OBSTETRICS & GYNECOLOGY

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

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

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

Date: Apr 15, 2022
To: "Shari Snow" ssnow@bsd.uchicago.edu;sgdgmb@aol.com
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-22-499

RE: Manuscript Number ONG-22-499

Association of Progestogens and Venous Thromboembolism Among Women of Reproductive Age

Dear Dr. Snow:

Thank you for sending us your work for consideration for publication in Obstetrics & Gynecology. Your manuscript has been reviewed by the Editorial Board and by special expert referees. The Editors would like to invite you to submit a revised version for further consideration.

If you wish to revise your manuscript, please read the following comments submitted by the reviewers and Editors. Each point raised requires a response, by either revising your manuscript or making a clear argument as to why no revision is needed in the cover letter.

To facilitate our review, we prefer that the cover letter you submit with your revised manuscript include each reviewer and Editor comment below, followed by your response. That is, a point-by-point response is required to each of the EDITOR COMMENTS (if applicable), REVIEWER COMMENTS, STATISTICAL EDITOR COMMENTS (if applicable), and EDITORIAL OFFICE COMMENTS below. Your manuscript will be returned to you if a point-by-point response to each of these sections is not included.

The revised manuscript should indicate the position of all changes made. Please use the "track changes" feature in your document (do not use strikethrough or underline formatting).

Your submission will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by May 06, 2022, we will assume you wish to withdraw the manuscript from further consideration.

EDITOR COMMENTS:

1. Please pay particular attention to the Statistical Editor's concern regarding the imbalance of risk factors between the two groups.

2. Please provide more detail on how the "index date" was matched in the control group.

3. The Precis should be rephrased to better reflect the overall findings of the study.

REVIEWER COMMENTS:

Reviewer #1: ONG-22-499

General:
1. This is a nested case-control study of privately-insured reproductive-aged U.S. women, comparing progestin use between patients with acute VTE vs. controls. This is an excellent use of this type of data, and the authors have done a good job in controlling for potential confounders. This data significantly adds to the literature.

Abstract:
2. Line 26 - ratio should either be 1:5 (since VTE patients are listed first and controls second), or the order of naming should be reversed.
3. Would suggest adding dosing information to methods (i.e. that dosage range included in primary analysis, specifically for NETA and MPA which do not have standard dosing as for contraception).

Intro:
4. This is an excellent summary of existing evidence and justification for this study.

Methods:
5. Suggest increasing use of active voice in this section. This is otherwise a very clear explanation of the process.

Results:
6. This is very clear, however since most readers will not download online supplemental appendices, it may be helpful to include more information about outcomes in the text and print tables. For instance, eTable 5 is very relevant to readers and would be nice if it were easier to access. For the primary outcome (represented in figure 2), it would be helpful to comment on dosing for NETA (what was the average dose, what was the adjusted risk at 5mg, being the most common starting dose, versus higher doses, etc).

Discussion:
7. The paragraph beginning on line 254 does a very good job of explaining pharmacology and potential mechanisms for findings.
8. It would be helpful to contextualize VTE risk with high-dose progestogens against use with estrogen-containing methods. The authors state that NETA doses provide a similar amount of estrogen to combined OCPs - are the VTE rates also similar?
9. The final paragraph on implications suggests that guideline changes are needed for progestin prescribing - guidelines are a very broad instrument meant to be easily understood and followed, and do not generally account well for nuanced type/dosing or patient-specific factors. While this data is compelling, I question the appropriateness of changing guidelines based on a single case-control study, and the risks of diminishing access to progestins may cause other issues. Would consider moderating this stance.

Tables and Figures:
10. Would suggest including information in footnote about why LNG-IUD was not significant (it's included in text but since tables should be able to stand alone and it's not immediately clear, would suggest stating here as well).

Reviewer #2:

OVERALL: This is an original research study describing a case-control study examining the association of risk of venous thromboembolism and progestogen use. This is a strong study given the large sample size and the authors address succinctly the strengths and limitations of using claims-data. The authors found an association with VTE risk and current use of higher dose progestogens (norethindone acetate, oral MPA and injectable DMPA). This study adds to the literature in the need to examine the role that progestogens (without concomitant use of estrogen) plays in the risk for thrombosis. The study did not require IRB approval and the STROBE and RECORD checklist is included with submission.

OVERALL:
- Consider spelling out all numbers less than 10.

INTRODUCTION:
- The aim of the study is clearly stated: evaluating association between current use of 7 progestins and incident acute VTE compared with non-use of any progestin.

- Line 51: When referencing the 22 studies that assess the association between progestin use and VTE, please state where and how those studies were found. Was a separate review conducted or were all references found in the 3 cited systematic reviews: Tepper 2016, Mantha 2012, and Glisic 2018? Some of the studies cited (Ref 4-12) are not about progestin-only methods and include estrogen containing methods.

- Lines 53-60: Suggest being more clear and citing references about dosage and potency of the different progestin-only methods and not just stating what is very low dose, low dose, moderate dose or high dose.

- Lines 57, 60: When presenting risks in the background, suggest stating it without the actual data from the cited study. For example, "a recent meta-analysis found that injectable DMPA had a 2.5-fold increased risk of VTE" and "Non-contraceptive progestins have also been associated with a 2.5-6-fold increased risk of VTE in 4 small studies."

- Lines 61-63: Be more specific about who and how "clinical guidelines and experts disagree" on use of higher dose progestins among those with increased VTE risk.

MATERIALS AND METHODS:
- Consider making a comment that prescription claims for non-LARC methods does not confirm that patient was taking the medication. Claims data is a proxy for use.

