigarettes" is redundant.

AUTHOR RESPONSE: This sentence is describing results for women who use both e-cigarettes and smoked combustible cigarettes during pregnancy. This section of text is needed to specify this. To make this clearer, we have rephrased this sentence to read:

“For respondents who used e-cigarettes and smoked combustible cigarettes during pregnancy, we observed no difference in...”

5. Discussion: 206-211 Recommend authors discuss why they think the interaction between daily e-cigarettes and combustibles appears to be protective for PTB/LBW versus daily e-cigarette use alone.

AUTHOR RESPONSE: This was an unexpected and interesting finding. The confidence intervals overlap the null, indicating there was no significant change in prevalence of preterm birth or low birthweight for combustible cigarette smokers who used e-cigarettes either daily or less frequently. We therefore interpreted this as a null association rather than a protective association. We believe this observation may be due to the fact that combustible cigarette smoking is strongly associated with preterm delivery and e-cigarette use may not further increase risk of preterm delivery among current smokers. We have added this to the discussion in lines 224-226 of the revised draft:

“Given combustible cigarette smoking on its own can double the risk of preterm birth, preterm birth rates are already high in this group, and it is

possible that prenatal e-cigarette use does not further increase the risk of preterm birth in addition to combustible cigarette use during pregnancy.”

6. 220-222 Recommend authors highlight the potential for intervention preconceptionally in women using combustible/e-cigarettes based on their work.

AUTHOR RESPONSE: We thank the Reviewer for raising this point. We do mention that substance use counselling, including counselling around e-cigarette use, should be done during preconception and prenatal care (line 262 of revision):

“Preconception and prenatal care can incorporate pregnancy-specific counselling, including asking pregnant patients about their tobacco product use (including e-cigarette, or vaping, products), advising patients to quit, assessing the willingness to quit, assisting by providing resources, and arranging follow-up visits”

7. 275-290 Excellent discussion of limitations.

AUTHOR RESPONSE: We thank the Reviewer for their comment.

STATISTICAL EDITOR COMMENTS:

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

1. Table 1: Need to enumerate all missing data. Should also compare statistically the groups, since those using e-cigarettes appear different in several characteristics from the non-users. Note especially the proportion smoking cigarettes among the 3 groups. It will be difficult to separate that influence from the use of e-cigarettes. Missing from these characteristics is any information re: BMI, wgt gain during pregnancy, parity or history of prior PTB.

AUTHOR RESPONSE: Missing data are outlined in Appendix 5 with the number of respondents missing each variable provided. Comparisons of groups were performed using chi-squared tests, and results are presented in Table 1. This table contains a footnote indicating what characteristics are significantly associated with e-cigarette use (at 0.05 significance level) based on chi-squared tests to compare the distribution of characteristics for groups of e-cigarette users and non-users. We additionally provide 95% confidence intervals for these proportions. The text in lines 162 to 168 outlined differences in characteristics for e-cigarette users vs. non-users. We agree with the statistical reviewer that it is difficult to separate the influence of combustible cigarette smoking, which was our reasoning for evaluating it as an effect modifier. Based on our a priori DAG (Appendix 4), BMI, parity and history of prior PTB were not identified in our minimum adjustment set. We, therefore, did not include these variables as adjustment variables. This was our primary reasoning; however, secondarily, these variables are also highly incomplete and would have increased the amount of missingness in our sample. For descriptive purposes, we have included

obesity, parity, and presence of an obstetric risk factor (which includes previous preterm birth) in our Table 1 and Appendix 7.

2. Table 2: There are many comparisons in this Table, without any adjustment for multiple hypothesis testing. Need to provide the counts for women in the various prevalences cited. In the section "Among women who smoked combustible cigarettes ...", the total is a small proportion of the total and those within each prevalence are small, compared to the overall group. Therefore there is much less power to have discerned any difference. For the last group, that is, those who did not smoke combustible cigarettes during pregnancy, the subsets for e-cigarette use are a subset of all those using e-cigarettes (see Table 1, respectively 73% and 36% during last 3 months of pregnancy).

AUTHOR RESPONSE: Thank you for these comments. Our comparisons include consideration of three outcomes of separate aetiology, each of which were planned a priori. Because we identified effect modification by combustible cigarette smoking, we also felt it appropriate to present estimated stratified by combustible cigarette smoking status.

We present effect estimates (stratified adjusted prevalence ratios) because the width of the confidence intervals for our adjusted weighted prevalence estimates provided indication of precision (absolute widths = (UCL–LCL) are $\leq 11\%$). We appreciate the need to provide unweighted counts in Table 2 to allow for better interpretation of power of our analyses. We have added three columns to the revised Table 2 to indicate the unweighted sample size for each exposure/outcome group. We also agree this is important to recognize as a limitation and have added the following text to the limitations section:

"Third, the unweighted number of e-cigarette users was not large (n=906) and consideration by categories of combustible cigarette smoking reduced the precision of some of our effect estimates and our ability to detect small difference in the prevalence of pregnancy outcomes."

