NOTICE: This document contains correspondence generated during peer review and subsequent revisions but before transmittal to production for composition and copyediting:

- 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: 09/16/2022
To: "Elizabeth A. Stewart" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-22-1448

RE: Manuscript Number ONG-22-1448

Oral GnRH Antagonists for the Treatment of Uterine Leiomyomas

Dear Dr. Stewart:

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 Oct 07, 2022, we will assume you wish to withdraw the manuscript from further consideration.

EDITOR COMMENTS:

Thank you for your submission!

We ask that you review the guidelines for the Clinical Expert Series sent by the invitation email and note that these articles are aimed at practicing clinicians, to help guide clinical practice. Although we do expect the review to be evidence-based, it is not meant to be a systematic review or meta-analysis format. Please review previous published CES, or our office can forward to you examples as needed.

Overall, the current manuscript reads more as a detailed literature review, with very granular details about specific trials and studies. It is difficult to read in its current form and heavy on data/references in the text.
The paper should be re-structured to provide clinical guidance which is then supported by literature, as opposed to a review of literature with some clinical guidance embedded. It is currently difficult to identify the clinical guidance within all the individual studies described and listed.

As illustrative examples:
1. Please shorten the introduction to closer to 1 page.
2. Page 6: please shorten the 1st paragraph: instead of listing all the approvals, please shorten and retain what is most relevant to practicing clinicians. If approval information is relevant, please consider a table.
3. Pages 16-18: It is less helpful to the clinician to read about all of the AEs that occurred in individual studies. Can these be summarized more briefly as a clinical impression or recommendation(s), that are then supported by these studies? 4. Consider the use of tables as needed to decrease the amount of granular content in the text.

Please use this approach for the entire manuscript.

REVIEWER COMMENTS:

Reviewer #1: The author presents a review of the use of GnRH antagonists with and without add-back therapy for treatment of uterine fibroids. In the section describing the results of the multiple different phases of studies, I would recommend including a summary sentence at the end of each paragraph (as was done in line 162). This gives the reader the overall conclusion from that phase of study which was likely used to develop the next phase.

Abstract, line 38: Add "temporary" prior to "worsening".
Abstract, lines 44-47: This is a very long and confusing sentence. Should be restated and broken into two sentences.
Abstract, line 48: Use of the word "conditions" seems to be indicating treatment other than for fibroids. Recommend changing to "presentation" or "severity".

Introduction, lines 69-80: This paragraph is mainly describing GnRH, however the opening sentence seems to indicate that the paragraph will discuss contraceptive steroids as a medical therapy for AUB-L. I recommend using a different introductory sentence.
Introduction, lines 109-113: Recommend deleting this paragraph as it is duplicative of lines 126-130.

Body, line 123: I would first recommend spending some time to describe the different pathophysiology of each of the GnRH antagonists mentioned (Ealgolix, Relugolix, Linzagolix) and why each one is being studied and marketed.

Body, lines 150-152: This sentence seems unnecessary here as you are simply defining the endpoints.

Body, line 154: Why were there two separate initial phase II studies of Elagolix? Are the two studies you are referring to the Archer and Carr studies? If so, please state this more clearly.

Body, lines 212-213: There were two different combination groups in this study. To which are you referring?

Body, lines 245-247: Delete this sentence. This has already been stated multiple times and does not have bearing to the discussion on change in bulk symptoms/fibroid volume.

Body, lines 249-252: These sentences seem duplicative as you go into detail in the subsequent paragraphs on each of the GnRH antagonists and their impact on uterine and leiomyoma volume.

Body, lines 279-281: Most of the data you presented on GnRH antagonists and uterine/leiomyoma volume demonstrated a significant reduction with monotherapy, but not really with ABT. Therefore, your concluding statement does not seem accurate. Additionally, and similar to GnRH agonists, uterine/leiomyoma volume returns to baseline within several months of discontinuation of treatment.

Body, line 320: How was the coexisting adenomyosis diagnosed?

Body, line 334: Need an overall concluding statement here regarding GnRH antagonists and adenomyosis.

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Body, line 369: Please be specific here as to what type of efficacy you are referring (AUB-L?).

Body, 371-373: Please be specific as to which GnRH antagonist combinations you are referring to.
Clinical Pearls, lines 432-424: What kind of medical treatments have patients been excluded from based on their fibroid volume or location?

