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)*
- Email correspondence between the editorial office and the authors*

*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.
RE: Manuscript Number ONG-18-1751

ULIPRISTAL ACETATE A NOVEL TREATMENT FOR DISSEMINATED PERITONEAL LEIOMYOMATOSIS

Dear Dr. Murji:

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 Nov 30, 2018, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

REVIEWER #1:

This is a well written case report about ulipristal acetate (UPA) for the treatment of disseminated peritoneal leiomyomatosis.

1. Is there any information as to the actual incidence of DPL?
2. Was there any DPL seen or suspected at the time of the patient's previous laparoscopies?
3. Are the pulmonary nodules thought to be DPL as well? Any speculation as to why these did not respond to UPA?
4. Line 162 uses citation #4 to discuss different agents used to treat DPL but the citation is about endometrial response to UPA.
5. The paragraph in the discussion regarding endometrial changes with UPA can be shortened to just a few sentences on this and the fact that endometrial surveillance is not needed.
6. The authors might be interested in this citation which is a good review of UPA and the liver issues in Europe: Fertil Steril. 2018 Sep;110(4):593-595. Liver injury and ulipristal acetate: an overstated tragedy? Donnez J.

REVIEWER #2:

Disseminated peritoneal leiomyomatosis (DPL) is a rare condition that, despite its name, may be encountered by practitioners from a spectrum of specialties because of its superficial appearance suggesting peritoneal carcinomatosis.

There is evidence that gonadotropin releasing hormone agonists (GnRH-a) can be effective in reducing and suppressing DPL disease burden, and there have been some reports in the literature describing the use of ulipristal acetate (UA) a selective progesterone receptor modulator for the same purpose.

The authors conclude that UA is a suitable substitute for GnRH-a that is absent hypoestrogenic side effects. However, this
case report suggests the potential for UA as maintenance therapy as this patient was "induced" with leuprolide acetate. Whether or not the same or similar initial volumetric reduction of measurable disease could have been accomplished with UA alone has not been described. The "Teaching Points" (Line 73) and conclusions should be rewritten with this concept.

I would also think that, if available and of adequate quality, photographs of disease at laparotomy and/or of the pulmonary nodules would add to this case report.

Specific Comments

1. Line 99. The term "pathophysiology" does not apply here. This is not a disordered physiological process. Instead, I would suggest 'pathogenesis'.

2. Line 102. I would suggest that your abbreviation would be improved by using 'GnRH-a' not "GnRH agonist"

3. Line 113. I would suggest that a more appropriate term than "combined oral contraception" would be 'combined estrogen and progestin oral contraception'.

4. Line 192. By limiting your description of where UPA has been approved to "Canada and Europe" you actually make an error, as there has been regulatory approval in many other countries. So I would revise this sentence accordingly.

5. Line 202. I would suggest modifying the sentence to allow an explanation the term "PEARL III extension study.", and later "PEARL IV".

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7. Line 219-227. This where you are making a jump by stating that UPA is an alternative for both initiating and maintaining suppression of these tumors.

EDITOR 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, as well as subsequent author queries. 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:
   1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.
   2. OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries.

2. Author Agreement Forms: Please note the following issues with your forms. Updated or corrected forms should be submitted with the revision.

   Jessica Papillon-Smith, MD - A form was not submitted with the original submission.

   Ally Murji, MD, MPH - Please include your signature on the journal's actual form.

   Please note:

   a) Any material included in your submission that is not original or that you are not able to transfer copyright for must be listed under I.B on the first page of the author agreement form.

   b) All authors must disclose any financial involvement that could represent potential conflicts of interest in an attachment to the author agreement form.

   c) All authors must indicate their contributions to the submission by checking the applicable boxes on the author agreement form.

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   * Substantial contributions to the conception or design of the work; OR
the acquisition, analysis, or interpretation of data for the work;

AND

* Drafting the work or revising it critically for important intellectual content;

AND

* Final approval of the version to be published;

AND

* Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The author agreement form is available online at http://edmgr.ovid.com/ong/accounts/agreementform.pdf. Signed forms should be scanned and uploaded into Editorial Manager with your other manuscript files. Any forms collected after your revision is submitted may be e-mailed to obgyn@greenjournal.org.