- Please clarify how progestogen exposure was defined as Table 1 needs to be matched up with how methods are prescribed and used.

- Patients were included only with continuous enrollment for the previous year before the index date so I assume that progestogen exposure was only examined in the same time period. If so, you may be misclassifying women using implants and LNG-IUDs who initiated before that year. Consider extending the exposure period to a longer period (e.g. 3-5 years before index date) in order to capture these users.

- In Table 1, current use is defined as within 28 days before the index date. Please describe more about how this works for LNG-IUDs and implants - were removal codes identified? Would only want to include those with implant/LNG-IUD insertion code without a removal code during the exposure period. So, if there was an insertion code at any time during the study period and no removal code, then exposure in the 28 days before the index date is assumed? Same for the other time periods.

- This applies to DMPA and pills, too - what's the specific window for DMPA (does injection 90 + 28 days before the index date count as "current use"?) What about pills that may be claimed in 3 month (or more) increments?

Reviewer #3: The authors present a nested control study on the association between progestins and VTE risk. This is a well done hypothesis generating study that is important given the amount of progestins currently being used for a variety of reasons.

Specific comments:
1) Line 77- please specific define what VTE Is (DVT +PE) if that is what your are using

2) Line 90- how did you define a superficial DVT?

3) Line 101: What was the logic in a 50:1 ratio--> this seems to be a high ratio and maybe falsely pushing your association.

4) Line 110--> why was megestrol acetate not included, this is a common progestin for pre-invasive disease of the endometrium and is commonly used.

5) Line 137--> If claims data did not allow you to determine indication, how can you accurately know what the indication for progestational therapy was?

6) Globally, the methods section is far to verbose and should be cut down; much of this should be moved to supplemental data.

7) The results section should be redone to include more of the data presented in the table. As written it is descriptive.

8) The discussion is well written and not overreaching.

STATISTICAL EDITOR COMMENTS:

Table 2: The cases and controls were well matched by study design, but the cases differed in multiple risk factors for VTE, e.g., obesity, smoking, atherosclerosis, HTN, CHF, cancer, hx of recent surgery, hospitalization or LE fracture. Do the results represent proper adjustment for all of these comorbidities? Do the results only apply to women with those comorbidities who are given progestogens? Also, the number of cases and controls for current or recent use of multiple progestogens are too few to allow for multivariable adjustment. Likely those aORs are over fitted. For the single progestogen dose groups, need to use propensity score matching to corroborate the conclusions.

lines 176-177, 204-206, Fig 2: Since the inference threshold was set at < 0.01, not < 0.05, then the CIs should all be 99%, not 95% CIs. Could put the 95% CIs in appendix, if desired (lines 183-184).

lines 194-195: What were the ORs for progesterone use among the 33.7% of cases and the 74.6% of controls who each had no identified risk factors for VTE? Similarly for the comparisons by chronicity?

EDITORIAL OFFICE COMMENTS:

1. If your article is accepted, the journal will publish a copy of this revision letter and your point-by-point responses as supplemental digital content to the published article online. You may opt out by writing separately to the Editorial Office at em@greenjournal.org, and only the revision letter will be posted.

2. When you submit your revised manuscript, please make the following edits to ensure your submission contains the required information that was previously omitted for the initial double-blind peer review:
* Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and at the end of the abstract. For industry-sponsored studies, describe on the title page how the funder was or was not involved in the study.
* Include clinical trial registration numbers, PROSPERO registration numbers, or URLs at the end of the abstract (if applicable).
* Name the IRB or Ethics Committee institution in the Methods section (if applicable).
* Add any information about the specific location of the study (ie, city, state, or country), if necessary for context.

3. Obstetrics & Gynecology's Copyright Transfer Agreement (CTA) must be completed by all authors. When you uploaded your manuscript, each coauthor received an email with the subject, "Please verify your authorship for a submission to Obstetrics & Gynecology." Please ask your coauthor(s) to complete this form, and confirm the disclosures listed in their CTA are included on the manuscript's title page. If they did not receive the email, they should check their spam/junk folder. Requests to resend the CTA may be sent to em@greenjournal.org.

4. ACOG uses person-first language. Please review your submission to make sure to center the person before anything else. Examples include: "Patients with obesity" instead of "obese patients," "Women with disabilities" instead of "disabled women," "women with HIV" instead of "HIV-positive women," "women who are blind" instead of "blind women."

5. Please add whether you received IRB or Ethics Committee approval or exemption to your Methods. Include the name of the IRB or Ethics Committee. If you received an exemption, explain why in this section.

6. 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:

CHEERS: economic evaluations of health interventions
CHERRIES: studies reporting results of Internet e-surveys
CONSERVE: reporting trial protocols and completed trials modified due to the COVID-19 pandemic and other extenuating circumstances
CONSORT: randomized controlled trials
MOOSE: meta-analyses and systematic reviews of observational studies
PRISMA: meta-analyses and systematic reviews of randomized controlled trials
PRISMA for harms: PRISMA for harms
RECORD: observational studies using ICD-10 data
STARD: studies of diagnostic accuracy
STROBE: observational studies
SQUIRE 2.0: quality improvement in health care studies

Include the appropriate checklist for your manuscript type upon submission, if applicable, and indicate in your cover letter which guideline you have followed. 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 www.equator-network.org/.

7. 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.

8. Make sure your manuscript meets the following word limit. The word limit includes the manuscript body text only (for example, the Introduction through the Discussion in Original Research manuscripts), and excludes the title page, précis, abstract, tables, boxes, and figure legends, reference list, and supplemental digital content. Figures are not included in the word count.

