OBSTETRICS & GYNECOLOGY

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: May 23, 2019
To: "Camran Nezhat"
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-762

RE: Manuscript Number ONG-19-762

Endometriosis-associated pain mechanisms and treatments

Dear Dr. Nezhat:

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 Jun 13, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: In this manuscript, the authors present a "current commentary" regarding management of endometriosis. Table 1 in the Obstetrics and Gynecology Instructions for Authors states for Current Commentaries the manuscript word count is 3000 words (12 pages) and the maximum number of references is 24. The abstract is limited to 300 words per this document. In this manuscript, the authors have an 87-word abstract, a nearly 3000-word manuscript but 65 references. I can appreciate the challenge of trying to pare down the references to fit the "rules" (and indeed there are portions of the manuscript that need citation despite the 65 references) but the problem appears to live in trying to force this topic into a manuscript type that is not ideal. The Instructions for Authors says about Current Commentaries that:

Current Commentary essays address issues, opinions, experiences, or perspectives of clinical relevance to the field of obstetrics and gynecology and obstetrician-gynecologists. Length should not exceed 3,000 words (approximately 12 manuscript pages; Table 1). The abstract should be a single paragraph that states what was done, what was found, and what the findings mean. Headings are not necessary in the body of the article but may be used if needed.

In fact, the manuscript is more of a review article than a commentary. There is some opinion but there is also more detail about anatomy and pathophysiology than would be expected of an "opinion" piece. Generally, the manuscript has some interesting details but overall, as a commentary, it lacks focus. As an example, the stated purpose of this piece is to be "a review of current literature and our clinical experience." A commentary is not a review of the literature. It could be the authors feel the diagnosis of endometriosis is too often made in error or that too many women are labeled with this diagnosis and have unnecessary procedures. Preparing a commentary citing this as the problem you seek to render clarity to via your opinions and experience would be a better commentary topic. I have the following specific comments/questions:

1) Why are their 6 authors? What did each contribute? If this is a commentary, expressing opinions, etc, are all in one voice regarding these opinions? My very cursory scan of recent Current Commentaries shows no more than 3 authors. Imagine going into a cafeteria and asking for opinions on the best dog breed. Opinions tend to winnow people into small groups.

2) The problem of pelvic pain is the problem of compounding imprecision. There are a lot of factors that go into why one woman has pain. The authors would appear to agree with this yet the background largely assumes that endometriosis found is always disease (clearly not the case). Stating, for example, "correct diagnosis...takes 6 to 10 years (a reference is needed here)" implies all preceding "wrong" diagnoses had no impact on the presenting symptoms OR that endometriosis was from the start the root of all the problems.

3) A reference is needed for line 40 - what evidence endorses the success of treatment varies with the surgeon's skill

and experience.

4) Much of pages 2-5 - up to Medical Mgmt Options - could be removed. Its great stuff but its largely anatomy and physiology and not opinion. Changing the article type is another approach where this could be included.

5) Line 121 - "due to its side-effects profile...it has garnered FDA-approval" makes no sense. The FDA didn't approve Lupron b/c of its adverse side-effects.

6) Line 152 - Discussing Floria is really kind of odd. There are no data to support this treatment option as any other CBD or other non-traditional approach. Batwing and eye of newt, based on the available evidence, could me mentioned here too...why Floria? On the other hand, where is there any mention of Bazedoxifene? There is HIGHLY compelling evidence for this treatment relative to weed.

7) I get the authors like cutting endometriosis out - me too. The counter argument should be featured, particularly in a woman who desires future fertility.

8) I am aware of the supportive data on pre-sacral neurectomy. It is unclear to me, however, how this fixes endometriosis. You could as likely do this for bladder pain - its central. Where do the authors see this procedure in their care of women with pain with and without endometriosis?

9) Picture doesn't add much. The IHP is deep to the peritoneum thus it's kind of misleading to show a picture of an intact peritoneum and label it the IHP. The fact that a LUNA didn't work is b/c the nerves are a) deep to the surface and b) too spread out to be meaningfully impacted with an ablation focused over just the uterosacral ligament.

Overall, the manuscript is mixed up. Is it a review or a commentary? It's kind of neither at the moment.

