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: Jun 01, 2020
To: "Elizabeth Ferries-Rowe" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-1027

RE: Manuscript Number ONG-20-1027

EXPERT REVIEW: Evaluation and Treatment Options for Primary Dysmenorrhea

Dear Dr. Ferries-Rowe:

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).

Due to the COVID-19 pandemic, your paper will be maintained in active status for 30 days from the date of this letter. If we have not heard from you by Jul 01, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: Difficult to review a topic that could be a chapter rather than an article, but the authors have done a good job. In several places the literature discussion reverts the reference to 'dysmenorrhea' rather than specify whether it was primary dysmenorrhea, and given the title it should either be clear, or state no such data. Given current situation, I thought at least a nod to remote or virtual diagnosis is important. Line 59 begs that question as would the remote work make them more likely to work. And of the ones missing work how many just don't have proper access to menstrual products? In the general discussion from 64-70 how long does primary dysmenorrhea persist, and likelihood of resolving by pregnancy?

Diagnosis lines 72-74 has age of menarche resolved, and of the later diagnosed cases, what % can be attributed to missed endometriosis? Line 78 seems to have odd grammar. And then later in the article in line 103 they refer to GI symptoms but don't mention bloating or gas in line 79. Would be nice to clarify the link of smoking with primary dysmenorrhea, we are mostly talking about children. So ?persistence of symptoms? LIne 86, can start emperic therapy, should it read more about "do" start with empiric therapy, not sure I've ever seen a dysmenorrhea client who hasn't tried something.

Line 88 could easily slip in a reference to remote visits. Line 95 would you want to included which prostanoids as this article is directed at board certified OBGs. Line 97, is there data as to a specific level of prog that stabilizes the lysosomes or for a specific amount of days?

Not a big point but line 184 could use prescriber or provider.

Line 208, and some of the other supplements discussed. Lack of US formulary for dosing and product specificity is a problem. Line 225 should they talk about omega-3 studies (which is main component of the fish oil). Line 250 refers to 'these points' should they be specific for acupressure and puncture points. I could envision providers wanting to recommend self acupressure.

Line 274, sexual activity discussion probably should be pulled out of yoga and exercise, and unclear if this has been studied in adolescent and what exactly that means? How does that help us manage a patient with primary dysmenorrhea. Is it organism, masturbation, it seems to be in the title of that section and not really explained.

Line 125 back pain, not particularly important. but would say the mechanism is pretty vague here.

Line 132 later there is discussion on analgesic effect, but would think it should be referenced here as well. And the

reference to 'her family' is a bit odd, there seems to be a need for consistency as to whether we are talking adolescents, or longer term management (where hysterectomy and ablation come into the discussion). This would also be my comment for line 145 when they are talking about DVT risk which age group is this refering to.

Line 149 would use the generic medical dosage and medication name. Line 159 would people with primary dysmenorrhea be more likely to have pain with the irregular bleeding of LARC? There is no mention of teens and bone mass with DMPA, something that always gets asked, and there is data for.

Line 104 the reference to vasopressin, it vague, are there values, or more elucidation, as later in the paper the role of NSAIDs defers back to this molecule. Line 109, again, since for our journal, should be more specific about leukotrienes. Line 116 talks about reperfusion, but doesn't talk about the lack of perfusion with the contractions, so it's just a bit confusing. Is there specific data on amount of hypoxia or amount of blood flow reduced that would help us understand the physiology?

Reviewer #2: The authors present a well written and thorough expert review on evaluation and treatment options for primary dysmenorrhea. My only concerns are how much the manuscript differs or adds to the recent ACOG publication Committee Opinion 760 Dysmenorrhea and Endometriosis in the Adolescent. 2018

Abstract:
Line 43 Is it necessary to have a pelvic exam before empiric treatment? ACOG Committee Opinion 760 says a pelvic exam initially is not required. If the complaint is pain and primary amenorrhea that would be more concerning and there may be a need for an exam to rule out an obstructive anomaly.