Original Research: 3,000 words

9. Specific rules govern the use of acknowledgments in the journal. Please review the following guidelines and edit your title page as needed:

* 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 or indicate whether the meeting was held virtually).
* If your manuscript was uploaded to a preprint server prior to submitting your manuscript to Obstetrics & Gynecology, add the following statement to your title page: "Before submission to Obstetrics & Gynecology, this article was posted to a preprint server at: [URL]."
* Do not use only authors' initials in the acknowledgement or Financial Disclosure; spell out their names the way they appear in the byline.

10. Be sure that each statement and any data in the abstract are also stated in the body of your manuscript, tables, or figures. Statements and data that appear in the abstract must also appear in the body text for consistency. Make 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 manuscript.

In addition, the abstract length should follow journal guidelines. Please provide a word count.

Original Research: 300 words

11. 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.

12. The journal does not use the virgule symbol (/) in sentences with words, except with ratios. 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.

13. 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.

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

Express all percentages to one decimal place (for example, 11.1%"). Do not use whole numbers for percentages.

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

15. Please review examples of our current reference style at https://edmgr.ovid.com/ong/accounts/ifa_suppl_refstyle.pdf. 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 formal reference list. Please cite them on the line in parentheses.

If you cite ACOG documents in your manuscript, be sure the references you are citing are still current and available. Check the Clinical Guidance page at https://www.acog.org/clinical (click on "Clinical Guidance" at the top). If the reference is still available on the site and isn't listed as "Withdrawn," it's still a current document. In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript.

Please make sure your references are numbered in order of appearance in the text.

16. Figures 1-2: Please upload as figure files on Editorial Manager.

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

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.

***

If you choose to revise your manuscript, please submit your revision through Editorial Manager at http://ong.editorialmanager.com. Your manuscript should be uploaded as a Microsoft Word document. Your revision's cover letter should include a point-by-point response to each of the received comments in this letter. Do not omit your responses to the EDITOR COMMENTS (if applicable), the REVIEWER COMMENTS, the STATISTICAL EDITOR COMMENTS (if applicable), or the EDITORIAL OFFICE COMMENTS.

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

Again, your manuscript will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by May 06, 2022, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Jason D. Wright, MD
Editor-in-Chief

2020 IMPACT FACTOR: 7.661
2020 IMPACT FACTOR RANKING: 3rd out of 83 ob/gyn journals

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Jason D. Wright, MD
Editor-in-Chief
Obstetrics & Gynecology

May 5, 2022

Dear Dr. Wright,

We appreciate the thoughtful comments from the editors and reviewers on our manuscript entitled, “Association of Progestogens and Venous Thromboembolism Among Women of Reproductive Age.” Below are point-by-point responses (indented by ½ inch margin) with references to edits made to the manuscript and appendix. We hope that our detailed responses to the well stated concerns from the Statistical Editor have been addressed. For item #3, we would kindly ask for a short extension to complete this additional sensitivity analysis if it is still desired after reviewing our reply.

Sincerely,

Shari G. Snow, MD
Chief of Gynecology and Minimally Invasive Surgery
Associate Professor of Obstetrics and Gynecology
University of Chicago Medicine and Biological Sciences Division

EDITOR COMMENTS:

1. Please pay particular attention to the Statistical Editor's concern regarding the imbalance of risk factors between the two groups.

    See responses to the Statistical Editor’s comments below.

2. Please provide more detail on how the "index date" was matched in the control group.

The index date for cases was defined as the first date of claims including VTE diagnoses. Since controls do not have this occurrence, their index date was set to the index date of their matched case (e.g., if VTE claims were first identified on 1/1/2012 for a case, then its matched controls were assigned 1/1/2012 as their index date). Matching on time in this way ensured that controls have continuous enrollment during the same period of exposure as their matched case. We hope the revision in lines 119-121 addresses the ambiguity of the original statement.

3. The Precis should be rephrased to better reflect the overall findings of the study.

Our original precis highlighted the simply stated positive findings. We agree it did not capture equally important null associations for other progestogens. Our revision (lines 4-7) seeks to convey our overall impression instead. The conclusion of the abstract was accordingly adjusted as well (lines 47-50).

REVIEWER COMMENTS:

Reviewer #1: ONG-22-499

General:

1. This is a nested case-control study of privately-insured reproductive-aged U.S. women, comparing progestin use between patients with acute VTE vs. controls. This is an excellent use of this type of data, and the authors have done a good job in controlling for potential confounders. This data significantly adds to the literature.

Abstract:

2. Line 26 - ratio should either be 1:5 (since VTE patients are listed first and controls second), or the order of naming should be reversed.

We thank the reviewer for identifying this error. It has been corrected in line 29. This was also corrected in the results section, line 217.

3. Would suggest adding dosing information to methods (i.e. that dosage range included in primary analysis, specifically for NETA and MPA which do not have standard dosing as for contraception).

The reviewer brings up an important aspect of the methods in which progestogen exposure was treated as a binary variable, irrespective of dose, for the modified hierarchy and primary analysis. We hope an additional statement highlighting the variable dosing for oral progestogens in the secondary analyses in lines 37-38 adequately but succinctly addresses this detail within the abstract. We have also added descriptive statistics to the results section to more precisely address the actual dose range in this study population, lines 250-253.

Intro:

4. This is an excellent summary of existing evidence and justification for this study.

Methods:

5. Suggest increasing use of active voice in this section. This is otherwise a very clear explanation of the process.

> The reviewer makes a valid note that active voice generally improves readability. For the methods section, we have purposefully used passive voice to draw attention to the direct object of the verb. For example, the first sentence of the 2nd, 3rd, 4th, 5th, and 6th paragraphs use passive voice so that the leading phrase clearly identifies the topic for that paragraph (cases, exclusions, controls, exposures, and covariates, respectively). This structure may permit a reader to quickly skim these sections as if paragraph headers were used. We are open to specific suggestions for edits though.