Conclusions: Have any studies directly compared GnRH agonists with ABT to GnRH antagonists with ABT in regard to AE, specifically BMD loss? It is important to compare similar things when looking at outcomes.

Reviewer #2: Introduction well written. I wonder if you want to expand a bit on the role of contraceptive steroids, anti-progestins as well - just a few sentences to explain mechanism of action and indications or limitations of use.

Body is very thorough but perhaps a bit lengthy for the average reader. I wonder if some of the information that is captured in the summary Table 3 can be removed from text?

p 9 line 214 and on - is this published or only in abstract form? I would not cite abstract only data. Your reference here is also not replaced with a #

p 10 line 221 and on- same issue as above

p15 line 360 - I disagree that you can conclude no major congenital defects related to treatment due to very small N we

have available to evaluate; would say more data needed

p19 line 442- I think it is a bit of a stretch to say that medical treatment can be offered in cases where it was not previously possible... it is more that this provides yet another option that may be able to achieve better relief of fibroid symptoms with tolerable level of side effects

Tables/Figures are easy to read and additive to the text

STATISTICAL EDITOR COMMENTS:

Figs 1, 2: Although the differences vs the placebo groups are obvious, should include CIs to illustrate the variability of the point estimates. Should also indicate the statistical significance of the differences, either on the figure itself or in figure legend. Should include some concise use of these stats in main text.

line 231: Suggest rather than "Other specific endpoints" should be labeled as secondary endpoints.

Suggest listing secondary outcomes and adverse outcomes in separate Tables, with summaries in main text.

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

Use "Black" and "White" (capitalized) when used to refer to racial categories.

List racial and ethnic categories in tables in alphabetic order. Do not use "Other" as a category; use "None of the above" instead.

Please refer to "Reporting Race and Ethnicity in Obstetrics & Gynecology" at https://edmgr.ovid.com/ong/accounts/Race_and_Ethnicity.pdf.

5. ACOG uses person-first language. Please review your submission to make sure to center the person before anything else. Examples include: "People with disabilities" or "women with disabilities" instead of "disabled people" or "disabled women"; "patients with HIV" or "women with HIV" instead of "HIV-positive patients" or "HIV-positive women"; and "people who are blind" or "women who are blind" instead of "blind people" or "blind women."

6. The journal follows ACOG's Statement of Policy on Inclusive Language (https://www.acog.org/clinical-information/policy-and-position-statements/statements-of-policy/2022/inclusive-language). When possible, please avoid using

gendered descriptors in your manuscript. Instead of "women" and "females," consider using the following: "individuals;" "patients;" "participants;" "people" (not "persons"); "women and transgender men;" "women and gender-expansive patients;" or "women and all those seeking gynecologic care."

7. Figures 1-2: Has this been previously published in another source? If yes, both print and electronic (online) rights must be obtained from the holder of the copyright (often the publisher, not the author), and credit to the original source must be included in your manuscript. Many publishers have online systems for submitting permissions requests; please consult the publisher directly for more information.

8. All submissions that are considered for potential publication are run through CrossCheck for originality. The following lines of text match too closely to previously published works or need to be cited:

Please provide citation for lines 148-150.

9. 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.

10. 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.

Clinical Expert Series: 25 pages

11. 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.

12. Provide a short title of no more than 45 characters, including spaces, for use as a running foot. Do not start the running title with an abbreviation.

13. 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.

Clinical Expert Series: 250 words max

14. 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.

15. 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.

16. 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.

17. 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.

18. 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.

19. Figures 1-2: Please confirm that these are original to the manuscript. Should the legend include any information about "data from"?

20. 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.

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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 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 Oct 07, 2022, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Vivian W. Sung, MD, MPH
Deputy Editor, Gynecology–Elect

We appreciate the comments from the editor, reviewers, statistical editor, and editorial office for the opportunity to improve our previous submitted manuscript. Based on these comments, we have extensively revised the manuscript to make it more clinically focused and have removed much of the granular detailed information of study specific details. Furthermore, we shortened the introduction and all sections/subsections of the manuscript to be more focused in our discussion and have clarified specific points brought forth from the reviewers. We also added new information published since our prior submission as detailed in our cover letter.