Reviewer #2: This manuscript by Nezhat and colleagues is submitted as a Current Commentary, thus can be permitted if not expected to reflect the clinical opinions and practice of the authors and not be held to the standard of a comprehensive or exhaustive critical analysis of the body of data informing evidence-based clinical practice. Indeed, the authors acknowledge in the Background that this commentary represents a summary of "various treatment options used in our practice" based on a review of the current literature. As such, I think the authors have presented a very nice summary of the physiologic, anatomic, and clinical evidence that supports their practice. They have done a particularly good job of briefly summarizing the neuroanatomic and neuromodulatory basis of some of the pain symptoms that confront the treating surgeon.

While the authors acknowledge the complex nature of endometriosis-related pain, I think they fall somewhat short in providing a broader and richer sense of the existing literature which addresses the uncertainty of the relationship between endometriosis (particularly stages 1 and 2) and pain. In reading their manuscript, one could fairly conclude that this relationship is predictable, progressive, and falls fairly clearly into the largely surgical paradigm described by the authors. I think it is widely perceived that this is, in fact, not the case. Therefore, I would suggest that this manuscript, though admittedly (and I believe appropriately) a commentary on their practice, would be more valuable to the reader if the authors were to introduce and summarize some of these confounding observations. For example how best to explain that many women with endometriosis, particularly those with early stage disease, respond clinically in a manner similar to women whose pelvis appears free of disease at laparoscopy? Would this not suggest that the paradigm described might be either inapplicable or incomplete? Perhaps said more simply, I believe the manuscript would be stronger if the authors included a discussion of the very large body of data that do not so clearly support their paradigm. Treatment of pelvic pain associated with endometriosis (or not) is a confusing area of clinical research and treatment, and I think that their description does not quite do justice to the uncertainties.

Reviewer #3: In this paper the authors review the current literature on the potential mechanisms of endometriosis-associated pain and discuss the various treatment options used in their practice. Overall this is an excellent review on a very important topic and the authors serve the readers very well by including their extensive experience and recommendations in the understanding and the management of this chronic disease that affects so many patients world-wide. I have the following comments and questions:

1. On page 6, line 132- LNG-IUS releases 20 MCG not mg of LNG

2. Page 8 lines 173 and 174- "production of dopamine by the adrenal gland". Can you provide references for this? I was not aware that the adrenal gland is a major producer of dopamine.

3. It may be important to list potential complications and side effects with presacral neurectomy as listed for uterosacral resection on page 9.

4. I commend the authors for their discussion of the perioperative medical management of the endometriosis patients but it may be worth emphasizing the importance of medical suppression of disease before surgery to prevent ovulation and

reduce the vascularity of the disease and affected organs, and the importance of hormonal suppressive therapy postoperatively to reduce recurrences and which of these therapies may be best. For example the LNG IUS has been shown to reduce the risk of recurrence of pain endometriosis symptoms but not the recurrence of endometriomas, most likely because it does not inhibit ovulation as well as oral contraceptives (Chen et al. Postoperative maintenance therapy for endometriosis AJOG 2017)

5. Finally, I think an algorithm of the authors' recommendation or management of the endometriosis patient maybe helpful

ASSOC EDITOR - GYN

1 - Please adhere as closely as possible to Instructions for Authors (page 8, Table 1) to guide parameters for this submission as a Clinical Commentary. The paper will be rejected at the resubmit stage if the authors do not dramatically reduce the number of references and generally follow the established guidelines for this category. The highlights are pointed out by Reviewer #1

2 - I had mentioned at the time of the last manuscript review that we have a Clinical Expert Series paper coming out in a month or two from Tomasso Falcone. We will need to revise the authors re-submission in order to not have duplicative papers.

EDITORIAL OFFICE COMMENTS:

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

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

Any author agreement forms previously submitted will be superseded by the eCTA. During the resubmission process, you are welcome to remove these PDFs from EM. However, if you prefer, we can remove them for you after submission.

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

4. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Current Commentary articles should not exceed 12 typed, double-spaced pages (3,000 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, tables, boxes, figure legends, and print appendixes) but exclude references.

5. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

* All financial support of the study must be acknowledged.
* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.
* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

6. Provide a short title of no more than 45 characters (40 characters for case reports), including spaces, for use as a running foot.

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

8. 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: Current Commentary articles, 250 words. Please provide a word count.

9. 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.

10. 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.

11. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.

12. The Journal's Production Editor had the following to say about this manuscript:

"-Figure 1 and Figure 2 need to be uploaded as separate files into EM
-Note that only Figure 1 is in the manuscript and there is no image for Figure 2"

When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint.