Results:

6. This is very clear, however since most readers will not download online supplemental appendices, it may be helpful to include more information about outcomes in the text and print tables. For instance, eTable 5 is very relevant to readers and would be nice if it were easier to access. For the primary outcome (represented in figure 2), it would be helpful to comment on dosing for NETA (what was the average dose, what was the adjusted risk at 5mg, being the most common starting dose, versus higher doses, etc).

> The reviewer makes an excellent observation that the potential for a dose-response relationship might be missed by averaging dose for non-contraceptive progestogens in the primary (binary) analysis. We did not include the secondary analysis tables (chronicity or dose) in the main text due to increased Type I error with multiple testing and small sample sizes in each category (e.g., estimates from high dose use had wide CIs). However, we agree that descriptive data helps understand the magnitude of exposure studied even if statistical comparisons cannot be made between groups. eTable 5 has been moved to the main text as Table 3. We added the percent of users meeting criteria for “low” or “standard” dose and provide the median and interquartile ranges, see lines 250-253.

Discussion:

7. The paragraph beginning on line 254 does a very good job of explaining pharmacology and potential mechanisms for findings.

8. It would be helpful to contextualize VTE risk with high-dose progestogens against use with estrogen-containing methods. The authors state that NETA doses provide a similar amount of estrogen to combined OCPs - are the VTE rates also similar?

> We agree with the reviewer that the most clinically relevant active comparator group would be OCP users. We initially considered comparisons between published data on OCP use and VTE with our own findings. To directly answer the question, estimates of absolute risk in our study for DMPA and NETA (lines 243-249) are similar to those for OCP users in literature (at 15-24yo: 5 [3-8] excess VTEs per 10,000 woman-years; at 45-49yo: 9 [5-13] excess VTEs per 10,000 woman-years) though we cannot calculate rate over time estimates from the case-control design.
>
> In this case-control design, it is likely that the population of progestogen users is different from recent OCP users that were explicitly excluded due to unmeasured confounders and selection bias (i.e., OCP users are more likely than non-users to receive empiric

anticoagulation for VTE symptoms because of well-known risks). Healthy user bias in OCP studies likely does not apply for progestogens. This difference in baseline risk is best demonstrated by comparing the effect of covariate adjustment in these groups, where the ORs for OCP use often increase with more adjustment (Vinogradova et al., 2015) and ORs for progestogen use uniformly decreased in our study. We hope that the additional statement in lines 322-324 succinctly addressed this limitation of our data.

9. The final paragraph on implications suggests that guideline changes are needed for progestin prescribing - guidelines are a very broad instrument meant to be easily understood and followed, and do not generally account well for nuanced type/dosing or patient-specific factors. While this data is compelling, I question the appropriateness of changing guidelines based on a single case-control study, and the risks of diminishing access to progestins may cause other issues. Would consider moderating this stance.

The reviewer raises a well-founded concern about the scope of the concluding paragraph advising reconciliation in broad guidelines. Our intent was a call to action that guidelines could (1) acknowledge that the association of progestogen use and VTE is not completely understood and (2) spur interest in funding research that could assess causality. We agree it is too broad as currently written and would like to retract the specific instruction regarding clinical guidelines. See lines 333-335.

Tables and Figures:

10. Would suggest including information in footnote about why LNG-IUD was not significant (it's included in text but since tables should be able to stand alone and it's not immediately clear, would suggest stating here as well).

We thank the reviewer for raising our attention to this omission, and we agree that the figure should be able to stand alone. In our change to 99% CIs as requested by the Statistical Editor, this issue will be self-resolved.

Reviewer #2:

OVERALL: This is an original research study describing a case-control study examining the association of risk of venous thromboembolism and progestogen use. This is a strong study given the large sample size and the authors address succinctly the strengths and limitations of using claims-data. The authors found an association with VTE risk and current use of higher dose progestogens (norethindone acetate, oral MPA and injectable DMPA). This study adds to the literature in the need to examine the role that progestogens (without concomitant use of estrogen) plays in the risk for thrombosis. The study did not require IRB approval and the STROBE and RECORD checklist is included with submission.

OVERALL:

- Consider spelling out all numbers less than 10.

We have made this change throughout the main text and appendix.

INTRODUCTION:

- The aim of the study is clearly stated: evaluating association between current use of 7 progestins and incident acute VTE compared with non-use of any progestin.

- Line 51: When referencing the 22 studies that assess the association between progestin use and VTE, please state where and how those studies were found. Was a separate review conducted or were all references found in the 3 cited systematic reviews: Tepper 2016, Mantha 2012, and Glisic 2018? Some of the studies cited (Ref 4-12) are not about progestin-only methods and include estrogen containing methods.

  We thank the reviewer for their careful attention to references. Our research question was inspired by the systematic review by Tepper et al., which called for studies of adequate sample size to investigate the full spectrum of progestogens. We identified the other two systematic reviews and then manually reviewed all citations. We noted 17 studies relevant to the outcome of VTE. We did not produce another systematic review since one had been recently done by Glisic et al. but used similar search terms to identify 3 more recent relevant studies (references 7, 8, and 12). Reference 10 was not identified by any review likely due to omission of the terms progestin or progestogen in the abstract or key words. Reference 9 was designed to assess combined hormonal contraception (and so was not included in systematic reviews) but contains the current largest sample size of oral progestogen-only users (n=541 exposed cases), available only in the online supplement. To minimize the reference list length within word count restrictions, we cited the 3 literature reviews and the 5 additional studies described.