Introduction:
This is a good overview. As I pull up the Committee Opinion 760 and this manuscript the main difference is an in depth focus on primary dysmenorrhea and the pathophysiology Line 69-70.
Line 80 The association with age < 30 is confusing. Does this imply overlap with secondary dysmenorrhea? Assuming normal age of menses and no significant delay in puberty all primary dysmenorrhea would be < 30. The reference and table I found from citation #7 came from another study looking at chronic pelvic pain and dysmenorrhea in general. Factors predisposing women to chronic pelvic pain: systematic review. BMJ. 2006;332(7544):749-755.
Line 87 The need for a pelvic exam here is consistent with above comments. I would recommend just making the abstract consistent.
Line 90 Usually a TVUS would not be preformed in an adolescent unless sexually active and or a limited abdominal view.
Line 126-127 The parallel to CSS is interesting. Would this be a form of allodynia?
Line 147 The recommendation for lowering DVT risk by using a levonorgestrel combined OCP needs to be clarified. Reference #15 meta-analysis looked specifically at drospirenone and did not find a difference in DVTs. "drospirenone were compared with non-drospirenone-containing OCs (except those containing levonorgestrel only), VTE risk did not significantly increase (OR 1.13; 95% CI 0.94, 1.35)." The exception implies levonorgestrel only not as a combined. In fairness there is also enough conflicting DVT data a COMMITTEE OPINION Number 540 * November 2012 (reaffirmed 2016) was published putting the issue of progestins as a whole into context without favoring one over the other.
The remainder of treatment options and level of evidence for efficacy was thorough and balanced.
Line 237-238 Explain the placement of TENS in order to get the sympathetic hyogastric plexus and the afferent T11-12.
Line 292-299 The use of ablation is also a concern for failure in younger patients and higher rates of subsequent surgery and cost.
Line 305 The LUNA procedure was also done in combination with cutting the ligaments and associated POP case reports. Journal of Reproductive Medicine 41: 279-82.
Line 367 The comparison of EA and EA+IUD was an interesting cohort study. It looks like the combined EA and IUD group had lower rates of hysterectomy and failure vs. the EA only cohort. This should be discussed further because with primary dysmenorrhea and fertility it seems like an IUD cohort would be the more appropriate comparison. I worry about the way this option is presented in the context of most patients with primary dysmenorrhea are going to be younger. I could not get full text from this article but what was the avg. age of each cohort? J Minim Invasive Gynecol, 2015. 22(7): p. 1203-7.

Table 3
Excellent overview of options, dosing and cost.

Reviewer #3: Please upload Figure 1 as a figure file on Editorial Manager. Also, please confirm that the figure is original to the manuscript.

Reviewer #4: A thoughtful review, a few suggestions include:

1- As this is a review, it would be helpful if you give a very brief overview of the different prostaglandins and their function.

2- Please reference you 60% amenorrhea data on page 8. Also, it may be helpful to give a range and more references to the reader as the 60% figure looks exact when presented alone.

3-Please explain heat patch with "iron" on page 14. It is unclear if you mean a heat patch with exposed iron, which would be unsafe or supplemental or iron? Also please add references.

4- There is a heading for data on sexual activity, but no mention. Please add the data and references, or remove.

5- Hysterectomy is an often recommended and usually inappropriate option given to patients. It would be helpful if you could spend more time, review more references, and give much more data on this topic.

6- I specifically like and appreciate Figure 1. Thank you.

Again, a very nice review, but I think it doesn't quite make it as an "Expert Review" unless it contains more data, references, and data on both sides of controversial issues. I would be more satisfied with almost double the references and more data, pending word limits.

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. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:

A. OPT-IN: Yes, please publish my point-by-point response letter.
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Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page.

3. Tables, figures, and supplemental digital content should be original. The use of borrowed material (eg, lengthy direct quotations, tables, figures, or videos) is discouraged. If the material is essential, written permission of the copyright holder must be obtained.

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4. 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.

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.

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. ACOG is moving toward discontinuing the use of "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.

12. Tables 1 and 4 will be printed as Box 1 and Box 2. Please renumber Tables 2 and 3 to Tables 1 and 2. Be sure to correct the citations in the manuscript text.

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.

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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.

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

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

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

Again, your paper will be maintained in active status for 30 days from the date of this letter. If we have not heard from you by Jul 01, 2020, we will assume you wish to withdraw the manuscript from further consideration..

Sincerely,

The Editors of Obstetrics & Gynecology

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

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5 July 2020

Editorial Board – Obstetrics & Gynecology:

Thank you for the opportunity to revise our paper. We have paid careful attention to the editors and reviewers' comments, and our point-by-point responses are listed below. All authors have read the Instructions for Authors (http://edmgr.ovid.com/ong/accounts/authors.pdf).

