OBSTETRICS & GYNECOLOGY

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

**Date:** Dec 03, 2021
**To:** "Haim Arie Abenhaim" [redacted]
**From:** "The Green Journal" em@greenjournal.org
**Subject:** Your Submission ONG-21-2154

RE: Manuscript Number ONG-21-2154

Hormone Replacement Therapy, Synthetic Progestogens, and Breast Cancer Risk

Dear Dr. Abenhaim:

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).

Please be sure to address the Editor comments (see "EDITOR COMMENTS" below) in your point-by-point response.

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 Dec 24, 2021, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

Overall Comments:

This is a case-control study that seeks to identify whether exposure to specific hormone replacement therapy (HRT) formulations is associated with increased risk of breast cancer. The study has a large sample size and 7 year follow up time. Overall this data is consistent with what was previously found in the women's health initiative study and builds on those findings by identifying synthetic progestins as a risk factor for breast cancer development. The manuscript would benefit from a more through discussion of the differences in proposed biologic activity of these compounds and structural differences. Additionally, if feasible, a dose response regression analysis would further strengthen the authors' conclusions.

Specific Comments by Section:

Introduction:
Lines 40-49 are unnecessary. Reasonable to just state HRT is most effective treatment for vasomotor symptoms and WHI study supports increased risk of breast cancer with HRT use although the specific formulation was unclear.

Lines 50-52, would recommend expanding this and citing appropriate references. Specifically what is known about breast cancer risk with different estrogen and progesterone formulations (expand lines 54-55).

Lines 56-58: Consider including estrogen as well as progesterone in this statement.

Would include some brief introduction to the differences in structure and function that are known for bioidentical vs synthetic progestins

Methods:
Lines 73-74: Please describe what was done to confirm medication was received and used. Could pharmacy fill data for prescriptions be used to verify?

Line 76-77: Why was age 50 used? The average age of menopause is 52. Was menopausal status confirmed? Why were women over 75 excluded?

Line 97: Why was only binary exposure examined? It would strengthen the findings if a dose dependent relationship between synthetic progestins and breast cancer incidence were established.

Please provide the breakdown of specific medications these women received

Line 113-144: Why was analysis limited to this age range?

Results:
Provide p values for differences in baseline characteristics between groups.

Please list the p values in Table 2 and 3. Nonsignificant is insufficient as a p value approaching significance may be notable.

Discussion:
Lines 155-158: Please provide a reference for this statement

Overall discussion could be shortened and pre-clinical and clinical data can be written more succintly

Please clarify lines 177-178.

Consider commenting on what current prescribing habits are (ie. are many providers prescribing synthetic progestins)?

Reviewer #2: This is a population-based case-control study evaluating whether the specific formulation of HRT used in patients plays a role in the increased risk of breast cancer associated with HRT.

Introduction - please include the most widely used HRT regimen(s) prescribed currently for context ie how much excluding synthetic progestins would change current practice. this can be commented on later again in the discussion as well

Methods - although we less frequently prescribe HRT to patients with inherited genetic mutations predisposing them to breast cancer, you may consider this a covariate in your analysis

Discussion
- strong review of existing data in this field and how this study substantiates or fits in with the current literature
-you mention medroxyprogesterone acetate as the predominant synthetic progesterone prescribed in this study. It would be pertinent to mention the next few most frequent synthetic progestins prescribed in your discussion.
-figure 1 needs to be reformatted, unable to read in current font
-would be helpful to conclude with a look towards to the future and what next steps or studies should take place to propel these findings into widespread practice most efficiently

Reviewer #3: In this study, authors sought to evaluate association between the risk of breast cancer diagnosis and formulation of HRT, using a UK registry that contained data from 575 primary care practices comprising 7.5% of the population. In a nested case-control methodology, HRT use was associated with increased risk of breast cancer; synthetic progestins (and not any type of estrogen or bio-identical progesterone) were differentially associated with increased breast cancer risk.

In addition to the limitations posed and cited by authors for use of administrative data set, the following limit both the internal validity and generalizability of their findings;

1. Lack of data on important confounders, e.g., hereditary breast cancer syndrome variables (detailed genetic history, BRCA mutation etc) is problematic.

2. Important data on dose and length of exposure to HRT is very limiting. Most national societies have long recommended use of HRT at the lowest dose for the least amount of time (typically 2 years or less) leading to substantial practice changes. This differs significantly from the practice that existed when data from study's subjects were collected. Relevance to today's practice will be limited.

3. Lack of data on important social determinants of health- race, ethnicity, socio -economic status, education etc are lacking making generalizability limited.

4. As authors acknowledged, the study's findings are not novel.

STATISTICAL EDITOR COMMENTS:

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

lines 20-27: The ORs are adjusted, so should refer to them as adjusted ORs or aORs. Also, see comments re: Tables 2 and 3, so should omit the results from micronized progesterone, since it was based on low counts and too few to estimate the aOR. The only category large enough to generalize are those who received synthetic progesterone, the bioidentical progestogen or both in the Tables 2 and 3 are too few to generalize the conclusions.

Table 1: Should statistically compare the baseline characteristics that were not matched, ie, BMI, smoking, alcohol and medical history components.

Tables 2, 3: The cases and controls for bioidentical progestogen (and for both category) have very low counts. Hence, there is little statistical power to test the hypothesis and the adjustment with multiple variables is likely to result in an over fitted model. Should simply report those data, but omit any analyses, bases on low counts. Also, since CIs are included, the p-values are redundant and the column of p-values should be omitted.

EDITOR COMMENTS:

1. In the current Abstract-Conclusion, do you mean "mediated" instead of "mitigated"?

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

A. OPT-IN: Yes, please publish my point-by-point response letter.
B. OPT-OUT: No, please do not publish my point-by-point response letter.

3. 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:
* Include your title page information in the main manuscript file. The title page should appear as the first page of the document. Add any previously omitted Acknowledgements (ie, meeting presentations, preprint DOIs, assistance from non-byline authors).
* Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and in the body text. For industry-sponsored studies, the Role of the Funding Source section should be included in the body text of the manuscript.
* 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.

4. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA), which must be completed by all authors. When you uploaded your manuscript, each co-author received an email with the subject, "Please verify your authorship for a submission to Obstetrics & Gynecology." Please check with your coauthors to confirm that they received and completed this form, and that the disclosures listed in their eCTA are included on the manuscript's title page.

5. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric 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.

6. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 5,500 words. Stated word limits include the title page, précis, abstract, text, tables, boxes, and figure legends, but exclude references.

7. Title: Based on the current title, the reader would assume that your study is mainly about synthetic progestogens. Would you please edit your title?

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

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).
* 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]."

9. Provide a short title of no more than 45 characters, including spaces, for use as a running foot.

10. 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.

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.

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13. ACOG avoids using "provider." Please replace "provider" throughout your paper with either a specific term that defines the group to which are referring (for example, "physicians," "nurses," etc.), or use "health care professional" if a specific term is not applicable.

14. 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"). For percentages, do not exceed one decimal place (for example, 11.1%").

15. Line 226: Your manuscript contains a priority claim. We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

16. 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.

17. 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

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18. Figure 1 may be resubmitted with the revision as-is.

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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 Dec 24, 2021, 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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