For your convenience, we have provided a version of the manuscript where the changes from the original submission are indicated by colored text and point-by-point response to comments below. The **key issues requested are in bold text** and our reply follows.

EDITOR COMMENTS:

Thank you for your submission!

We ask that you review the guidelines for the Clinical Expert Series sent by the invitation email and note that these articles are aimed at practicing clinicians, to help guide clinical practice. Although we do expect the review to be evidence-based, it is not meant to be a systematic review or meta-analysis format. Please review previous published CES, or our office can forward to you examples as needed.

Overall, the current manuscript reads more as a detailed literature review, with very granular details about specific trials and studies. It is difficult to read in its current form and heavy on data/references in the text.
The paper should be re-structured to provide clinical guidance which is then supported by literature, as opposed to a review of literature with some clinical guidance embedded. It is currently difficult to identify the clinical guidance within all the individual studies described and listed.

-We thank the editor for reviewing our previous manuscript and providing this feedback. We have extensively revised our manuscript to make more clinically focused and have removed much of the granular detailed information of study specific details. Through this process, we have attempted to pull out important details to clinically summarize in each section/subsection with reference to tables and figures. To further appear less of a detailed literature review, we have moved our previous "Table 3" to create an "Appendix 1" that readers can reference, if desired, for study specific details.

As illustrative examples:
1. Please shorten the introduction to closer to 1 page.

-The introduction has been condensed to 1 page and 4 additional lines.

2. Page 6: please shorten the 1st paragraph: instead of listing all the approvals, please shorten and retain what is most relevant to practicing clinicians. If approval information is relevant, please consider a table.

- This "overview section" has been condensed and readers are now directed to Table 1 for further details regarding approvals. As recommended below, we have updated this section to be more clinically relevant.

3. Pages 16-18: It is less helpful to the clinician to read about all of the AEs that occurred in individual studies. Can these be summarized more briefly as a clinical impression or recommendation(s), that are then supported by these studies? 4. Consider the use of tables as needed to decrease the amount of granular content in the text.

Please use this approach for the entire manuscript.

-We thank the editor for this suggestion. We have greatly condensed the adverse events section to summarize important clinical details and also to discuss what was not seen in the trials that might have been expected. Data is now presented compared to placebo in an updated Table 2. Percent change in bone mineral density is further demonstrated in an updated Figure 2.

REVIEWER COMMENTS:

Reviewer #1: The author presents a review of the use of GnRH antagonists with and without add-back therapy for treatment of uterine fibroids. In the section describing the results of the multiple different phases of studies, I would recommend including a summary sentence at the end of each paragraph (as was done in line 162). This gives the reader the overall conclusion from that phase of study which was likely used to develop the next phase.

- Thank you. We have extensively revised and condensed our manuscript to make more clinically focused and made sure to include summary sentences at the end of each section for easier reading and transition.

Abstract, line 38: Add "temporary" prior to "worsening".

- We thank the reviewer for this important clarification. We have added “temporary” prior to “worsening” (line 35).

Abstract, lines 44-47: This is a very long and confusing sentence. Should be restated and broken into two sentences.

- We have broken the previous sentence into two separate sentences and restated for easier reading (lines 41-45).

Abstract, line 48: Use of the word "conditions" seems to be indicating treatment other than for fibroids. Recommend changing to "presentation" or "severity".

-We agree this is an important distinction and have changed wording from “conditions” to reviewer’s recommendation of “presentations.” (line 46)

Introduction, lines 69-80: This paragraph is mainly describing GnRH, however the opening sentence seems to indicate that the paragraph will discuss contraceptive steroids as a medical therapy for AUB-L. I recommend using a different introductory sentence.

- We thank the reviewer for this recommendation. We have rephrased this paragraph to briefly expand on the role of contraceptive steroids and progestins (recommended by reviewer #2) and transitioned discussion on the role of GnRH antagonists to the following paragraph (lines 71-80).

Introduction, lines 109-113: Recommend deleting this paragraph as it is duplicative of lines 126-130.

- This paragraph has now been deleted as part of condensing the introduction.

Body, line 123: I would first recommend spending some time to describe the different pathophysiology of each of the GnRH antagonists mentioned (Ealgolix, Relugolix, Linzagolix) and why each one is being studied and marketed.