When you submit your revision, art saved in a digital format should accompany it. Please upload each figure as a separate file to Editorial Manager (do not embed the figure in your manuscript file).

If the figures were created using a statistical program (eg, STATA, SPSS, SAS), please submit PDF or EPS files generated directly from the statistical program.

Figures should be saved as high-resolution TIFF files. The minimum requirements for resolution are 300 dpi for color or black and white photographs, and 600 dpi for images containing a photograph with text labeling or thin lines.

Art that is low resolution, digitized, adapted from slides, or downloaded from the Internet may not reproduce.

13. 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 http://edmgr.ovid.com/acd/accounts/ifauth.htm.

Please note that 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.

***

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 and that each author has given approval to the final form of the revision.

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Jun 13, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

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

____
In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: https://www.editorialmanager.com/ong/login.asp?a=r). Please contact the publication office if you have any questions.

Dear Dr Chescheir, Associated editors and Reviewers,

We would like to take this opportunity to thank you for significant amount of time you have spent on this paper. Your recommendations have been excellent, and we have followed them one by one. We believe it has made the paper much stronger and will contribute significantly to your readership. The only factor that we could not address as required are the references. According to your guidelines maximum references are 24, we have decreased the references from 65 to 25. If this is not acceptable, we would be happy to delete one more reference. Thank you again for your consideration.

Below please find the response to the reviewers and editors as well as auditorial office.

Best regards,

Camran Nezhat, MD

Reviewer #1: In this manuscript, the authors present a "current commentary" regarding management of endometriosis. Table 1 in the Obstetrics and Gynecology Instructions for Authors states for Current Commentaries the manuscript word count is 3000 words (12 pages) and the maximum number of references is 24. The abstract is limited to 300 words per this document. In this manuscript, the authors have an 87-word abstract, a nearly 3000-word manuscript but 65 references. I can appreciate the challenge of trying to pare down the references to fit the "rules" (and indeed there are portions of the manuscript that need citation despite the 65 references) but the problem appears to live in trying to force this topic into a manuscript type that is not ideal. The Instructions for Authors says about Current Commentaries that:

Current Commentary essays address issues, opinions, experiences, or perspectives of clinical relevance to the field of obstetrics and gynecology and obstetrician-gynecologists. Length should not exceed 3,000 words (approximately 12 manuscript pages; Table 1). The abstract should be a single paragraph that states what was done, what was found, and what the findings mean. Headings are not necessary in the body of the article but may be used if needed.

In fact, the manuscript is more of a review article than a commentary. There is some opinion but there is also more detail about anatomy and pathophysiology than would be expected of an "opinion" piece. Generally, the manuscript has some interesting details but overall, as a commentary, it lacks focus. As an example, the stated purpose of this piece is to be "a review of current literature and our clinical experience." A commentary is not a review of the literature. It could be the authors feel the diagnosis of endometriosis is too often made in error or that too many women are labeled with this diagnosis and have unnecessary procedures. Preparing a commentary citing this as

the problem you seek to render clarity to via your opinions and experience would be a better commentary topic. I have the following specific comments/questions:

Thank you, we have followed all your instructions as you have recommended to fit the Current Commentary. It is 2273 words; the number of authors has been decreased to 4.

1) Why are their 6 authors? What did each contribute? If this is a commentary, expressing opinions, etc, are all in one voice regarding these opinions? My very cursory scan of recent Current Commentaries shows no more than 3 authors. Imagine going into a cafeteria and asking for opinions on the best dog breed. Opinions tend to winnow people into small groups.

Thank you, we have decreased the number of authors from 6 to 4 as per guideline table and we have acknowledged the other authors in the text.

2) The problem of pelvic pain is the problem of compounding imprecision. There are a lot of factors that go into why one woman has pain. The authors would appear to agree with this yet the background largely assumes that endometriosis found is always disease (clearly not the case). Stating, for example, "correct diagnosis…takes 6 to 10 years (a reference is needed here)" implies all preceding "wrong" diagnoses had no impact on the presenting symptoms OR that endometriosis was from the start the root of all the problems.

Thank you, as stated by the reviewer pelvic pain in women is a complex issue. Here we are only expressing our experience in endometriosis related pain in patients.