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 will be transitioning as much as possible to use of the reVITALize definitions, and we encourage authors to familiarize themselves with them. The obstetric data definitions are available at http://links.lww.com/AOG/A515, and the gynecology data definitions are available at http://links.lww.com/AOG/A935.

4. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Case Reports should not exceed 8 typed, double-spaced pages (2,000 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and appendixes).

5. Specific rules govern the use of acknowledgments in the journal. Please edit your acknowledgments or provide more information in accordance with 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 signature on the journal's author agreement 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 short title of no more than 40 characters, including spaces, for use as a running foot.

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: Case Reports, 125 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. If you choose to revise your manuscript, please submit your revision via Editorial Manager for Obstetrics & Gynecology at http://ong.editorialmanager.com. It is essential that your cover letter list point-by-point the changes made in response to each criticism. Also, please save and submit your manuscript in a word processing format such as Microsoft Word.

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

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 Nov 30, 2018, we will assume you wish to withdraw the manuscript from further consideration.
Sincerely,

John O. Schorge, MD
Associate Editor for Gynecology

2017 IMPACT FACTOR: 4.982
2017 IMPACT FACTOR RANKING: 5th out of 82 ob/gyn journals

In compliance with data protection regulations, please contact the publication office if you would like to have your personal information removed from the database.
Dear Editors,

Thank you for reviewing our manuscript titled, “Ulipristal Acetate a Novel Treatment for Disseminated Peritoneal Leiomyomatosis” (ONG-18-1751). We greatly appreciate your consideration of our manuscript for publication in Obstetrics & Gynecology and value your insightful feedback.

We trust that you will find our response to the reviewers’ comments and editorial suggestions below acceptable and will kindly accept our manuscript for publication in your journal. We look forward to hearing from you soon.

Sincerely,

Samantha Benlolo MD, Jessica Papillon-Smith MD, Ally Murji MD MPH
Responses to Reviewer Comments

We OPT IN for publication of our responses. Yes, please publish my response letter and subsequent email correspondence related to author queries.

REVIEWER #1:

This is a well written case report about ulipristal acetate (UPA) for the treatment of disseminated peritoneal leiomyomatosis.

1. Is there any information as to the actual incidence of DPL?
   DPL is extremely rare and we did not find an exact incidence for the condition. Several papers describe fewer than 200 cases reported. Due to the lack of information, we have not added information about incidence in the manuscript.

2. Was there any DPL seen or suspected at the time of the patient's previous laparoscopies?
   There was no mention of any suspicious nodules at the time of her prior laparoscopies. We included this information in line 92.

3. Are the pulmonary nodules thought to be DPL as well? Any speculation as to why these did not respond to UPA?
   It is unclear whether the pulmonary nodules are associated with DPL or if they are unrelated as they have never been biopsied (line 127-128). It would certainly be interesting to get a pathologic diagnosis of the nodules should they ever require biopsy.

4. Line 162 uses citation #4 to discuss different agents used to treat DPL but the citation is about endometrial response to UPA.
   We have corrected the citation (line 136 and 139).

5. The paragraph in the discussion regarding endometrial changes with UPA can be shortened to just a few sentences on this and the fact that endometrial surveillance is not needed.
   Thank you, we have edited that paragraph to make it more concise.

6. The authors might be interested in this citation which is a good review of UPA and the liver issues in Europe: Fertil Steril. 2018 Sep;110(4):593-595. Liver injury and ulipristal acetate: an overstated tragedy? Donnez J.
   Thank you for suggesting this well written article, we have included it in our references.

REVIEWER #2:

Disseminated peritoneal leiomyomatosis (DPL) is a rare condition that, despite its name, may be encountered by practitioners from a spectrum of specialties because of its superficial appearance suggesting peritoneal carcinomatosis.
There is evidence that gonadotropin releasing hormone agonists (GnRH-a) can be effective in reducing and suppressing DPL disease burden, and there have been some reports in the literature describing the use of ulipristal acetate (UA) a selective progesterone receptor modulator for the same purpose.

The authors conclude that UA is a suitable substitute for GnRH-a that is absent hypoestrogenic side effects. However, this case report suggests the potential for UA as maintenance therapy as this patient was "induced" with leuprolide acetate. Whether or not the same or similar initial volumetric reduction of measurable disease could have been accomplished with UA alone has not been described. The "Teaching Points" (Line 73) and conclusions should be rewritten with this concept.