- We thank the reviewer for this excellent recommendation and have updated the "overview section" (starting at line 83) to be more clinical to review the development of the three oral GnRH antagonists. We have further removed detailed discussion of FDA approvals (recommended by editor) from this section and now point readers to Table 1 for further details.

Body, lines 150-152: This sentence seems unnecessary here as you are simply defining the endpoints.

- This sentence has now been deleted as part of condensing the section "Efficacy of oral GnRH antagonists on the primary endpoint of abnormal uterine bleeding" (starting at line 116) to make more clinically focused.

Body, line 154: Why were there two separate initial phase II studies of Elagolix? Are the two studies you are referring to the Archer and Carr studies? If so, please state this more clearly.

- This sentence has now been deleted.

Body, lines 212-213: There were two different combination groups in this study. To which are you referring?

- This sentence has now been deleted.

Body, lines 245-247: Delete this sentence. This has already been stated multiple times and does not have bearing to the discussion on change in bulk symptoms/fibroid volume.

- This sentence has been deleted.

Body, lines 249-252: These sentences seem duplicative as you go into detail in the subsequent paragraphs on each of the GnRH antagonists and their impact on uterine and leiomyoma volume.

- These sentences have also been deleted.

Body, lines 279-281: Most of the data you presented on GnRH antagonists and uterine/leiomyoma volume demonstrated a significant reduction with monotherapy, but not really with ABT. Therefore, your concluding statement does not seem accurate. Additionally, and similar to GnRH agonists, uterine/leiomyoma volume returns to baseline within several months of discontinuation of treatment.

-We thank the reviewer for pointing out this important concept and have rephased our concluding statement to reflect significant reduction with monotherapy, but only modest changes with ABT.

Furthermore, we clarify that volumes appear to return to baseline with discontinuation of treatment (lines 179-180).

Body, line 320: How was the coexisting adenomyosis diagnosed?

-We have clarified that adenomyosis was "diagnosed by radiologic evidence (transvaginal ultrasound and/or MRI) of any type (focal or diffuse) at baseline." (lines 187-188)

Body, line 334: Need an overall concluding statement here regarding GnRH antagonists and adenomyosis.

-We thank the reviewer for this recommendation. We have included an overall concluding statement for oral GnRH antagonists and adenomyosis. (lines 202-204)

Body, lines 359-362: As a comparator, what is the rate of pregnancy in studies looking at GnRH agonists?

-We appreciate this question from the reviewer and have inserted text into the updated manuscript to state that although rare, breakthrough ovulation and pregnancies likewise are reported with antagonists (lines 206-235). There is not sufficient data to comment on pregnancy rates.

Body, line 369: Please be specific here as to what type of efficacy you are referring (AUB-L?).

- This sentence has been deleted.

Body, 371-373: Please be specific as to which GnRH antagonist combinations you are referring to.

- We have clarified both monotherapy vs. add-back combinations from pivotal phase III trials and have updated Figure 2 for further clarification and added references (lines 248-250).

Clinical Pearls, lines 432-424: What kind of medical treatments have patients been excluded from based on their fibroid volume or location?

- This sentence has been deleted as part of restructuring this paragraph.

Conclusions: Have any studies directly compared GnRH agonists with ABT to GnRH antagonists with ABT in regard to AE, specifically BMD loss? It is important to compare similar things when looking at outcomes.

- We thank the reviewer for this excellent question and have added information about the comparative study of relugolix monotherapy and the GnRH agonist leuprolide acetate (lines 244-245). Unfortunately agonists have not been used as a comparator for regimens with ABT.

Reviewer #2: Introduction well written. I wonder if you want to expand a bit on the role of contraceptive steroids, anti-progestins as well - just a few sentences to explain mechanism of action and indications or limitations of use.

-We appreciate this excellent recommendation and have rephrased the second paragraph (lines 61-70) to briefly expand on the role of contraceptive steroids and progestins

Body is very thorough but perhaps a bit lengthy for the average reader. I wonder if some of the information that is captured in the summary Table 3 can be removed from text?

-We thank the reviewer for this comment. We have extensively revised our manuscript to make more clinically focused and have removed much of the granular detailed information of study specific details. Through this process, we have attempted to pull out important details to clinically summarize in each section/subsection with reference to tables and figures. To further appear less of a detailed literature review, we have moved our previous "Table 3" to create an "Appendix 1" that readers can reference, if desired, for study specific details.