"Because of its complex nature, it can take 6 to 10 years to diagnose endometriosis and its symptomatology varies tremendously (1-2). Most patients experience cyclic pelvic pain with menses, but some experience symptoms of noncyclic pelvic pain, such as dyspareunia, dyschezia and dysuria. Of importance, pain severity does not correlate with the amount of endometrial tissue formed. Many patients present only with unexplained infertility. As Giudice states, "infertility results from the toxic effects of the inflammatory process on gametes and embryos, compromised fimbrial function, and eutopic endometrium that is resistant to the action of progesterone and is inhospitable to embryonic implantation (3)." However, it can produce symptoms that mimic other diseases, including: irritable bowel syndrome, interstitial cystitis,

vascular, musculoskeletal, neurological, psychological diseases, obesity, anorexia, thyroid dysfunction, autoimmune disorders and heart disease.”

3) A reference is needed for line 40 - what evidence endorses the success of treatment varies with the surgeon's skill and experience.

Thank you, this line has been deleted from the paper.

4) Much of pages 2-5 - up to Medical Mgmt Options - could be removed. Its great stuff but its largely anatomy and physiology and not opinion. Changing the article type is another approach where this could be included.

Thank you, as reviewers #2 and #3 have expressed their pleasure with this section, and as such wanted to keep it, and in order to please this reviewer we have kept this section but shortened it significantly and provided our experience.

“One component of our initial treatment is the utilization of combined oral contraceptive pills, which are effective in decreasing pain as well as in preventing postoperative recurrence (12). For those who cannot tolerate or have contraindications to estrogen, we recommend the use of progestins like medroxyprogesterone acetate, norethindrone acetate, or levonorgestrel. However, there are patients who have decreased receptor sensitivity and are essentially resistant to progestins. This is a result of aberrant gene expression in the eutopic endometrium that leads to progesterone resistance (13). For patients who are unable to tolerate oral medications, we recommend the levonorgestrel-releasing intrauterine system (LNG-IUS), since it reduces pain and recurrence (4,14). However, LNG-IUS does not inhibit ovulation and the recurrence of endometriomas. For those patients that have failed the previous options, we recommend using the GnRH agonist with add back therapy to prevent bone loss and to ease side effects. Patients taking GnRH agonists for endometriosis may develop resistance, since endometrial-like tissue expresses aromatase and produces its own estradiol. ”

5) Line 121 - "due to its side-effects profile…it has garnered FDA-approval" makes no sense. The FDA didn't approve Lupron b/c of its adverse side-effects.

Thank you, this sentence has been deleted.

6) Line 152 - Discussing Floria is really kind of odd. There are no data to support this treatment option as any other CBD or other non-traditional approach. Batwing and eye of newt, based on the available evidence, could me mentioned here too…why Floria? On the other hand, where is there any mention of Bazedoxifene? There is HIGHLY compelling evidence for this treatment relative to weed.

Thank you, we have deleted the section about Foria. We have added our experience with Bazedoxifene.

"Our experience is mixed with GnRH antagonist, aromatase inhibitors and bazedoxifene along with conjugated estrogens. Some patients obtain pain relief from these medications while others discontinue them prematurely due to high expectations of fast mitigation of symptoms."

"Since their use was legalized in California, tetrahydrocannabinol (THC) and cannabidiol (CBD), either separately or in combination, present an alternative option for many of our patients. Patients prefer these compounds over opioids, and their use is associated with less nausea and constipation. The use of THC/CBD is especially beneficial for mitigating postoperative pain, and their use does not have the addictive concerns associated with opioid use."

7) I get the authors like cutting endometriosis out - me too. The counter argument should be featured, particularly in a woman who desires future fertility.

Thank you, we have added discussion about management of endometriosis in women who desire future fertility. "Several noninvasive diagnostic tests for endometriosis like BCL6 and endometrial function tests are recently becoming available. These tests are especially important for asymptomatic infertility patients and for younger patients for whom we

recommend egg preservation if possible. We individualize management of ovarian endometriosis and endometriomas based on the patient's age, fertility desires, family history of ovarian cancer and type of endometriomas (4). For many infertility patients, restoration of anatomy along with methodical and meticulous treatment of endometriosis can lead to natural conception or increase in overall IVF success (19). The treatment of endometriosis needs to be thorough to be effective."

8) I am aware of the supportive data on pre-sacral neurectomy. It is unclear to me, however, how this fixes endometriosis. You could as likely do this for bladder pain - its central. Where do the authors see this procedure in their care of women with pain with and without endometriosis?