EDITOR 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:

AUTHOR RESPONSE: OPT-IN: Yes, please publish my point-by-point response letter.

2. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA). 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. The following co-authors have not completed their form:

Jennifer M. Bombard (zwf@cdc.gov)
Michelle M. O'Hegarty (izr0@cdc.gov)
Ruben A. Smith (eyb4@cdc.gov)

AUTHOR RESPONSE: We have confirmed that all co-authors have completed their eCTA form.

3. If your study is based on data obtained from the National Center for Health Statistics, please review the Data Use Agreement (DUA) for Vital Statistics Data Files that you or one of your coauthors signed. If your manuscript is accepted for publication and it is subsequently found to have violated any of the terms of the DUA, the journal will retract your article. The National Center for Health Statistics may also terminate your access to any future vital statistics data.

AUTHOR RESPONSE: Our article does not use data obtained from NCHS. Our analyses are in line with our initial data use agreement with CDC PRAMS.

4. For studies that report on the topic of race or include it as a variable, authors must provide an explanation in the manuscript of who classified individuals' race, ethnicity, or both, the classifications used, and whether the options were defined by the investigator or the participant. In addition, the reasons that race/ethnicity were assessed in the study also should be described (eg, in the Methods section and/or in table footnotes). Race/ethnicity must have been collected in a formal or validated way. If it was not, it should be omitted. Authors must enumerate all missing data regarding race and ethnicity as in some cases, missing data may comprise a high enough proportion that it compromises statistical precision and bias of analyses by race.

Use "Black" and "White" (capitalized) when used to refer to racial categories. The nonspecific category of "Other" is a convenience grouping/label that should be avoided, unless it was a prespecified formal category in a database or research instrument. If you use "Other" in your study, please add detail to the manuscript to describe which patients were included in that category.

AUTHOR RESPONSE: We can confirm that our manuscript capitalizes the use of "Black" and "White." We have replaced "Other, non-Hispanic" with the full description of race/ethnicities included here. This was previously included as a footnote.

5. All studies should follow the principles set forth in the Helsinki Declaration of 1975, as revised in 2013, and manuscripts should be approved by the necessary authority before submission. Applicable original research studies should be reviewed by an institutional review board (IRB) or ethics committee. This review should be documented in your cover letter as well in the Methods section of the body text, with an explanation if the study was considered exempt. If your research is based on a publicly available data set approved by your IRB for exemption, please provide documentation of this in your cover letter by submitting the URL of the IRB website outlining the exempt data sets or a letter from a representative of the IRB. In addition, insert a sentence in the Methods section stating that the study was approved or exempt from approval. In all cases, the complete name of the IRB should be provided in the manuscript.

AUTHOR RESPONSE: The PRAMS study protocol has been approved by the Institutional Review Boards of CDC and each participating site. Our study was reviewed and approved by the Pregnancy Risk Assessment Monitoring System (PRAMS) Working Group. We have added text outlining IRB approval and review and approval by the PRAMS working group in the revised text of the Methods in lines 79-81:

“The PRAMS study protocol has been approved by the Institutional Review Boards of CDC and each participating site. Our study proposal was reviewed and approved by the Pregnancy Risk Assessment Monitoring System (PRAMS) Working Group.”

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 data definitions at https://urldefense.proofpoint.com/v2/url?u=https-3A__www.acog.org_practice-2Dmanagement_health-2Dit-2Dand-2Dclinical-2Dinformatics_revitalize-2Dobstetrics-2Ddata-2Ddefinitions&d=DwlGaQ&c=ggVugHHq3rzouXkEXdxBNQ&r=-O1oqMTjF2hpZa7nkSERnYhXDr3fNvLy04YDoyD-OLg&m=uGXR6plsPWLHSA3tgL4WjEEJNoxGtwu1acjhoHNRezc&s=h-j3oIBWLxMuWVrqXVXELj-35gpVkp04Y2x0Qwegevo&e= and the gynecology data definitions at https://urldefense.proofpoint.com/v2/url?u=https-3A__www.acog.org_practice-2Dmanagement_health-2Dit-2Dand-2Dclinical-2Dinformatics_revitalize-2Dgynecology-2Ddata-2Ddefinitions&d=DwlGaQ&c=ggVugHHq3rzouXkEXdxBNQ&r=-O1oqMTjF2hpZa7nkSERnYhXDr3fNvLy04YDoyD-OLg&m=uGXR6plsPWLHSA3tgL4WjEEJNoxGtwu1acjhoHNRezc&s=hJngQIMHleV0yoVUAmfN6oNXkc-l4sxTRlxwvKH8s1A&e= . If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

AUTHOR RESPONSE: We have reviewed the standard obstetric and gynaecology data definitions and confirm that revitalize definitions have been used where appropriate in our manuscript.