We believe our manuscript is much improved based on these changes, and we look forward to your feedback. For ease of review, we have included both the document with tracked changes and a final version without tracked changes. The line numbers referenced in our responses below refer to the final version without tracked changes.

Sincerely,
Elizabeth Ferries-Rowe
Elizabeth Corey
Johanna Archer

REVIEWER COMMENTS:

Reviewer #1, comment 1: *Difficult to review a topic that could be a chapter rather than an article, but the authors have done a good job. In several places the literature discussion reverts the reference to 'dysmenorrhea' rather than specify whether it was primary dysmenorrhea, and given the title it should either be clear, or state no such data*.

Response: The introductory discussion on the impact of dysmenorrhea does not distinguish between the two, especially since they are as yet undefined in the paper. However, we have added the clarification that the majority of menstrual pain in ovulatory women is primary dysmenorrhea. [Lines 79-80] Further discussion in the paper is explicit as it applies to primary dysmenorrhea.

Given current situation, I thought at least a nod to remote or virtual diagnosis is important. Line 59 begs that question as would the remote work make them more likely to work.

Response: We agree that the recent increase in telemedicine has provided new opportunities to diagnose and treat primary dysmenorrhea without necessitating an initial office visit. We have also added a line about telemedicine and the role for remote work or school in mitigating the impact of dysmenorrhea. [Lines 61, 105-108]

And of the ones missing work how many just don't have proper access to menstrual products?

Response: In the current literature, missed work is attributed specifically to menstrual-related symptoms, including dysmenorrhea. However, the role of inadequate supplies was not specifically addressed in the available studies. We have included a note on the role of unmet

hygiene needs and pointed to it as an area for future study about menstrual-related absenteeism attributed to dysmenorrhea. [Lines 66-70]

In the general discussion from 64-70 how long does primary dysmenorrhea persist, and likelihood of resolving by pregnancy?

Response: We have expanded our discussion to include the fact that primary dysmenorrhea is often improved by childbirth, although not necessarily by pregnancy that ends in spontaneous or therapeutic abortion. We have added additional sources to support this point. [Lines 95-99]

Reviewer #1, comment 2: *Diagnosis lines 72-74 has age of menarche resolved, and of the later diagnosed cases, what % can be attributed to missed endometriosis?*

Response: This line was meant to convey that ovulatory cycles usually start within 12 months of menarche, but that for some adolescents cycles do not become ovulatory until 2 years after menarche. We have reworded to clarify that. Pain two years after menarche would still be consistent with primary dysmenorrhea if cycles are not ovulatory until then. Pain in adolescents who are ovulatory at a year and then develop pain more than a year after ovulatory cycles begin would be more concerning for endometriosis. [Lines 83-85]

Line 78 seems to have odd grammar.

Response: We agree that it was unclear and have reworded it to be more clear. [Lines 88-90]

And then later in the article in line 103 they refer to GI symptoms but don't mention bloating or gas in line 79.

Response: Various sources report different GI symptoms associated with primary dysmenorrhea, and the range of GI symptoms is fairly broad and non-specific. We have worked to ensure continuity in the paper that still recognizes the broad range of symptoms. [Line 90, 131]

Would be nice to clarify the link of smoking with primary dysmenorrhea, we are mostly talking about children. *So ?persistence of symptoms?*

Response: It is true that primary dysmenorrhea presents in adolescents, but symptoms often persist into young adulthood – an age at which many people who smoke cigarettes first start. We have added a parenthetical remark to the discussion of risk factors to include that studies are generally performed in adults with a diagnosis of primary dysmenorrhea based on menstrual pain with no identified secondary cause and a history consistent with onset with ovulatory cycles. Those women who smoke are more likely to experience ongoing dysmenorrhea. [Line 90-93]

LIne 86, can start empiric therapy, should it read more about "do" start with empiric therapy, not sure I've ever seen a dysmenorrhea client who hasn't tried something.

Response: That is a good point. We have reworded the line to read “patients … are candidates for empiric therapy”. This wording is intended to reflect that they may already have tried something, but that either way treatment as though it is primary dysmenorrhea is appropriate. [Line 102-103]

Line 88 could easily slip in a reference to remote visits.

