OBSTETRICS & GYNECOLOGY

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- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*

**The corresponding author has opted to make this information publicly available.*

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Questions about these materials may be directed to the *Obstetrics & Gynecology* editorial office: obgyn@greenjournal.org.

Date: May 07, 2021
To: "Jacqueline A Bohn"[redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-21-732

RE: Manuscript Number ONG-21-732

Stepwise Approach to the Management of Endometriosis-Related Dysmenorrhea: A cost-effectiveness analysis

Dear Dr. Bohn:

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 May 28, 2021, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

Review of Manuscript ONG-21-732 "Stepwise approach to the management of endometriosis-related dysmenorrhea: A cost effectiveness analysis"

Bohn and colleagues have submitted a cost-effectiveness analysis evaluating 3 different sequential medical treatment strategies followed by surgery for dysmenorrhea related to endometriosis as compared to immediate or surgical management only. Like all cost effectiveness studies, this one models potential outcomes based predominantly on published material although occasionally expert opinion is utilized. At several times in the manuscript, the sentence construction is such that to me it seemed that they were comparing medical therapies versus surgery when in fact they were comparing sequential medical and surgery therapy versus immediate surgery. I have the following questions and comments.

Précis - Isn't the comparison sequential therapy - medical therapy followed by surgery? Since this is the case, consider noting these are effective compared to either primary surgery without medical therapy or immediate surgery or similar - as written it almost makes it sound like surgery has no role.

Abstract - Can you define surgical therapy in the abstract - LSC ablation/excision? Hysterectomy? Something else?

Introduction - Line 90 - Is there a standard definition(s) or way to assess/grade endometriosis associated dysmenorrhea? If so please expound here.
Line 95-6 - Do you mean definitive therapy for endometriosis? Managing a specific symptom(s)?
Line 100 - There is some cost effectiveness data as you cite in this sentence.

Methods - Line 119-121 - See comment about as it relates to defining this population?

Results - Line 188 - consider noting in this sentence that something along the lines of, "…non-primary surgical strategies 1, 2, and 3…"

Discussion - Line 233-5 - Again these are sequential therapies which all include surgery so this statement needs to make it clear you are comparing to immediate surgery rather than a sequential management approach.
Line 236 - I would consider noting that "…while potentially cost-effective…" this is probably not the favored approach, although the caveats you provide are important ones.
Line 251-3 - Clearly a limitation is what is meant by surgery and what are the range of outcomes.

Tables - Table 1&2 - No comments

Figures - Figure 1 - Decision tree diagram is fine
Figure 2 - Perhaps supplementary as you can reference this information in the manuscript (which you did)
Figure 3 - I think this is important for the reasons noted above - women that need a third therapy and either can't receive timely surgery or are concerned about surgery.
Figure 4- No Comments.

Reviewer #2:

This is an interesting and useful manuscript that takes on the difficult task of assessing the cost effectiveness of various approaches to treating
pelvic pain associated with endometriosis. This manuscript is somewhat unique and has many excellent attributes as an attempt to put a cost effectiveness lenses on treatment of a common disease. Linking it to clinical practice is a challenge.
Comments are as follows:
One of the clinical difficulties encountered is how to approach the GnRH antagonist/Agonist drugs. Many will not use them without a surgical diagnosis due to the expense and side effect profiles. Others treat early feeling
that the vast majority of those with endometriosis do respond well making surgery unnecessary.
I wonder how the cost model might help
guide clinical practice.
The six month timeline for response is often what is reported in the literature for clinical studies yet
a sequential approach of to get to 3 medications is not reasonable and would not be acceptable in most cases.
Another area not considered are the physical and radiology findings always used to guide practice. These results would likely change the approach and effect the model. Is there a bridge between the model's findings and practice. The discussion section might find some space for the makings of the bridge using Table 2 as an anchor.

Reviewer #3:

Thank you for the opportunity to review this paper about a stepwise approach to the management of endometriosis-related dysmenorrhea. Although it has many ideas that go in a correct direction for the treatment of this disease today in 2021, it also leaves me a lot of perplexity. I agree with the idea from which this study starts (we must make it clear that medical treatments can be the way of recovery for many patients with endometriosis today and very costs effective) but the study design seems to me too theoretical and not very applicable for many reasons in our gynecological practice.
Ok for many possible strategies but NSAIDs are not a suitable treatment for endometriosis, but they are only a mask of the problems, so I would cancel this path/proposal. All pathways must include a role for hormonal treatments, the ethiopathogenetic treatements for this estrogens dependent disease.
For SARCs, model inputs were based on combined hormonal contraceptives: why not progestin only pills?
For LARCs, model inputs were based on the 52 mg levonorgestrel intrauterine system: why not etonogestrel implant? It works very well in this disease.
Followed by surgery if no improvement…what surgery are you talking about for dysmenorrhea? hysterectomy? what solution do you propose in patients who want to maintain fertility? For young women?
Strategy 2 (NSAID, SARC/LARC, surgery) vs. Strategy 3 (NSAID, SARC/LARC, LARC or trial of GnRH modulators, surgery), I think that the first decision between SARC or LARC…is not just a model, this choice depends directly and completely on the will of the patient who must be compliant with the treatment for a long time. In this disease setting, the most important aspect is to promote the woman's compliance to medical treatments with all the necessary means!!!
I am a doctor who focuses on medical treatments for endometriosis, but you can never talk about the weight of the possible side effects that these treatments can give to our patients. In most cases it's not a question of ineffectiveness, it's a question of side effects. So these models are quite useless, counseling is the first aspect to consider.

STATISTICS EDITOR COMMENTS:

Lines 169-170, 204-205: Need to include the tornado diagrams, either in main text or in supplemental material.

lines 170-172, 179-181: As pointed out by the Authors, one cannot assume a normal distribution when sampling the costs or probabilities in the model. The Authors acknowledge a right skewing of costs since the range is from 1/2 to 2x the point estimate. Likely higher costs would have a strong influence on willingness to pay or on cost of QALYs. What shape parameters were used for the beta and gamma distributions to assure that the higher end of costs were adequately represented in the model? What sensitivity analyses were done to show that the conclusions were robust to an underestimate of costs or their distribution?

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. 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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B. OPT-OUT: No, please do not publish my point-by-point response letter.

2. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA). Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page. Each of your coauthors received an email from the system, titled "Please verify your authorship for a submission to Obstetrics & Gynecology." Each author should complete the eCTA if they have no yet done so.

3. Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), observational studies using ICD-10 data (ie, RECORD), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluations of health interventions (ie, CHEERS), quality improvement in health care studies (ie, SQUIRE 2.0), and studies reporting results of Internet e-surveys (CHERRIES). Include the appropriate checklist for your manuscript type upon submission. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at http://ong.editorialmanager.com. In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, RECORD, CHEERS, SQUIRE 2.0, or CHERRIES guidelines, as appropriate.

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. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 5,500 words. Stated word limits include the title page, précis, abstract, text, tables, boxes, and figure legends, but exclude references.

6. 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).
* If your manuscript was uploaded to a preprint server prior to submitting your manuscript to Obstetrics & Gynecology, add the following statement to your title page: "Before submission to Obstetrics & Gynecology, this article was posted to a preprint server at: [URL]."

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

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 limit for Original Research articles is 300 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. In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.

If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts.

Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1%").

12. 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.

13. Please review examples of our current reference style at http://ong.editorialmanager.com (click on the Home button in the Menu bar and then "Reference Formatting Instructions" document under "Files and Resources). Include the digital object identifier (DOI) with any journal article references and an accessed date with website references. Unpublished data, in-press items, personal communications, letters to the editor, theses, package inserts, submissions, meeting presentations, and abstracts may be included in the text but not in the reference list.

In addition, the American College of Obstetricians and Gynecologists' (ACOG) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite ACOG documents in your manuscript, be sure the reference you are citing is still current and available. If the reference you are citing has been updated (ie, replaced by a newer version), please ensure that the new version supports whatever statement you are making in your manuscript and then update your reference list accordingly (exceptions could include manuscripts that address items of historical interest). If the reference you are citing has been withdrawn with no clear replacement, please contact the editorial office for assistance (obgyn@greenjournal.org). In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript (exceptions could include manuscripts that address items of historical interest). All ACOG documents (eg, Committee Opinions and Practice Bulletins) may be found at the Clinical Guidance page at https://www.acog.org/clinical (click on "Clinical Guidance" at the top).

14. Figures 1-2: okay
Figure 3: Is this available at a higher resolution?
Figure 4: okay

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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.

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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. Do not omit your responses to the Editorial Office or Editors' comments.

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 May 28, 2021, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

John O. Schorge, MD
Associate Editor, Gynecology

2019 IMPACT FACTOR: 5.524
2019 IMPACT FACTOR RANKING: 6th out of 82 ob/gyn journals

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June 6, 2021

Dwight J. Rouse, MD, MSPH
Editor-in-Chief
Obstetrics & Gynecology

Dear Dr. Rouse:

Enclosed please find the revised manuscript titled, "Stepwise Approach to the Management of Endometriosis-Related Dysmenorrhea: A cost-effectiveness analysis". We would like to thank you and the reviewers for the careful consideration given to our manuscript and your willingess to reconsider this manuscript with revision. My co-authors and I have considered the comments and recommendations and revised the manuscript accordingly. All authors have read and approved the revised version of this paper. Please refer to the paragraphs below as we respond to each reviewer's comments.