Thank you for this very insightful comment. We agree that an initial treatment with the GnRH-a may have been necessary/beneficial for the successful maintenance of symptoms on UPA (amended in the teaching points, line 67-69 and conclusions, line 194-196).

I would also think that, if available and of adequate quality, photographs of disease at laparotomy and/or of the pulmonary nodules would add to this case report.

We agree, but unfortunately we do not have any available photographs to contribute to the report.

Specific Comments

1. Line 99. The term "pathophysiology" does not apply here. This is not a disordered physiological process. Instead, I would suggest 'pathogenesis'.

Thank you – revised, line 78.

2. Line 102. I would suggest that your abbreviation would be improved by using 'GnRH-a' not "GnRH agonist"

Thank you – revised to GnRH-a throughout the manuscript.

3. Line 113. I would suggest that a more appropriate term than "combined oral contraception" would be 'combined estrogen and progestin oral contraception'.

Thank you – revised line 93.

4. Line 192. By limiting your description of where UPA has been approved to "Canada and Europe" you actually make an error, as there has been regulatory approval in many other countries. So I would revise this sentence accordingly.

Thank you – revised line 167.

5. Line 202. I would suggest modifying the sentence to allow an explanation the term "PEARL III extension study." and later "PEARL IV".

We modified that paragraph to make it more succinct at the recommendation of Reviewer #1’s comments (line 176). We have deleted references to the PEARL studies.
6. Line 212. I am not sure that liver injury has been clearly related to PRMs, and clearly, the term "unrelated to the duration of treatment" cannot be concluded. So this should be rewritten to simply state that there are, as yet, reports of an association.

   Thank you – revised line 180-181.

7. Line 219-227. This where you are making a jump by stating that UPA is an alternative for both initiating and maintaining suppression of these tumors.

   Thank you – revised line 194-196.

EDITOR 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, as well as subsequent author queries. 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:
   1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.
   2. OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries.

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   Jessica Papillon-Smith, MD - A form was not submitted with the original submission.  
   Thank you, submitted.

   Ally Murji, MD, MPH - Please include your signature on the journal's actual form.
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   Please note:

   a) Any material included in your submission that is not original or that you are not able to transfer copyright for must be listed under I.B on the first page of the author agreement form.

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   **Word count from Precis to Discussion is 1771. Total pages are 10, double spaced, times new roman, including Cover page, Precis and Abstract on their own pages as per Instructions for Authors.**

5. Specific rules govern the use of acknowledgments in the journal. Please edit your acknowledgments or provide more information in accordance with 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 signature on the journal's author agreement form verifies that permission
has been obtained from all named persons.
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6. Provide a short title of no more than 40 characters, including spaces, for use as a running foot.
   **Listed on the cover page: Ulipristal Acetate and Leiomyomatosis**

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.

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   **Word count provided at the end of the Abstract.**

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We hope these changes address the reviewer’s concerns and thank you once again for your valuable feedback that has helped to improve this manuscript.

Sincerely,

Samantha Benlolo MD
Hi Daniel  
Thank you for going through the manuscript and editing it. 
I have gone through your changes and approve of all of them. 
I agree with the change in the title. 
I have added the dates of the meeting in the attached manuscript.

Please let us know if there is anything else you need from our end.

Warm regards,
Ally

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Ally Murji MD, MPH, FRCS(C)  
Minimally Invasive Gynecology  
Assistant Professor - University of Toronto  
Mount Sinai Hospital

From: Daniel Mosier <dmosier@greenjournal.org>
Sent: November 30, 2018 2:22 PM
To: Murji, Dr. Ally
Subject: Manuscript Revisions: ONG-18-1751R1

Dear Dr. Murji,

Thank you for submitting your revised manuscript. It has been reviewed by the editor, and there are a few issues that must be addressed before we can consider your manuscript further:

1. Please note the minor edits and deletions throughout. Please let us know if you disagree with any of these changes.
2. LINE 1: Do you approve the edited title?
3. LINE 20: Please add the dates of the meeting.

Please let me know if you have any questions. Your prompt response to these queries will be appreciated; please respond no later than COB on Tuesday, December 4th.

Sincerely,
-Daniel Mosier