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- We have removed all abstract references.

p 10 line 221 and on- same issue as above

- Again, we have removed all abstract references.

p15 line 360 - I disagree that you can conclude no major congenital defects related to treatment due to very small N we have available to evaluate; would say more data needed

- We appreciate the reviewer's comment and have added that more data is needed. (lines 233-234)

p19 line 442- I think it is a bit of a stretch to say that medical treatment can be offered in cases where it was not previously possible... it is more that this provides yet another option that may be able to achieve better relief of fibroid symptoms with tolerable level of side effects

- We appreciate the reviewer's comment and have rephrased this sentence to clarify that," These results suggest that oral GnRH antagonists can be considered for patients as another treatment option when hysterectomy would be the only surgical or interventional therapy to provide efficacy." (lines 275-277)

Tables/Figures are easy to read and additive to the text

-We thank the review and have updated below with this extensive revision.

Previous Table 1 (remains Table 1): Minimally updated to remove trade names from recommendation of below "Table Checklist."
Previous Table 2: Removed with extensive revision of previous manuscript in effort to make more clinically focused.
Previous Table 3 (now Appendix 1): We have updated to include recent linzagolix publication and transitioned to create an Appendix in effort to appear less of a detailed literature review while also providing a reference that readers can access, if desired.

Previous Table 4 (now Table 2): Updated to include recent linzagolix publication with inclusion of both doses with and without add-back compared to placebo.

Figure 1: Updated to include recently published linzagolix information with two doses alone and in combination with add-back. Three oral GnRH antagonists separated by color coding and monotherapy regimens have cross hatching.

Figure 2: Also updated to include recently published linzagolix information with two doses alone and in combination with add-back. Three oral GnRH antagonists separated by same color coding and monotherapy regimens have cross hatching. Percent change updated to from baseline instead of from placebo since linzagolix reported from baseline. Hip data not available for linzagolix.

STATISTICAL EDITOR COMMENTS:

Figs 1, 2: Although the differences vs the placebo groups are obvious, should include CIs to illustrate the variability of the point estimates. Should also indicate the statistical significance of the differences, either on the figure itself or in figure legend. Should include some concise use of these stats in main text.

- We appreciate the statistical editor's comments and review of previous manuscript. We have extensively revised our previous manuscript as well as both figures in an effort to make more clinically focused. With updated figures, placebo bars have been removed to better compare among the three oral GnRH antagonists (identified by color coding) and to allow for easier reading with less busy figures. Since we do not have the data, we are not able to calculate confidence intervals.

line 231: Suggest rather than "Other specific endpoints" should be labeled as secondary endpoints.

- We thank the statistical editor for this recommendation and have updated to "SECONDARY ENDPOINTS". (line 125)

Suggest listing secondary outcomes and adverse outcomes in separate Tables, with summaries in main text.

- We have extensively revised our manuscript to make more clinically focused and have removed much of the granular detailed information of study specific details. Through this process, we have attempted to pull out important details to clinically summarize in each section/subsection with reference to tables and figures. To further appear less of a detailed literature review, we have moved our previous "Table 3" to create an "Appendix 1" that readers can reference, if desired, for study specific details.

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.**

-We have clarified that there was no funding for this 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.

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

Use "Black" and "White" (capitalized) when used to refer to racial categories.

- With our extensive revision, we have ensured appropriate capitalization for racial categories.

List racial and ethnic categories in tables in alphabetic order. Do not use "Other" as a category; use "None of the above" instead.

Please refer to "Reporting Race and Ethnicity in Obstetrics & Gynecology" at https://nam12.safelinks.protection.outlook.com/?url=https%3A%2F%2Fedmgr.ovid.com%2Fong%2Faccounts%2FRace_and_Ethnicity.pdf&data=05%7C01%7CStewart.Elizabeth%40mayo.edu%7C0f7d0e1d1e9f408aadd108da980a96a6%7Ca25fff9c3f634fb29a8ad9bdd0321f9a%7C0%7C0%7C637989468658699136%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=FKdXIBafhi9hgxNO86jXS7ct9wUJKXPvsK0uJCuIHJc%3D&reserved=0.