*Thank you, we have made appropriate changes, "*In contrast, laparoscopic presacral neurectomy was 87% efficacious in reducing severe midline pelvic pain (2,4,7,8). We find this procedure especially effective in patients with mild or no endometriosis (17). The adverse effects associated with presacral neurectomy are constipation, bladder and urinary complaints (17). On the average, we perform presacral neurectomy in approximately one percent of our patients."

9) Picture doesn't add much. The IHP is deep to the peritoneum thus it's kind of misleading to show a picture of an intact peritoneum and label it the IHP. The fact that a LUNA didn't work is b/c the nerves are a) deep to the surface and b) too spread out to be meaningfully impacted with an ablation focused over just the uterosacral ligament.

Thank you, the picture has been deleted.

Overall, the manuscript is mixed up. Is it a review or a commentary? It's kind of neither at the moment.

Thank you, the manuscript is a commentary. We also have tried to follow the instructions on reviewers 2 and 3 who were very positive about it.

Reviewer #2: This manuscript by Nezhat and colleagues is submitted as a Current Commentary, thus can be permitted if not expected to reflect the clinical opinions and practice of the authors and not be held to the standard of a comprehensive or exhaustive critical analysis of the body of data informing evidence-based clinical practice. Indeed, the authors acknowledge in the Background that this commentary represents a summary of "various treatment options used in our practice" based on a review of the current literature. As such, I think the authors have presented a very nice summary of the physiologic, anatomic, and clinical evidence that supports their practice. They have done a particularly good job of briefly summarizing the neuroanatomic and neuromodulatory basis of some of the pain symptoms that confront the treating surgeon.

While the authors acknowledge the complex nature of endometriosis-related pain, I think they fall somewhat short in providing a broader and richer sense of the existing literature which addresses the uncertainty of the relationship between endometriosis (particularly stages 1 and 2) and pain. In reading their manuscript, one could fairly conclude that this relationship is predictable, progressive, and falls fairly clearly into the largely surgical paradigm described by the authors. I think it is widely perceived that this is, in fact, not the case. Therefore, I would suggest that this manuscript, though admittedly (and I believe appropriately) a commentary on their practice, would be more valuable to the reader if the authors were to introduce and summarize some of these confounding observations. For example how best to explain that many women with endometriosis, particularly those with early stage disease, respond clinically in a manner similar to women whose pelvis appears free of disease at laparoscopy? Would this not suggest that the paradigm described might be either inapplicable or incomplete? Perhaps said more simply, I believe the manuscript would be stronger if the authors included a discussion of the very large body of data that do not so clearly support their paradigm. Treatment of pelvic pain associated with endometriosis (or not) is a confusing area of clinical research and treatment, and I think that their description does not quite do justice to the uncertainties.

T*hank you very much, we appreciate your kind comments.*

"Endometriosis behaves like a great imposter. Because of its complex nature, it can take 6 to 10 years to diagnose endometriosis and its symptomatology varies tremendously (1-2). Most patients experience cyclic pelvic pain with menses, but some experience symptoms of noncyclic pelvic pain, such as dyspareunia, dyschezia and dysuria. Of importance, pain severity does not correlate with the amount of endometrial tissue formed. Many patients present only with

unexplained infertility. As Giudice states, “infertility results from the toxic effects of the inflammatory process on gametes and embryos, compromised fimbrial function, and eutopic endometrium that is resistant to the action of progesterone and is inhospitable to embryonic implantation (3).” However, it can produce symptoms that mimic other diseases, including irritable bowel syndrome, interstitial cystitis, vascular, musculoskeletal, neurological, psychological diseases, obesity, anorexia, thyroid dysfunction, autoimmune disorders and heart disease.”

Reviewer #3: In this paper the authors review the current literature on the potential mechanisms of endometriosis-associated pain and discuss the various treatment options used in their practice. Overall this is an excellent review on a very important topic and the authors serve the readers very well by including their extensive experience and recommendations in the understanding and the management of this chronic disease that affects so many patients world-wide. I have the following comments and questions:

Thank you very much, we appreciate your kind comments.

1. On page 6, line 132- LNG-IUS releases 20 MCG not mg of LNG

Thank you, this has been corrected.

2. Page 8 lines 173 and 174- "production of dopamine by the adrenal gland". Can you provide references for this? I was not aware that the adrenal gland is a major producer of dopamine.

Thank you, this has been corrected. It was not meant to mean major producer of dopamine. “Acupuncture also increases the pain threshold and leads to production of neurohumoral factors, such as dopamine, nitric oxide, noradrenaline, acetylcholine and others.”

