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.*

Personal or nonessential information may be redacted at the editor's discretion.

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

Date: Sep 10, 2019
To: "Sheryl A Kingsberg" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-1522

RE: Manuscript Number ONG-19-1522

Clinical Impact of Early or Surgical Menopause

Dear Dr. Kingsberg:

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 Oct 01, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: Review of Manuscript ONG-19-1522 "Clinical impact of early or surgical menopause."

Kinsberg and colleagues have submitted a clinical experts series manuscript summarizing the clinical impact of premature menopause in women among various organ systems, the rationale for this possible increase and therapeutic options to mitigate these impacts.

Minor point - some of the subject heading are followed by colons while others are not. While this is a very comprehensive review, at time although some of the referenced literature is strongly supportive of the points the author is making it almost seems overwhelming with a lack of focus. For instance, while POI is extremely problematic and associated with health consequences, I would argue there is little a practicing OB/GYN can do to prevent this.

Perhaps, the authors should focus on: (1) the prevention of premature surgical menopause for whom ovarian preservation is both indicated and a reasonable consideration and (2) unique issues form women with hereditary cancer syndromes. Such a review could be very powerful in terms of helping to prevent unindicated oophorectomy in low risk women and improving the care of high-risk women. In terms of the hereditary cancer syndromes (predominantly BRCA related reviewed), the authors provide a very nice summary of the issues unique to women with pathogenic variants in various cancer susceptibility genes. I have the following questions and comments for the authors.

Introduction - Do we know if all chemotherapy induced menopause is abrupt or is it somewhere in between gradual early menopause and surgical menopause? Does this vary based on chemotherapeutic agent(s)? Line 62 - Do we have any more recent data about the rate of BSO prior to menopause? It appears these references are at least 5 years old and with the increased uptake of opportunistic salpingectomy, there may have been a pendulum swing back the other way. Line 64-69 - while I agree with these statements in generally, this still will represent a minority of women that experience premature surgical menopause. Although it is likely that additional mutations will be discovered in the future that are associated with an increased risk of ovarian cancer and thus may necessitate early RRSO, again this will only have an incremental impact on this current number. Moreover, there are ongoing clinical trials evaluating salpingectomy with planned delayed oophorectomy in high risk women based on genetic test results and if feasible without significant increased cancer risk, may allow the performance of oophorectomy closer to the age of menopause.

Pathophysiology - May want to mention more on the potential deleterious impacts of hysterectomy with ovarian conservation alluded to in lines 113-114.

Management of Early Menopause… - Lines 551-3 are extremely important and need to be emphasized more if possible. In addition the most recent publication from Kotsopoulos was very provocative and although as noted was a prospective

cohort warrants some additional comments in the manuscript as it is unlikely RCTs will be performed in the near term if at all to shed light on these questions.

Tables - Table 1 - is there a way or ways to provide objective data in this table about how estrogen has a positive effect? Table 2 is fine although could be expanded to add a column or columns that specifically evaluated the role of a specific agent for a specific menopausal related issue.

Reviewer #2: An excellent review, with some well-needed opinions on controversial issues.

Specific suggestions include:

1- Line 72- Whenever you mention differences in symptoms/effects, please include the quantity, such as you did for VMS here (70% vs 90%), as it allows the reader to determine clinical significance. Sleep disturbances and QOL are mentioned but not quantified, and you have sufficient references to retrieve the actual effect.

2- Line 157- 66% increased risk, was it stat sig? and how much?

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8- Lines 300-350- Instead of always being picky, GSM and HSDD data was wonderfully explained and quantified. Really terrific!

9- Line 363- Care to comment on discrepancy of no difference in sexual function for peri-menopausal after TAH? Maybe just too early at year one?

10- Line 538- Up to Date is more opinion than peer-reviewed, and I don't suggest using their opinions. I think you do an excellent job at presenting the facts and stating your conclusions after lines 560. I would prefer not to give Up to Date the status of a Cochran review.

Again, a wonderful manuscript, not just as a review, but as a compilation of the data and your interpretation when conclusions are lacking in the literature.

Reviewer #3: Overall, I found this to be a very thorough review of the relevant literature around this extensive topic. The article was organized according to health risks/symptoms and although these issues are interconnected, I didn't find the article overly repetitive. This is a very timely article as well. There are more and more women suffering from early menopause and literature can be contradictory about the safest method of management. The SOFT/TEXT trials add the additional question of what to do with women with non-BRCA breast cancer on adjuvant treatments and whether or not ovarian ablation is beneficial. The cancer literature often fails to address issues other than cancer recurrence and more articles like this are needed to help sort through the vast amount of conflicting literature. I think this article provides a sensible and easy to understand overview.