5. ACOG uses person-first language. Please review your submission to make sure to center the person before anything else. Examples include: "People with disabilities" or "women with disabilities" instead of "disabled people" or "disabled women"; "patients with HIV" or "women with HIV" instead of "HIV-positive patients" or "HIV-positive women"; and "people who are blind" or "women who are blind" instead of "blind people" or "blind women."

- With our extensive revision, we have reviewed for person-first language.

6. The journal follows ACOG's Statement of Policy on Inclusive Language (https://nam12.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.acog.org%2Fclinical-information%2Fpolicy-and-position-statements%2Fstatements-of-policy%2F2022%2Finclusive-language&data=05%7C01%7CStewart.Elizabeth%40mayo.edu%7C0f7d0e1d1e9f408aadd108da980a96a6%7Ca25fff9c3f634fb29a8ad9bdd0321f9a%7C0%7C0%7C637989468658855379%7CUnkno

wn%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=9kl4ixMLYOhqH1xllus7rXWzwRAmBKJE%2Ft7H16Gt0F8%3D&reserved=0). **When possible, please avoid using gendered descriptors in your manuscript. Instead of "women" and "females," consider using the following: "individuals;" "patients;" "participants;" "people" (not "persons"); "women and transgender men;" "women and gender-expansive patients;" or "women and all those seeking gynecologic care."**

- With our extensive revision, we attempted to avoid using gendered descriptors as much as possible.

7. Figures 1-2: Has this been previously published in another source? If yes, both print and electronic (online) rights must be obtained from the holder of the copyright (often the publisher, not the author), and credit to the original source must be included in your manuscript. Many publishers have online systems for submitting permissions requests; please consult the publisher directly for more information.

-Both figures are original and have been updated with recent linzagolix information and for easier reading. Data used in figures was obtained from published pivotal phase III clinical trials. This is now specifically stated in each figure legend and references for these trials have been inserted.

8. All submissions that are considered for potential publication are run through CrossCheck for originality. The following lines of text match too closely to previously published works or need to be cited:

Please provide citation for lines 148-150.

- This sentence has now been deleted as part of condensing the section “Efficacy of oral GnRH antagonists on the primary endpoint of abnormal uterine bleeding” (starting at line 116) to make more clinically focused. This sentence was previously defining endpoints and was deleted with recommendation from reviewer #1. A similar sentence has been included for a more clinical approach of reduction in menstrual blood loss and references were inserted from the pivotal phase III trials.

9. 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://nam12.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%7CStewart.Elizabeth%40mayo.edu%7C0f7d0e1d1e9f408aadd108da980a96a6%7Ca25fff9c3f634fb29a8ad9bdd0321f9a%7C0%7C0%7C637989468658855379%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=mvZqKuy4yGQ4ffGbBb0g75a253XxxB04drbXxJjfMNQ%3D&reserved=0 and the gynecology data definitions at https://nam12.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%7CStewart.Elizabeth%40mayo.edu%7C0f7d0e1d1e9f408aadd108da980a96a6%7Ca25fff9c3f634fb29a8ad9bdd0321f9a%7C0%7C0%7C637989468658855379%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3

D%7C3000%7C%7C%7C&sdata=iTbG3xYS7j90dUU2LGi1I0%2Fc5cDcE%2FQj4VdhzRwrztg%3D&reserved=0. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

10. 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.

Clinical Expert Series: 25 pages

- We have extensively revised our manuscript to make more clinically focused and have removed much of the granular detailed information of study specific details. Our manuscript word count has decreased to 3392 and manuscript is less than allotted 25 pages.

11. 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.

12. Provide a short title of no more than 45 characters, including spaces, for use as a running foot. Do not start the running title with an abbreviation.

- We have included a short tile (“Oral Antagonists for Uterine Leiomyomas”) that is 39 characters including spaces.

13. 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.

Clinical Expert Series: 250 words max

- With our extensive revision, we have ensured that statements in abstract are also stated in the body of manuscript, tables, or figures. The word count of revised abstract is 249/250 words.