- Lines 53-60: Suggest being more clear and citing references about dosage and potency of the different progestin-only methods and not just stating what is very low dose, low dose, moderate dose or high dose.

  The reviewer raises an excellent concern regarding assignment of progestogens to arbitrary categories of very low, low, moderate, and high. Bergendal et al. (2009, 2014) have been the only group to tackle the challenge of meaningfully grouping different progestogen formulations relevant to VTE risk. These determinations were approximated to the dose required to suppress ovulation or follicular development. This measure is a simple proxy for the systemic exposure from progestogens with different activity and potency at various receptors (progesterone, androgen, glucocorticoid, mineralocorticoid). We modified this hierarchy to add non-contraceptive progestogens (Prog, MPA, and NETA) using the same approach with typical dosing to determine the rank order. We hope that the additional clarifying statement in lines 64-66 will provide better context of the existing literature from which we used the categorical assignment of progestogen dose. Accordingly, we removed a repetitive phrase from the methods in lines 149-150.

- Lines 57, 60: When presenting risks in the background, suggest stating it without the actual data from the cited study. For example, "a recent meta-analysis found that injectable DMPA had a 2.5-fold increased risk of VTE" and "Non-contraceptive progestins have also been associated with a 2.5-6-fold increased risk of VTE in 4 small studies."

  We thank the reviewer for this suggestion and hope the changes to lines 71-72 and lines 74-75 improve readability accordingly.

- Lines 61-63: Be more specific about who and how "clinical guidelines and experts disagree" on use of higher dose progestins among those with increased VTE risk.

  The reviewer brings up a good point for clarification since we do not express the direction of this disagreement on existing studies by guidelines and experts. We hope

our revision on lines 76-80 clarifies that guidelines (e.g., ACOG, reference 19) generally do not restrict use of any progestogens with respect to VTE risk factors but that some authors have called this into question for higher dose options (DMPA, NETA). Huvinen et al. (2021) authored an excellent narrative review of NET and NETA and serves as an example of such commentary. Our revision uses the more appropriate term author instead of expert in this context.

MATERIALS AND METHODS:

- Consider making a comment that prescription claims for non-LARC methods does not confirm that patient was taking the medication. Claims data is a proxy for use.

We agree that this important limitation should be acknowledged in the methods section, see line 133. If desired for word count, it could be removed from lines 309-310 in the discussion.

- Please clarify how progestogen exposure was defined as Table 1 needs to be matched up with how methods are prescribed and used.

The reviewer identifies an important distinction in measuring exposures in this study, which we hope will be clearer with a small adjustment (see line 132-134 and line 142-143). Progestogen exposure was defined by the prescriptions or medical/pharmacy claims. The full details (e.g., medication names, diagnosis codes, procedure codes, etc.) are provided in the appendix (p3, eMethods). This level of detail is recommended by the RECORD-PE guidelines to ensure exposures were adequately captured and matched to appropriate time windows.

The exposure characteristics in Table 1 were used to generate secondary/ sensitivity analyses for recency (current, recent), dose (weighted average daily dose), and chronicity (new, chronic, prior, former). The terms must be broad enough to apply to oral and non-oral formulations (recency and chronicity) and for continuous or cyclic use (dose). These characterizations and terms mirror many other published pharmacoepidemiological studies.

- Patients were included only with continuous enrollment for the previous year before the index date so I assume that progestogen exposure was only examined in the same time period. If so, you may be misclassifying women using implants and LNG-IUDs who initiated before that year. Consider extending the exposure period to a longer period (e.g. 3-5 years before index date) in order to capture these users.

The reviewer makes an excellent observation of a limitation from left-truncation of LARC device exposure. Unfortunately the requirement for continuous enrollment was a major contributor to case exclusion, and sample size would have been inadequate using an such an extended surveillance period. Also, since the non-user reference group was so large, under-ascertainment of devices was unlikely to meaningfully affect the summary odds ratio. We can include a statement to this effect in the limitations section if desired and balanced against word count restraints.

- In Table 1, current use is defined as within 28 days before the index date. Please describe more about how this works for LNG-IUDs and implants - were removal codes identified? Would only want to include those with implant/LNG-IUD insertion code without a removal code during

the exposure period. So, if there was an insertion code at any time during the study period and no removal code, then exposure in the 28 days before the index date is assumed? Same for the other time periods.

> The eMethods (appendix p3, “progestogen exposure definitions,” 3rd paragraph) detail how insertion and removal codes were identified and reconciled when one or other was identified in isolation. eTable 10 contains relevant codes. We did not address them in the main text due to the tedious nature of the explanation. Briefly, exposure after an insertion code was assumed to continue through the index date if no removal code was identified prior to that date.

- This applies to DMPA and pills, too - what's the specific window for DMPA (does injection 90 + 28 days before the index date count as "current use"?) What about pills that may be claimed in 3 month (or more) increments?

> See above response and eMethods (appendix p3, “progestogen exposure definitions,” 2nd and 3rd paragraph). eTable 10 contains relevant codes. Briefly, exposure was continued from the start date (prescription fill date or injection date) until an end date (90 days for DMPA, based on days supply for pills). For example, if DMPA was administered 100 days before the index date, the exposure ends 10 days before the index date. Since the end of exposure falls within 28 days of the index date, this meets current use criteria.

Reviewer #3: The authors present a nested control study on the association between progestins and VTE risk. This is a well done hypothesis generating study that is important given the amount of progestins currently being used for a variety of reasons.