Response: We agree that this is important to mention in the current health care landscape and have included it in the manuscript. [Line 105-108]

Line 95 would you want to include which prostanoids as this article is directed at board certified OBGs.

Response: Many prostanoids are potentially implicated in primary dysmenorrhea, with data available specifically for $PGF_{2\square}$ and PGE_2 and leukotrienes C4 and D4. This additional level of detail has been included in the manuscript. [Line 123, 135]

Line 97, is there data as to a specific level of prog that stabilizes the lysosomes or for a specific amount of days?

Response: Although specific levels are not reported, this finding explains why pain begins with ovulatory cycles because the decrease in circulating progesterone after ovulation initiates the pathway. This has been explained more clearly in the manuscript. [Line 117-120].

Not a big point but line 184 could use prescriber or provider.

Response: Thank you for this point. We have adjusted the terminology. [Line 240]

Line 208, and some of the other supplements discussed. Lack of US formulary for dosing and product specificity is a problem.

Response: This point is true for most of the non-NSAID, non-hormonal treatment options. When available, we have included dosing based on study dosing. However, we have also included a statement discussing that this is an issue for many treatment options. [Line 245-246]

Line 225 should they talk about omega-3 studies (which is main component of the fish oil).

Response: We have added language to be more specific about omega-3 as the component of fish oil proposed to be valuable for treatment of primary dysmenorrhea. [Line 284-286]

Line 250 refers to 'these points' should they be specific for acupressure and puncture points. I could envision providers wanting to recommend self-acupressure.

Response: Three acupressure and acupuncture points have been specifically studied and treatment for primary dysmenorrhea. These points include the auricle and the SP6 and SP9 points, which are described in the manuscript. [Line 313-317]

Line 274, sexual activity discussion probably should be pulled out of yoga and exercise, and unclear if this has been studied in adolescent and what exactly that means? How does that help us manage a patient with primary dysmenorrhea. Is it orgasm, masturbation, it seems to be in the title of that section and not really explained.

Response: Sexual activity is often included in non-medical options for treatment of dysmenorrhea, but there is a lack of data specifically regarding sexual activity and primary dysmenorrhea. Additionally, there is a lack of good data delineating which component of sexual activity is beneficial for dysmenorrhea in general. For these reasons, we have removed sexual activity from this manuscript.

Line 125 back pain, not particularly important. but would say the mechanism is pretty vague here.

Response: Back pain is one visceral pain syndrome that can be associated with central sensitization syndrome (CSS). We have included additional information on CSS to better describe the mechanism and its associated pain syndromes. [Line 159-166].

Line 132 later there is discussion on analgesic effect, but would think it should be referenced here as well. And the reference to 'her family' is a bit odd, there seems to be a need for consistency as to whether we are talking adolescents, or longer term management (where hysterectomy and ablation come into the discussion). This would also be my comment for line 145 when they are talking about DVT risk which age group is this referring to.

Response: Because primary dysmenorrhea presents in adolescents and may continue into adulthood, treatment approach will vary by age and stage of life. We have included a statement that recognizes this longitudinal approach to treatment. For example, family involvement is more appropriate for adolescents, while hysterectomy may be option for older patients who do not desire fertility. [Line 174-180] We have also included a new reference to discuss the risk of DVT as related to age. [Line 188-190]

Line 149 would use the generic medical dosage and medication name.

Response: This has been corrected in the manuscript to use generic name and dosage. [Line 198]

Line 159 would people with primary dysmenorrhea be more likely to have pain with the irregular bleeding of LARC? There is no mention of teens and bone mass with DMPA, something that always gets asked, and there is data for.

Response: Because primary dysmenorrhea is associated with ovulatory cycles, the non-ovulatory irregular bleeding associated with LARC would not be expected to be associated with pain caused by primary dysmenorrhea. The bone mineral density loss associated with DMPA appears to recover after discontinuation, but the fracture risk after use in adolescence is unknown. Because the amenorrhea associated with DMPA can significantly improve pain, shared decision making that incorporates benefits and unknown future risk of fracture is most appropriate. [Line 209-216]

Line 104 the reference to vasopressin, it vague, are there values, or more elucidation, as later in the paper the role of NSAIDs defers back to this molecule.

