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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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Date: May 13, 2022
To: "Susan C. Modesitt" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-22-663

RE: Manuscript Number ONG-22-663

Clinical Expert Series: Endometrial hyperplasia

Dear Dr. Modesitt:

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 Jun 03, 2022, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

Thank you for the opportunity to review this well written and highly informative manuscript.
my comments are minor:
1. would use gender neutral language (eg patients instead of women in line 108). there is really not a lot but I would try to eliminate
2. line 187 I question the word main as in main risk factor
3. line 193 the sentence that starts Chronic unopposed estrogen is unclear-- sounds like the obese patients are taking estrogen.
4. The content in lines 273-9 is repeated in the paragraph that starts at line 300. additionally, I would include Kemi Doll's data about these cut offs not necessarily applying for Black women
5. section starting on line 324 should include GOG 167 data. even though you go into more data later it is worth mentioning this here because the reference is old retrospective data
6. line 484 should be stronger than consider

Reviewer #2:

The authors provide a comprehensive review of endometrial hyperplasia, also known as endometrial intraepithelial

neoplasia. Major sections emphasize histology, risk factors, prevention, screening, evaluation, and management.

1) The distinction between atypical endometrial hyperplasia and endometrial intraepithelial carcinoma is significant. From an organizational standpoint, it is important to discuss under histology. The EIC section goes somewhat off topic at the end (lines 155-158) where the authors discuss PTEN IHC in the context of atypical hyperplasia.
2) The section on primary prevention also includes discussion of treatment/management. In particular, the discussion regarding metformin discusses reversal of endometrial hyperplasia and endometrial carcinoma—much of the material (lines 246-264) in the last paragraph should be included in the management section. Furthermore, the recommendations for metformin should be more specific, either giving recommendation on when to add, or being less strong in the discussion of using metformin as an additional option.
3) The section on malignant progression risks (lines 323-335) should be included in the initial section on histology where the authors discuss the distinction between atypical hyperplasia and endometrial carcinoma.

Reviewer #3:

The authors present a well written review on the management of EIN and atypical endometrial hyperplasia. Overall this is well written although a bit verbose and I dont have many comments other than:
1) I would include some more data on sentinel LN sampling in this population
2) I would spend some time on side effects of progestational therapy and management of this. Also, present data on surveillance and re-sampling times.

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.

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* 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. 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.

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Clinical Expert Series: 6250 words

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* 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.
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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.

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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 Jun 03, 2022, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,
John O. Schorge, MD
Deputy Editor, Gynecology

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

RESPONSE TO REVIEWER COMMENTS:

Reviewer #1:

Thank you for the opportunity to review this well written and highly informative manuscript.

my comments are minor:

1. would use gender neutral language (eg patients instead of women in line 108). there is really not a lot but I would try to eliminate

> We have tried to eliminate as much as possible and have marked changes (e.g. original numbers line 36, line 108, line 176, 185, 218 etc.). we did leave the word women in some portions of the manuscript where the references specifically cite female/women in their publication in terms of incidence or outcomes (original lines 51, 166, 188 etc.)

2. line 187 I question the word main as in main risk factor

> We have changed main to "one of the strongest"

3. line 193 the sentence that starts Chronic unopposed estrogen is unclear-- sounds like the obese patients are taking estrogen.

> This is a good point and we have changed this to "Production of endogenous excess estrogen"

4. The content in lines 273-9 is repeated in the paragraph that starts at line 300. additionally, I would include Kemi Doll's data about these cut offs not necessarily applying for Black women

> This is an excellent point about the racial disparities in the cut offs and we thank the reviewer for pointing out. We have added the data and the reference about the 5 fold more missed cancers in black women using the 4 mm cut off.
>
> We opted to keep the expanded information about the data on endometrial stripe in asymptomatic women also in the section on ultrasound even though the final recommendation was listed earlier because it is such a common scenario and felt that the specifics were important to go through on the ultrasound section. Happy to remove if desired by the editors.

5. section starting on line 324 should include GOG 167 data. even though you go into more data later it is worth mentioning this here because the reference is old retrospective data

> We have added to this section the 43% co-existence of cancer at time of hysterectomy here.

6. line 484 should be stronger than consider

> We agree and have changed from consider to recommend.

Reviewer #2:

The authors provide a comprehensive review of endometrial hyperplasia, also known as endometrial intraepithelial neoplasia. Major sections emphasize histology, risk factors, prevention, screening, evaluation, and management.

1) The distinction between atypical endometrial hyperplasia and endometrial intraepithelial carcinoma is significant. From an organizational standpoint, it is important to discuss under histology. The EIC section goes somewhat off topic at the end (lines 155-158) where the authors discuss PTEN IHC in the context of atypical hyperplasia.

We felt that it is important to stress an option for clinicians in case their pathologists are questioning the EIC versus EIN diagnosis so opted to leave this section in and highlight in the heading the pitfalls of confusing the two entities.

2) The section on primary prevention also includes discussion of treatment/management. In particular, the discussion regarding metformin discusses reversal of endometrial hyperplasia and endometrial carcinoma—much of the material (lines 246-264) in the last paragraph should be included in the management section. Furthermore, the recommendations for metformin should be more specific, either giving recommendation on when to add, or being less strong in the discussion of using metformin as an additional option.

As suggested, we moved the section to the treatment section and softened the language by adding potentially in terms of use.

3) The section on malignant progression risks (lines 323-335) should be included in the initial section on histology where the authors discuss the distinction between atypical hyperplasia and endometrial carcinoma.

We have moved as suggested to the new line 163 following the histology section.

Reviewer #3:

The authors present a well written review on the management of EIN and atypical endometrial hyperplasia. Overall this is well written although a bit verbose and I dont have many comments other than:

1) I would include some more data on sentinel LN sampling in this population

Additional data has been added and reviewed in this section.

2) I would spend some time on side effects of progestational therapy and management of this. Also, present data on surveillance and re-sampling times

There are limited data on any comparison of resampling times but the expert consensus is included (lines 728-731) along with the recommendations

We opted not to include management of progestational side effects as it is within the purview and scope of most practicing OB/GYN's –we can add if desired.

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.

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* 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.

None of this was required.

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.

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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."

We have endeavored to do this

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://nam11.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.acog.org%2Fpractice-management%2Fhealth-it-and-clinical-informatics%2Frevitalize-obstetrics-data-definitions&data=05%7C01%7Csmodesi%40emory.edu%7C50bc69cb6293422b288e08da38172163%7Ce004fb9cb0a4424fbcd0322606d5df38%7C0%7C0%7C637883969621818601%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=5CtNs6WB8P%2FegS24fOn1AvLHwz9WU0mTtQvBh2P5pEQ%3D&reserved=0 and the gynecology data definitions at https://nam11.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.acog.org%2Fpractice-management%2Fhealth-it-and-clinical-informatics%2Frevitalize-gynecology-data-definitions&data=05%7C01%7Csmodesi%40emory.edu%7C50bc69cb6293422b288e08da38172163%7Ce004fb9cb0a4424fbcd0322606d5df38%7C0%7C0%7C637883969621818601%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=QxIWddAzq8KIwbJr0GYMMhiIMOnW2iE12MMcZRzwU2k%3D&reserved=0. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

This has been done

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Clinical Expert Series: 6250 words

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* 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.

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

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We have complied with all of these requirements

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10. 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.

We have complied

11. 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.

As this is a review, we simply used the data as presented in quoted articles

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

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

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14. Figures 1-3: okay

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