My only recommendation for this article is that the authors are more clear as to what is opinion vs what is supported in the literature. There are many statements in this article that are not sourced, and it is unclear to me whether this is the expert opinion of the authors or whether this was derived from published literature. Examples of this are but are not limited to:

1. Lines 53 to 55: "Chemotherapy-induced menopause . . .. compared to natural menopause"
2. Lines 174-176: "Unfortunately, these changes are . . .. the age of NM"
3. Lines 202-203: "Multiple clinical studies. . . prevented with HT"
4. Lines 214-215: "Anxiety symptoms are associated . . .. performance"

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:
A. OPT-IN: Yes, please publish my point-by-point response letter.
B. OPT-OUT: No, please do not publish my point-by-point response letter.

2. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page.

3. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric and gynecology data definitions at https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

4. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: CES articles should not exceed 25 typed, double-spaced pages (6,250 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.

5. 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).

6. Provide a précis on the second page, for use in the Table of Contents. The précis is a single sentence of no more than 25 words that states the conclusion(s) of the report (ie, the bottom line). The précis should be similar to the abstract's conclusion. Do not use commercial names, abbreviations, or acronyms in the précis. Please avoid phrases like "This paper presents" or "This case presents."

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

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

8. 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.

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

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

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

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

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

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Oct 01, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

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

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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.

Dear Editors,

Thank you for allowing us to revise and resubmit our clinical experts series manuscript. Our responses to the reviewers are below.

Sincerely,

Sheryl A Kingsberg, PhD

Kingsberg and colleagues have submitted a clinical expert series manuscript summarizing the clinical impact of premature menopause in women among various organ systems, the rationale for this possible increase and therapeutic options to mitigate these impacts.

Minor point - some of the subject headings are followed by colons while others are not.

Thank you. This has been corrected.

While this is a very comprehensive review, at time although some of the referenced literature is strongly supportive of the points the author is making it almost seems overwhelming with a lack of focus. For instance, while POI is extremely problematic and associated with health consequences, I would argue there is little a practicing OB/GYN can do to prevent this.

While POI is problematic and not preventable, one of the main goals of our manuscript is to educate and inform clinicians of the data supporting the benefits of treating early menopause of any cause and why management must include HT until the natural age of menopause.

Perhaps, the authors should focus on: (1) the prevention of premature surgical menopause for whom ovarian preservation is both indicated and a reasonable consideration and (2) unique issues for women with hereditary cancer syndromes.

We agree these are important subgroups of women with premature menopause, but believe it is critical to include the other subgroups of women with early menopause.

Such a review could be very powerful in terms of helping to prevent unindicated oophorectomy in low risk women and improving the care of high-risk women. In terms of the hereditary cancer syndromes (predominantly BRCA related reviewed), the authors provide a very nice summary of the issues unique to women with pathogenic variants in various cancer susceptibility genes. I have the following questions and comments for the authors.

We agree that one of the most powerful messages of this review is to help OBGYNs avoid performing unindicated BSO. We will make this point more powerfully but feel it is critical to include all women experiencing early menopause. Gynecologists need to understand the consequences and management for all women who experience any early menopause.

Introduction - Do we know if all chemotherapy induced menopause is abrupt or is it somewhere in between gradual early menopause and surgical menopause? Spontaneous (natural)

Yes thank you for helping us clarify our statement (line 53-54). We have revised this sentence to say "Surgical menopause is abrupt and the level of circulating hormones is substantially reduced compared to natural menopause whereas chemotherapy induced menopause can be rapid or more gradual depending on the woman's baseline ovarian reserve, gonadotoxicity of the chemotherapy agent(s) and the number of cycles of chemotherapy."

Line 62 - Do we have any more recent data about the rate of BSO prior to menopause? It appears these references are at least 5 years old and with the increased uptake of opportunistic salpingectomy, there may have been a pendulum swing back the other way.

The reviewer's point is well-taken. We have added additional data and references.

Line 64-69 - while I agree with these statements in generally, this still will represent a minority of women that experience premature surgical menopause. Although it is likely that additional mutations will be discovered in the future that are associated with an increased risk of ovarian cancer and thus may necessitate early RRSO, again this will only have an incremental impact on this current number. Moreover, there are ongoing clinical trials evaluating salpingectomy with planned delayed oophorectomy in high risk women based on genetic test results and if feasible without significant increased cancer risk, may allow the performance of oophorectomy closer to the age of menopause.

Thank you for the comment. We agree that the number of mutation carriers undergoing RRSO represents a minority of women with premature menopause. We believe it is important however to highlight this group of women for several reasons. These women are typically younger, and are more reluctant to consider hormone therapy after RRSO because of the fear of cancer. In addition, clinicians are more reluctant to use HT in mutation carriers, again because of the concern of cancer and lack of understanding of the data. Our CES highlights these women in the hopes of education of clinicians about the benefit, and lack of additional cancer risk of HT until age 51 in these women.

Pathophysiology - May want to mention more on the potential deleterious impacts of hysterectomy with ovarian conservation alluded to in lines 113-114.

Added one reference with HR risk.