14. Only standard abbreviations and acronyms are allowed. A selected list is available online at https://nam12.safelinks.protection.outlook.com/?url=http%3A%2F%2Fedmgr.ovid.com%2Fong%2Faccounts%2Fabbreviations.pdf&data=05%7C01%7CStewart.Elizabeth%40mayo.edu%7C0f7d0e1d1e9f408aadd108da980a96a6%7Ca25fff9c3f634fb29a8ad9bdd0321f9a%7C0%7C0%7C637989468658855379%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=VcPJpyCTz5V%2F0wKV3ECTIHSImc2m5lFMjArqEWUV6VE%3D&reserved=0. 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.

- With our revision, we have referenced the above select list of abbreviations and used as appropriate making sure to spell out the first time they are used. For example, we have kept the approved abbreviation “AUB-L” but removed “HMB” to just write out heavy menstrual bleeding. Furthermore, we spelled out “Gonadotrophin-Releasing Hormone” (instead of GnRH) in the title to avoid use of abbreviations.

15. 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.

- In revision, we avoided using “provider” and changed to “health care professional”. (line 307)

16. 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 extensively revised our manuscript to make more clinically focused and have removed much of the granular detailed information of study specific details. The revision does not include p values. Furthermore, we have expressed percentages to one decimal place as much as possible in the revision. There are rare incidences in which percentages to one decimal place are not provided in referenced studies and data is not available to manually calculate.

17. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available at
https://nam12.safelinks.protection.outlook.com/?url=http%3A%2F%2Fedmgr.ovid.com%2Fong%2Faccounts%2Ftable_checklist.pdf&data=05%7C01%7CStewart.Elizabeth%40mayo.edu%7C0f7d0e1d1e9f408aadd108da980a96a6%7Ca25fff9c3f634fb29a8ad9bdd0321f9a%7C0%7C0%7C637989468658855379%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=UfL6Eca4BbmzJtsbZr5zg6lBMmnIgCBfwZak04Ta350%3D&reserved=0.
- We have reviewed the Table Checklist and made sure it was incorporated in table revisions. For example, in Table 1 we slightly revised to remove Trade Names and removed shading in all tables.

18. Please review examples of our current reference style at
https://nam12.safelinks.protection.outlook.com/?url=https%3A%2F%2Fedmgr.ovid.com%2Fong%2Faccounts%2Fifa_suppl_refstyle.pdf&data=05%7C01%7CStewart.Elizabeth%40mayo.edu%7C0f7d0e1d1e9f408aadd108da980a96a6%7Ca25fff9c3f634fb29a8ad9bdd0321f9a%7C0%7C0%7C637989468658855379%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=drP4nB6W6r%2BE3rBsYhwo8N1q6xJs2XWqEUYyLtxGH8c%3D&reserved=0. Include the digital object identifier (DOI) with any journal article references and an accessed date with website references.

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

- References have been updated from provided examples to journal's current reference style. We have made sure to include DOI with journal article references and accessed date with website references. Although abstracts may be included, we removed previous in text cited abstracts with this extensive revision.

19. Figures 1-2: Please confirm that these are original to the manuscript. Should the legend include any information about "data from"?

-Both figures are original and have been updated with recent linzagolix information and for easier reading. Data used in figures was obtained from published pivotal phase III clinical trials. This is now

specifically stated in each figure legend and references for these trials have been inserted.

20. 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 https://nam12.safelinks.protection.outlook.com/?url=http%3A%2F%2Flinks.lww.com%2FLWW-ES%2FA48&data=05%7C01%7CStewart.Elizabeth%40mayo.edu%7C0f7d0e1d1e9f408aadd108da980a96a6%7Ca25fff9c3f634fb29a8ad9bdd0321f9a%7C0%7C0%7C637989468658855379%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=3%2FsbgdDwuyPy029Uy9QPTCga%2F9UMFIeutWJlBghtaF4%3D&reserved=0. The cost for publishing an article as open access can be found at https://nam12.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwkauthorservices.editage.com%2Fopen-access%2Fhybrid.html&data=05%7C01%7CStewart.Elizabeth%40mayo.edu%7C0f7d0e1d1e9f408aadd108da980a96a6%7Ca25fff9c3f634fb29a8ad9bdd0321f9a%7C0%7C0%7C637989468658855379%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=k8dknxjiUDZT8h5kBanhhaQQvyoDw9bEMzpoDqp%2B%2BCg%3D&reserved=0.

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