3. It may be important to list potential complications and side effects with presacral neurectomy as listed for uterosacral resection on page 9.

Thank you, we have made appropriate changes. “The adverse effects associated with presacral neurectomy include constipation, bladder and urinary complaints, etc.… (17).”

4. I commend the authors for their discussion of the perioperative medical management of the endometriosis patients but it may be worth emphasizing the

importance of medical suppression of disease before surgery to prevent ovulation and reduce the vascularity of the disease and affected organs, and the importance of hormonal suppressive therapy postoperatively to reduce recurrences and which of these therapies may be best. For example the LNG IUS has been shown to reduce the risk of recurrence of pain endometriosis symptoms but not the recurrence of endometriomas, most likely because it does not inhibit ovulation as well as oral contraceptives (Chen et al. Postoperative maintenance therapy for endometriosis AJOG 2017)

Thank you, we have made appropriate changes. "We believe it is imperative for preoperative medical suppression of endometriosis to inhibit ovulation and to avoid removal of functional cysts that might look like endometriomas. Post-operative hormonal suppression is important to decrease recurrence and should be individualized depending on severity of the disease, patient's symptoms and fertility goals.

For patients who unable to tolerate oral medications, we then recommend the levonorgestrel-releasing intrauterine system (LNG-IUS) as it reduces pain and recurrence (4,14)."

5. Finally, I think an algorithm of the authors' recommendation or management of the endometriosis patient maybe helpful

Thank you, we have added an algorithm that could be useful for your readership.

ASSOC EDITOR - GYN

1 - Please adhere as closely as possible to Instructions for Authors (page 8, Table 1) to guide parameters for this submission as a Clinical Commentary. The paper will be rejected at the resubmit stage if the authors do not dramatically reduce the number of references and generally follow the established guidelines for this category. The highlights are pointed out by Reviewer #1

Thank you, we have followed all the guidelines, as number of references we decreased from 65 to 25. Is this acceptable, if not please let us know and we will cut it down more.

2 - I had mentioned at the time of the last manuscript review that we have a Clinical Expert Series paper coming out in a month or two from Tomasso Falcone. We will need to revise the authors re-submission in order to not have duplicative papers.

Thank you for all your efforts, for editorial office management.

OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.

2. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author

agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Thank you, we hope we have done it properly.

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

Thank you we have used it, please if you do not mind checking to make sure we have done it properly.

4. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Current Commentary articles should not exceed 12 typed, double-spaced pages (3,000 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, tables, boxes, figure legends, and print appendixes) but exclude references.

Thank you we have followed your instructions for Current commentary

5. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

* All financial support of the study must be acknowledged.
* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.
* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

Thank you, we have followed all the instructions and guidelines

6. Provide a short title of no more than 45 characters (40 characters for case reports), including spaces, for use as a running foot.
Thank you, we have provided title. "Endometriosis and pain."

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

Thank you, we have added the following sentence to the abstract and we are using it as a precis. "Endometriosis is an enigmatic disease; we provide our opinion on its management based on our clinical experience and review of current literature."

8. 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: Current Commentary articles, 250 words. Please provide a word count.

Thank you, we have made sure our abstract follows the guidelines, we have 104 words.

9. 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.

Thank you, we have followed the guidelines.

10. 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.

Thank you, we have used appropriate symbols.

11. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.

Thank you, we have reviewed the table and followed the guidelines.

12. The Journal's Production Editor had the following to say about this manuscript:

"-Figure 1 and Figure 2 need to be uploaded as separate files into EM
-Note that only Figure 1 is in the manuscript and there is no image for Figure 2"

When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint.

When you submit your revision, art saved in a digital format should accompany it. Please upload each figure as a separate file to Editorial Manager (do not embed the figure in your manuscript file).

If the figures were created using a statistical program (eg, STATA, SPSS, SAS), please submit PDF or EPS files generated directly from the statistical program.

Figures should be saved as high-resolution TIFF files. The minimum requirements for resolution are 300 dpi for color or black and white photographs, and 600 dpi for images containing a photograph with text labeling or thin lines.

Art that is low resolution, digitized, adapted from slides, or downloaded from the Internet may not reproduce.

Thank you, we have done as you have recommended.

13. 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 http://edmgr.ovid.com/acd/accounts/ifauth.htm.

Please note that 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.

Thank you, we will be looking forward to your email.