Response: The role of vasopressin in primary dysmenorrhea is uncertain, and data is conflicting. Some data support a role based on vasoconstriction and pathological uterine contractions, but subsequent data did not find similar results. Threshold values for causing pain were not identified in those studies that suggested a role. We have included in the discussion that vasopressin may be involved, but that available data is limited and conflicting. [Line 137-144]

Line 109, again, since for our journal, should be more specific about leukotrienes.

Response: As mentioned above, leukotrienes C4 and D4 appear to be most associated with primary dysmenorrhea and has been included in the manuscript. [Line 135]

Line 116 talks about reperfusion, but doesn't talk about the lack of perfusion with the contractions, so it's just a bit confusing. Is there specific data on amount of hypoxia or amount of blood flow reduced that would help us understand the physiology?

Response: Contractions are associated with restricted blood flow to the myometrium, while increased basal tone and poorly coordinated contractions limit reperfusion and creates greater hypoxia-associated pain than in women without primary dysmenorrhea. This has been clarified in the manuscript. [Line 149-152]

Reviewer #2, comment 1*: The authors present a well written and thorough expert review on evaluation and treatment options for primary dysmenorrhea. My only concerns are how much the manuscript differs or adds to the recent ACOG publication Committee Opinion 760 Dysmenorrhea and Endometriosis in the Adolescent. 2018*

Response: Thank you for this comment. Our review exclusively focuses on primary dysmenorrhea. We believe that our review presents a more in-depth discussion of the pathophysiology and treatment options.

Reviewer #2, comment 2*:*
Abstract: Line 43 Is it necessary to have a pelvic exam before empiric treatment? ACOG Committee Opinion 760 says a pelvic exam initially is not required. If the complaint is pain and primary amenorrhea that would be more concerning and there may be a need for an exam to rule out an obstructive anomaly.

Response: We agree that it is not necessary to perform a pelvic exam when patients have a history consistent with primary dysmenorrhea. A pelvic exam should be considered when evaluating for causes of secondary dysmenorrhea if initial empiric treatments fail. We have modified this in the revised manuscript (Line 43-44, 103-104)

Reviewer #2, comment 3*: Introduction:*
This is a good overview. As I pull up the Committee Opinion 760 and this manuscript the main difference is an in depth focus on primary dysmenorrhea and the pathophysiology Line 69-70.

Response: Thank you for the positive feedback.

Reviewer #2, comment 4:
Line 80 The association with age < 30 is confusing. Does this imply overlap with secondary dysmenorrhea? Assuming normal age of menses and no significant delay in puberty all primary dysmenorrhea would be < 30. The reference and table I found from citation #7 came from another study looking at chronic pelvic pain and dysmenorrhea in general. Factors predisposing women to chronic pelvic pain: systematic review. BMJ. 2006;332(7544):749-755.

Response: Thank you for spotting this error; this has been corrected. As per the primary article, the listed risk factors apply to dysmenorrhea in general, not just primary dysmenorrhea. (Line 91)

Reviewer #2, comment 5:
Line 87 The need for a pelvic exam here is consistent with above comments. I would recommend just making the abstract consistent.

Response: Agree - this has been changed and is now consistent (Line 104-105)

Reviewer #2, comment 6:
Line 90 Usually a TVUS would not be performed in an adolescent unless sexually active and or a limited abdominal view.

Response: We agree. Radiologic testing is listed as either an “abdominal or transvaginal ultrasound.” (Line 111-112)

Reviewer #2, comment 7:
Line 126-127 The parallel to CSS is interesting. Would this be a form of allodynia?

Response: Yes. CSS has two main characteristics involving heightened sensitivity to pain (allodynia) and to touch (hyperalgesia). This has been clarified. (Line 160)

Reviewer #2, comment 8:
*Line 147 The recommendation for lowering DVT risk by using a levonorgestrel combined OCP needs to be clarified. Reference #15 meta-analysis looked specifically at drospirenone and did not find a difference in DVTs. "drospirenone were compared with non-drospirenone-containing OCs (except those containing levonorgestrel only), VTE risk did not significantly increase (OR 1.13; 95% CI 0.94, 1.35)." The exception implies levonorgestrel only not as a combined. In fairness there is also enough conflicting DVT data a COMMITTEE OPINION Number 540 * November 2012 (reaffirmed 2016) was published putting the issue of progestins as a whole into context without favoring one over the other.*
The remainder of treatment options and level of evidence for efficacy was thorough and balanced.