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

AUTHOR RESPONSE: We can confirm that our manuscript meets space limitations and is 22 pages long (double-spaced) – not including references.

8. 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).

AUTHOR RESPONSE: This study did not receive any financial support. This paper was not presented at any scientific or professional organization meeting.

9. 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 limit for Original Research articles is 300 words. Please provide a word count.

AUTHOR RESPONSE: We confirm that we have reviewed the abstract to ensure continuity with the manuscript and the word count is within limit (current word count: 247).

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

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

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

AUTHOR RESPONSE: No P-values are provided in the abstract; only effect estimates and corresponding confidence intervals are provided in the abstract. We have also not exceeded three decimals for our P-values and have not exceeded one decimal place for percentages in our Results and Tables.

11. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: https://urldefense.proofpoint.com/v2/url?u=http-3A_edmgr.ovid.com_ong_accounts_table-5Fchecklist.pdf&d=DwlGaQ&c=qqVugHHq3rzouXkEXdxBNQ&r=-O1oqMTjF2hpZa7nkSERnYhXDr3fNvLy04YDoyD-OLg&m=uGXR6plsPWLHSA3tgL4WjEEJNoxGtwu1acjhoHNRezc&s=9KZE2TkomTUbTTgt saFpjMhJa389fiWn1Tkjbfj_e8&e= .

AUTHOR RESPONSE: We confirm that we have reviewed the journal's table checklist and our revised tables conform to the journal's style.

12. Please review examples of our current reference style at https://urldefense.proofpoint.com/v2/url?u=http-3A_ong.editorialmanager.com&d=DwlGaQ&c=qqVugHHq3rzouXkEXdxBNQ&r=-O1oqMTjF2hpZa7nkSERnYhXDr3fNvLy04YDoyD-OLg&m=uGXR6plsPWLHSA3tgL4WjEEJNoxGtwu1acjhoHNRezc&s=nD0GZTsbVY5MY8LZ30qMEIPkJU14ZlqL7qLGAq0BRc4&e= (click on the Home button in the Menu bar and then "Reference Formatting Instructions" document under "Files and Resources"). Include the digital object identifier (DOI) with any journal article references and an accessed date with website references. Unpublished data, in-press items, personal communications, letters to the editor, theses, package inserts, submissions, meeting presentations, and abstracts may be included in the text but not in the reference list.

In addition, 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 at the Clinical Guidance page at <https://urldefense.proofpoint.com/v2/url?u=https->

[3A www.acog.org/clinical&d=DwlGaQ&c=ggVugHHq3rzouXkEXdxBNQ&r=-O1ogMTjF2hpZa7nkSERnYhXDr3fNvLy04YDoyD-OLg&m=uGXR6plsPWLHSA3tgL4WjEEJNoxGtwu1acjhoHNRezc&s=yKhX7AJgeJdccc-2hhUZ6lpXgWqFW8WzIJMQwKirmDA&e=](http://www.acog.org/clinical&d=DwlGaQ&c=ggVugHHq3rzouXkEXdxBNQ&r=-O1ogMTjF2hpZa7nkSERnYhXDr3fNvLy04YDoyD-OLg&m=uGXR6plsPWLHSA3tgL4WjEEJNoxGtwu1acjhoHNRezc&s=yKhX7AJgeJdccc-2hhUZ6lpXgWqFW8WzIJMQwKirmDA&e=) (click on "Clinical Guidance" at the top).

AUTHOR RESPONSE: We confirm we have read the journals guidelines for referencing and our manuscript conforms to journal policy.

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

Figure 1: Please upload as a figure file on Editorial Manager. Please update the bars to solid colors.

AUTHOR RESPONSE: We have uploaded as a separate file for Figure 1 in its original source and have updated the bars to solid colors.

14. Please change the portion of the acknowledgement thanking the working group members to Appendix 1. ("We thank the Pregnancy Risk Assessment Monitoring System (PRAMS) Working Group members..."). Renumber the subsequent appendixes in the manuscript text and appendixes file.

AUTHOR RESPONSE: We have retained acknowledgement of the working group and moved mention of the specific members to Appendix 1, as recommended.

Each supplemental file in your manuscript should be named an "Appendix," numbered, and ordered in the way they are first cited in the text (do not use wording such as "supplemental Table 1"). Do not order and number supplemental tables, figures, and text separately. References cited in appendixes should be added to a separate References list in the appendixes file.

AUTHOR RESPONSE: We have revised our Appendixes according these guidelines.