Management of Early Menopause… - Lines 551-3 are extremely important and need to be emphasized more if possible. In addition the most recent publication from Kotsopoulos was very provocative and although as noted was a prospective cohort warrants some additional comments in the manuscript as it is unlikely RCTs will be performed in the near term if at all to shed light on these questions.

Thank you. We have made an effort to emphasize this point within the limitations of our word count. Your point about the lack of RCT's is well taken. We have added additional comments and references.

Tables - Table 1 - is there a way or ways to provide objective data in this table about how estrogen has a positive effect?

We are not sure exactly what the reviewer is looking for regarding objective data. We acknowledge that the references in the far right column reflect studies that demonstrate the consequences of the lack of estrogen but there are few studies demonstrating the improvement in these consequences by the addition of estrogen. The focus of our CES is to demonstrate the importance of prevention of these conditions by maintaining premenopausal HT levels until the age of NM

Table 2 is fine although could be expanded to add a column or columns that specifically evaluated the role of a specific agent for a specific menopausal related issue.

Thank you. We have added information to the table, including new approved formulations and we have changed the title to better reflect the products and indications.

Our table lists approved hormone therapy options for menopause symptoms (primarily VMS). They are not approved for specific menopause related symptoms. Further there are no head to head trials comparing these agents to each other in specific symptom areas.

Reviewer #2: An excellent review, with some well-needed opinions on controversial issues.

Specific suggestions include:

1- Line 72- Whenever you mention differences in symptoms/effects, please include the quantity, such as you did for VMS here (70% vs 90%), as it allows the reader to determine clinical significance. Sleep disturbances and QOL are mentioned but not quantified, and you have sufficient references to retrieve the actual effect.

We appreciate the reviewer noting the inconsistency and have added quantification within each section. Most studies refer to QoL as changes in mood, well-being, sexual function and other subjective endpoints vs a specific construct. We address QoL in the context of VMS.

2- Line 157- 66% increased risk, was it stat sig? and how much?

Revised in manuscript.

3- Line 190- 79% to 76% reduction in joint pain that was stat sig to 0.001, how was that measured?, and then was the next 63 vs 57% stat sig?

Revised in the manuscript

4- Line 217- In the PAOS, could you give more details on how memory (short vs long term, etc) was measured to determine its significance, and quantify please.

The manuscript has been revised to include verbal memory and processing speed as measures of verbal memory.

Due to word limitations we did not include the test details (Buschke Selective Reminding Test, the Digit Symbol Substitution Test (DSST) and the Symbol Copy Task).

5- Line 234- Describe , than quantify plaque formation measure and if it was stat sig please

Manuscript was revised

6- Line 238- Details on how age 43 was determined/selected?

Due to word limitations we decided to remove this section, as other additions to the manuscript revisions took priority

7- Line 280- How was signif reduced mental health measured and quantify please?

Profile of Moods added to manuscript

8- Lines 300-350- Instead of always being picky, GSM and HSDD data was wonderfully explained and quantified. Really terrific!

Thank you!

9- Line 363- Care to comment on the discrepancy of no difference in sexual function for peri-menopausal after TAH? Maybe just too early at year one?

We agree that measurement at 1 year might be too early and commented in the manuscript.

10- Line 538- Up to Date is more opinion than peer-reviewed, and I don't suggest using their opinions. I think you do an excellent job at presenting the facts and stating your conclusions after lines 560. I would prefer not to give Up to Date the status of a Cochran review.

Thank you. Your point is well taken and the manuscript has been revised.

Again, a wonderful manuscript, not just as a review, but as a compilation of the data and your interpretation when conclusions are lacking in the literature.

Reviewer #3: Overall, I found this to be a very thorough review of the relevant literature around this extensive topic. The article was organized according to health risks/symptoms and although these issues are interconnected, I didn't find the article overly repetitive. This is a very timely article as well. There are more and more women suffering from early menopause and literature can be contradictory about the safest method of management. The **SOFT/TEXT trials add the additional question of what to do with women with non-BRCA breast cancer on adjuvant treatments and whether or not ovarian ablation is beneficial.** The cancer literature often fails to address issues other than cancer recurrence and more articles like this are needed to help sort through the vast amount of conflicting literature. I think this article provides a sensible and easy to understand overview.

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We have attempted to clarify referenced statements throughout the manuscript.

1. Lines 53 to 55: "Chemotherapy-induced menopause . . .. compared to natural menopause"

Thank you. Reference added.

2. Lines 174-176: "Unfortunately, these changes are . . .. the age of NM"

We believe the totality of the data presented in this manuscript supports this statement as fact and not opinion. All of the references support this statement.

3. Lines 202-203: "Multiple clinical studies. . . prevented with HT"

Thank you. Reference added.

4. Lines 214-215: "Anxiety symptoms are associated . . .. performance"

Each statement regarding anxiety symptoms and cognitive performance include a study reference.

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

We choose A. Opt-In