Specific comments:

1) Line 77- please specific define what VTE Is (DVT +PE) if that is what your are using

> The opening sentence of the introduction (line 50-51) defines VTE as DVT, PE, or both, but the reviewer makes an excellent suggestion to remind the reader of this definition when it is relevant again in the methods. Please see revision to line 91. In accordance with STROBE/ RECORD-PE reporting guidelines, additional details and the discrete ICD-9 and ICD-10 diagnoses codes used are provided in appendix (page 3, “case and control selection”).

2) Line 90- how did you define a superficial DVT?

> We thank the reviewer for bringing an error to our attention. We describe that “superficial VTE” was evaluated as a covariate, but the definition in the appendix is for superficial venous thrombophlebitis. We meant to consistently use the nomenclature of “superficial venous thrombosis” (Table 2) to emphasize its difference from the defining diagnoses of VTE. All instances have been corrected to this preferred term. This is corrected on line 107-108 and in all tables/ footnotes. The diagnosis codes for superficial venous thrombosis are provided in the appendix, eTable 10, in accordance with RECORD-PE guidelines.

3) Line 101: What was the logic in a 50:1 ratio--> this seems to be a high ratio and maybe falsely pushing your association.

We agree with the concerns of the reviewer that including matched controls beyond a 4:1 or 5:1 ratio in the analysis would not be likely to improve estimates of a true association. The initial match at 50:1 was performed for statistical efficiency in control selection but only a 5:1 ratio was used for the analysis (lines 129-130; Figure 1, right side). Some exclusion criteria were applied in a discrete time window around the index date (e.g., no estrogen use or pregnancy within 84 days of the index date was permitted). It was impossible to know prior to matching if controls were eligible for a specific case. By starting with 50 possible matches based on year of birth alone, we felt each stratum was very likely to retain at least 5 matches after exclusions. Excess controls were removed randomly to avoid selection bias. Only 2 cases did not meet this threshold and were excluded as noted in Figure 1.

4) Line 110--> why was megestrol acetate not included, this is a common progestin for pre-invasive disease of the endometrium and is commonly used.

We decided to exclude megestrol acetate (lines 108-113) for three reasons. First, endometrial intraepithelial neoplasia (where pathology at time of hysterectomy is often up-staged) and metastatic or recurrent uterine and breast cancers are indications for progestogen use that may directly mediate VTE occurrence. In contrast, need for contraception and benign menstrual disorders have not been strongly associated with VTE. Given the differential risk of residual confounding, we did not feel our study design could effectively assess this exposure. Secondly, megestrol acetate is less commonly used in our study population of women 15-49 years old than other progestogens, so we did not anticipate the study would be powered to include it as an exposure. Third, other studies (references 16, 32, and 33) have already discussed significant associations with VTE for megestrol acetate, noting that it is typically used in a different population of women than other progestogens.

5) Line 137--> If claims data did not allow you to determine indication, how can you accurately know what the indication for progestational therapy was?

The reviewer highlights an important limitation of these data as noted in the methods, lines 135-138 and in the discussion, lines 318-321. We considered using associated diagnosis codes around the time of new prescriptions to account for this, but the pharmacy claims data did not include a unique indication for each prescription. Patients may use progestogens for 1 or multiple concurrent indications (e.g., dysmenorrhea/ contraception, endometriosis/ abnormal uterine bleeding). Ascertainment of diagnosis codes would still not permit accurate attribution, especially since codes related to contraception are significantly underreported. We do not attempt to control for indication for use but describe that some formulations (NET and Implant) are most often used for contraception only and others (Prog, MPA, and NETA) are not approved for contraception. An important consideration therefore is that the L-IUD and DMPA can be effectively used for both indications, have no direct estrogen-containing equivalent method, and had different VTE associations that were congruent with the underlying dose-response hypothesis.

6) Globally, the methods section is far to verbose and should be cut down; much of this should be moved to supplemental data.

We acknowledge the tedious detail for portions of the methods and agree with the reviewer that some of these specifications are not essential for the average reader. We felt it important however to address as many items as possible from the RECORD-PE checklist in the main text. Two segments were moved to the appendix as suggested, see lines 88-90 and lines 138-142, and one was omitted, lines 167-172.

We welcome suggestions for additional content permitted to be moved to the appendix given the extensive requests for detail from the reporting guidelines. In particular, the descriptions of exclusions (lines 105-117) and covariates (lines 156-163) could be moved to the appendix if preferred. In the main text for those sections, we would instead reference Figure 1 and Table 2, respectively.

7) The results section should be redone to include more of the data presented in the table. As written it is descriptive.

The adjusted estimates from the primary analysis have been added to the text, lines 231-237. We had initially omitted these to conserve word count since they are available in Figure 2 and are best communicated with other relevant tabular data.

8) The discussion is well written and not overreaching.

STATISTICAL EDITOR COMMENTS:

Table 2: The cases and controls were well matched by study design, but the cases differed in multiple risk factors for VTE, e.g., obesity, smoking, atherosclerosis, HTN, CHF, cancer, hx of recent surgery, hospitalization or LE fracture. Do the results represent proper adjustment for all of these comorbidities? Do the results only apply to women with those comorbidities who are given progestogens? Also, the number of cases and controls for current or recent use of multiple progestogens are too few to allow for multivariable adjustment. Likely those aORs are over fitted. For the single progestogen dose groups, need to use propensity score matching to corroborate the conclusions.