Response: Thank you - we have clarified this point in the paper. There is limited data regarding the type of progesterone and DVT risk though some evidence suggests the risk may be lowest with a second generation oral contraceptive compared to a third generation. The risk may be even higher with drospirenone. However, data is inconclusive, and this is now reflected in the paper (Lines 192-197)

Reviewer #2, comment 9:
Line 237-238 Explain the placement of TENS in order to get the sympathetic hypogastric plexus and the afferent T11-12.

Response: The placement of the TENS unit has been further described in our paper (Lines 299-302)

Reviewer #2, comment 10:
Line 292-299 The use of ablation is also a concern for failure in younger patients and higher rates of subsequent surgery and cost.

Response: This has now been addressed in the paper (Lines 371-372)

Reviewer #2, comment 11:
Line 305 The LUNA procedure was also done in combination with cutting the ligaments and associated POP case reports. Journal of Reproductive Medicine 41: 279-82.

Response: The LUNA procedure has been clarified and the possible association with POP is now addressed (Lines 377-380)

Reviewer #2, comment 12:
Line 367 The comparison of EA and EA+IUD was an interesting cohort study. It looks like the combined EA and IUD group had lower rates of hysterectomy and failure vs. the EA only cohort.

This should be discussed further because with primary dysmenorrhea and fertility it seems like an IUD cohort would be the more appropriate comparison. I worry about the way this option is presented in the context of most patients with primary dysmenorrhea are going to be younger. I could not get full text from this article but what was the avg. age of each cohort? J Minim Invasive Gynecol, 2015. 22(7): p. 1203-7.

Response: Thank you for this comment. We added a cautionary sentence that appropriate candidates must be done with childbearing (Line 454). The average age was early 40s in this particular study.

Reviewer #2, comment 13:
Table 3
Excellent overview of options, dosing and cost.

Response: Thank you for the positive feedback.

Reviewer #3: Please upload Figure 1 as a figure file on Editorial Manager. Also, please confirm that the figure is original to the manuscript.

Response: Our Figure 1 is original.

Reviewer #4: A thoughtful review, a few suggestions include:

1. As this is a review, it would be helpful if you give a very brief overview of the different prostaglandins and their function.

Response: We added additional description of prostaglandins and their function. [Lines 121-130]

2. Please reference you 60% amenorrhea data on page 8. Also, it may be helpful to give a range and more references to the reader as the 60% figure looks exact when presented alone.

Response: This estimate was not accurate, and we have referenced the correct percentage of amenorrhea. [Line 205-206]

3. Please explain heat patch with "iron" on page 14. It is unclear if you mean a heat patch with exposed iron, which would be unsafe or supplemental or iron? Also please add references.

Response: This is a marketed heat patch and we clarified how the iron was incorporated and given a reference as to its function. [Line 339-345]

4. There is a heading for data on sexual activity, but no mention. Please add the data and references or remove.

Response: We removed the sexual activity heading based on lack of data specifically applying to primary dysmenorrhea.

5. Hysterectomy is an often recommended and usually inappropriate option given to patients. It would be helpful if you could spend more time, review more references, and give much more data on this topic.

Response: We have added two additional references with additional text with regard to hysterectomy in a young patient population. [Lines 387-400]

6. I specifically like and appreciate Figure 1.

Thank you. Kind of you to say that.

Again, a very nice review, but I think it doesn't quite make it as an "Expert Review" unless it contains more data, references, and data on both sides of controversial issues. I would be more satisfied with almost double the references and more data, pending word limits.

Response: We have attempted to address the reviewer's comments above and have added additional references.

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. 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:

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We have reworked the table to comply with these guidelines.

4. 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.

We have no concerns regarding standard data definitions.

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.
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* 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).

So noted.

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

A short title is provided.

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."

A précis is provided on the second page.

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We reviewed the abstract, and believe it is consistent with the text.

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.

We have avoided non-standard abbreviations throughout the text.

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.

This has been corrected.

11. ACOG is moving toward discontinuing the use of "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.

We replaced the term provider throughout the paper.

12. Tables 1 and 4 will be printed as Box 1 and Box 2. Please renumber Tables 2 and 3 to Tables 1 and 2. Be sure to correct the citations in the manuscript text.

We have corrected the numbering of the tables.

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.

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