The statistical editor raises several important questions regarding the adjustment for confounders through study design and analytic methods. We humbly submit the following responses to each point. First, the ability to adjust for measured confounders is dependent on the opportunity for ascertainment and on coding accuracy. In this study using administrative claims data, we were primarily restricted to using ICD-9 and ICD-10 diagnosis codes and used validated code sets whenever possible (appendix: eMethods and eTable 12). Covariates were selected based established VTE risk factors from epidemiological studies of VTE and from similar case-control studies. Some factors such as obesity and history of smoking were certainly underestimated compared to epidemiological data, but not likely to significantly confound overall findings (see line 314-316 in limitations). Within the limits of the source data required to provide an ideal sample size, we felt this approach was adequate and comparable to other similar case-control study designs. Other studies on progestogens and VTE have included far fewer confounders.

Second, we felt the method of adjustment by conditional logistic regression was appropriate based on study design and the large sample size, where the number of cases (21,405) exceeded 1,000 times the number of covariates (16). The rare frequency

of progestogen use should not impair the ability to adjust for the independent odds ratios for measured covariates (provided for NETA as one example, eTable 3). This method is a common approach for matched case-control studies and should provide relevant estimates for progestogen users with or without the measured VTE risk factors. It does not address bias from confounding due to unmeasured baseline differences in exposed and unexposed populations. In lieu of a randomized trial, one option to make the cases and controls more similar would be propensity score or multiple factor matching on comorbidities. As noted in the STROBE reporting guidelines (box 2), matching on multiple risk factors to create more similar case-control sets will introduce bias as well, and the control population will no longer reflect the general population (though already limited by exclusion criteria in our study). Age and time are critical universal matching factors because of the significant impact on progestin use frequency (eFigure 3 and eFigure 4) and are often employed in pharmacoepidemiological studies on VTE.

Regarding propensity score matching, there are additional limitations for case-control studies compared with the more typical application to cohort studies (Mansson et al., 2007; doi.org/10.1093/aje/kwm069). Effect modification may result from artifact when a true association exists, and residual confounding would still not be excluded. Use of propensity scores might also require separate study populations if covariates remained unbalanced from differences between users of progestogen types. For example, younger age increases likelihood of use for DMPA and Implant but decreases likelihood for Prog. A cohort study for each progestogen with propensity score matching would have been a stronger design but would have significantly reduced statistical efficiency. Covariate-adjustment of the propensity score alone has been discouraged by some authors (Williamson and Forbes, 2014; doi.org/10.1111/resp.12312) and would not likely provide a substantially different estimate (Shah et al., 2005; doi.org/10.1016/j.jclinepi.2004.10.016). Indeed, we elected for case-control design (and the resultant large sample size) so that hypotheses generated on a dose-response relationship between progestogens and VTE might spur future research that could better address the above issues. We added lines 123-126 in the methods and lines 321-322 in the limitations to highlight our rationale.

Finally, we agree that there are too few users of multiple progestogens (mixed use) to support a separate model. To account for this, all users of more than one progestogen were assigned a primary exposure based the highest dose option from modified hierarchy (see lines 145-149). For example, a current user of both DMPA and the Implant would have been classified as being exposed to only DMPA in the analysis. We felt this would not affect summary estimates since users of multiple progestogens represented 3% or less of all progestogen users among cases and controls.

We greatly appreciate the inquires of the statistical editor and hope that these responses adequately address the concerns for study design and analytic approach.

lines 176-177, 204-206, Fig 2: Since the inference threshold was set at < 0.01, not < 0.05, then the CIs should all be 99%, not 95% CIs. Could put the 95% CIs in appendix, if desired (lines 183-184).

This change has been made to all results in text, tables, and figure 2. We appreciate the suggestion to include the original data in the appendix but will defer to avoid confusion

by the reader. Our intent with using 95% CIs was to improve comparability with prior similar studies (Bergendal et al., 2014; Lidegaard et al., 2012) that used the same. One of the largest studies on the association of OCPs and VTE (Vinogradova et al., 2015) similarly used a 1% threshold for significance and 95% CIs. However, we acknowledge that this is non-standard and gladly present the 99% CIs instead.

lines 194-195: What were the ORs for progesterone use among the 33.7% of cases and the 74.6% of controls who each had no identified risk factors for VTE? Similarly for the comparisons by chronicity?

Residual confounding by indication is the most important source of bias in our study, but we are limited in the capacity to address this due to the rare outcome and rare exposure being studied. A sensitivity analysis excluding all measurable VTE risk factors would reduce the sample size to ~7,200 cases matched 3.75:1 to controls and would likely be underpowered to assess associations within the expected effect size range. Excluding all risk factors also increases weighting of common, weak VTE risk factors such as hypertension and decreases weighting of rare, strong VTE risk factors like hemiplegia/ paraplegia. Further, we cannot create a population without any risk factors from this routinely collected health data since we cannot measure all exposures like recent prolonged travel, immobilization, and family history.

Nonetheless we appreciate the information that this sensitivity analyses could provide, though likely with wide CIs. If still desired, we ask for a short extension to allow for statistical computation and revision to the manuscript text and appendix tables.

EDITORIAL OFFICE COMMENTS:

1. If your article is accepted, the journal will publish a copy of this revision letter and your point-by-point responses as supplemental digital content to the published article online. You may opt out by writing separately to the Editorial Office at em@greenjournal.org, and only the revision letter will be posted.

We accept publication of these responses.

2. When you submit your revised manuscript, please make the following edits to ensure your submission contains the required information that was previously omitted for the initial double-blind peer review:

* Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and at the end of the abstract. For industry-sponsored studies, describe on the title page how the funder was or was not involved in the study.

* Include clinical trial registration numbers, PROSPERO registration numbers, or URLs at the end of the abstract (if applicable).

* Name the IRB or Ethics Committee institution in the Methods section (if applicable).

* Add any information about the specific location of the study (ie, city, state, or country), if necessary for context.

The funding information with disclaimer required by the NIH are added to the title page and abstract. The institutional IRB name was added to lines 213-214.

3. Obstetrics & Gynecology's Copyright Transfer Agreement (CTA) must be completed by all authors. When you uploaded your manuscript, each coauthor received an email with the subject, "Please verify your authorship for a submission to Obstetrics & Gynecology." Please ask your coauthor(s) to complete this form, and confirm the disclosures listed in their CTA are included on the manuscript's title page. If they did not receive the email, they should check their spam/junk folder. Requests to resend the CTA may be sent to em@greenjournal.org.

A statement on disclosures was added to the title page. All authors attest to no disclosures.

4. ACOG uses person-first language. Please review your submission to make sure to center the person before anything else. Examples include: "Patients with obesity" instead of "obese patients," "Women with disabilities" instead of "disabled women," "women with HIV" instead of "HIV-positive women," "women who are blind" instead of "blind women."

The manuscript has been reviewed thoroughly. We identified one change, line 329.

5. Please add whether you received IRB or Ethics Committee approval or exemption to your Methods. Include the name of the IRB or Ethics Committee. If you received an exemption, explain why in this section.

Rationale for exemption due to de-identified data is included, line 213.

6. 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:

CHEERS: economic evaluations of health interventions

CHERRIES: studies reporting results of Internet e-surveys

CONSERVE: reporting trial protocols and completed trials modified due to the COVID-19 pandemic and other extenuating circumstances

CONSORT: randomized controlled trials

MOOSE: meta-analyses and systematic reviews of observational studies

PRISMA: meta-analyses and systematic reviews of randomized controlled trials

PRISMA for harms: PRISMA for harms

RECORD: observational studies using ICD-10 data

STARD: studies of diagnostic accuracy

STROBE: observational studies

SQUIRE 2.0: quality improvement in health care studies

Include the appropriate checklist for your manuscript type upon submission, if applicable, and indicate in your cover letter which guideline you have followed. 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 www.equator-network.org/.

> The RECORD-PE checklist was provided in the original submission, though page numbers have changed with our revisions. If the checklist will be published, we can update the page numbers in the final version, since these will change again.

7. 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.

> The reVITALize definitions are not relevant to this manuscript.

8. Make sure your manuscript meets the following word limit. The word limit includes the manuscript body text only (for example, the Introduction through the Discussion in Original Research manuscripts), and excludes the title page, précis, abstract, tables, boxes, and figure legends, reference list, and supplemental digital content. Figures are not included in the word count.

Original Research: 3,000 words

> Current word count at 3,163 exceeds this maximum to address the reviewer comments. We humbly request exception to the word max to allow for these clarifications. Otherwise, we have made 2 suggestions to move some of the methods to the appendix in response to reviewer #3, comment #6. If permissible, this edit would reduce word count below 3,000.

9. Specific rules govern the use of acknowledgments in the journal. Please review the following guidelines and edit your title page as needed:

* 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 or indicate whether the meeting was held virtually).

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* Do not use only authors' initials in the acknowledgement or Financial Disclosure; spell out their names the way they appear in the byline.

The only relevant addition from item #9 is that portions of this work were presented at two meetings of professional organizations. This information was added to the title page.

10. Be sure that each statement and any data in the abstract are also stated in the body of your manuscript, tables, or figures. Statements and data that appear in the abstract must also appear in the body text for consistency. Make 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 manuscript.

In addition, the abstract length should follow journal guidelines. Please provide a word count.

Original Research: 300 words

The revised abstract contains 310 words to address reviewer comments. If needed, a lower word count could be managed by deleting the proposed addition to the methods clarifying the binary treatment of exposure in the primary analysis, line 37, or by replacing the conclusion with the shorter summary from the Precis.

11. 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.

Though most acronyms used for progestogens are not included on the provided list, we feel strongly that using the full names throughout decreases readability. We took great care to try to use established acronyms from literature whenever possible. One exception is that we preferred LNG-IUD given it is more commonly used in American syntax than LNG-IUS. We are open to changing this if specifically desired.

12. The journal does not use the virgule symbol (/) in sentences with words, except with ratios. 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.

Two corrections were made for line 111 and Table 2.

13. 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.

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

Express all percentages to one decimal place (for example, 11.1%"). Do not use whole numbers for percentages.

> We have removed P values in all instances of the text where effect size and CI are provided. With the change to 99% CI, we agree this is not needed. We reviewed all usage of percentages in the text and tables. eTable 1 was updated accordingly.

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

> We have reviewed our tables for compliance with these guidelines. eTable 1 uses separate sub-headings. However, we feel this is appropriate to reduce redundancy and given its location in the supplement. Also, blank cells are explained in the footnote.

15. Please review examples of our current reference style at https://edmgr.ovid.com/ong/accounts/ifa_suppl_refstyle.pdf. Include the digital object identifier (DOI) with any journal article references and an accessed date with website references.

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If you cite ACOG documents in your manuscript, be sure the references you are citing are still current and available. Check the Clinical Guidance page at https://www.acog.org/clinical (click on "Clinical Guidance" at the top). If the reference is still available on the site and isn't listed as "Withdrawn," it's still a current document. In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript.

Please make sure your references are numbered in order of appearance in the text.

> We have reviewed the references to ensure compliance with these instructions.

16. Figures 1-2: Please upload as figure files on Editorial Manager.

> Figures 1 and 2 are provided as separate .pptx files and remain as images within the revised manuscript for ease of reference.

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We decline the option for open access availability.