Reviewer's Comments to Author:

Reviewer 1, Comment 1
Bohn and colleagues have submitted a cost-effectiveness analysis evaluating 3 different sequential medical treatment strategies followed by surgery for dysmenorrhea related to endometriosis as compared to immediate or surgical management only. Like all cost effectiveness studies, this one models potential outcomes based predominantly on published material although occasionally expert opinion is utilized. At several times in the manuscript, the sentence construction is such that to me it seemed that they were comparing medical therapies versus surgery when in fact they were comparing sequential medical and surgery therapy versus immediate surgery. I have the following questions and comments.
Thank you for the review of our work.

Reviewer 1, Comment 2
Précis - Isn't the comparison sequential therapy - medical therapy followed by surgery? Since this is the case, consider noting these are effective compared to either primary surgery without medical therapy or immediate surgery or similar - as written it almost makes it sound like surgery has no role.
Thank you for raising this point. We have edited the Precis to reflect that the comparison is sequential medical and surgical management compared to surgical management alone while remaining within the word count requirements for the precis.
Page 2, Line 30-31
"All sequential therapies (medical followed by surgical management) for endometriosis-related dysmenorrhea were cost-effective when compared to surgical management alone."

Reviewer 1, Comment 3
Abstract - Can you define surgical therapy in the abstract - LSC ablation/excision? Hysterectomy? Something else?
We have clarified the text as requested. The manuscript was edited to define the surgical technique: laparoscopic ablation or excision, resection of deep infiltrating endometriosis, and resection of endometrioma by cystectomy. These were the described techniques utilized in the publication used as the basis for the probability of improvement with surgery. Due to word limitations in the abstract, this clarification was added to the methods section of the manuscript.
Page 6, Line 123-125

"Surgical management included laparoscopic ablation or excision of endometriosis, resection of deep infiltrating endometriosis and resection of endometrioma by cystectomy."

Reviewer 1, Comment 4
Introduction - Line 90 - Is there a standard definition(s) or way to assess/grade endometriosis associated dysmenorrhea? If so please expound here.
The manuscript was edited to expand upon the most commonly used definitions of endometriosis associated dysmenorrhea. There is not currently a standard way to grade endometriosis associated dysmenorrhea.
Page 5, Line 92-93
"Multiple strategies exist for the treatment of endometriosis-related dysmenorhea, which is defined as cyclic pelvic pain occuring during the menstrual cycle."

Reviewer 1, Comment 5
Line 95-6 - Do you mean definitive therapy for endometriosis? Managing a specific symptom(s)?
The manuscript was edited to clarify this part of the introduction.
Page 5, Line 98-102
"The optimal surgical technique for treatment of endometriosis is currently unknown; there is a paucity of conflicting data around the effectiveness of surgical management. Surgical interventions can range from excision/laser ablation of endometriosis, nerve sparing peritoneal stripping, excision of deep infiltrating nodules, bowel resection and hysterectomy with or without bilateral salpingo-oophorectomy."

Reviewer 1, Comment 6
Line 100 - There is some cost effectiveness data as you cite in this sentence.
Thank you for raising this point. We have edited the language to capture in more nuanced detail what cost-effectiveness data currently exists.
Page 5, Lines 105-108
"Despite the recognized cost burden of this disease, cost-effectiveness data on the various treatment strategies is limited. Previous studies have investigated the direct and indirect costs regarding endometriosis, however there are no prior studies that evalute the cost-effectiveness of a stepwise regimen to guide management."

Reviewer 1, Comment 7
Methods - Line 119-121 - See comment about as it relates to defining this population?
Our apologies, we are uncertain as to the reviewer's request. Can you please clarify?

Reviewer 1, Comment 8
Results - Line 188 - consider noting in this sentence that something along the lines of, "…non-primary surgical strategies 1, 2, and 3…"
Thank you, we have incorporated the suggested change. The manuscript was edited to clarify that strategies 1, 2, and 3 are sequential medical then surgical management as well as to keep consistency with the edits throughout the revision.
Page 9, Line 203-204
"Regarding QALYS, we found that strategies 1, 2, and 3 (sequential medical then surgical management) resulted in at least one million higher QALYs than strategy 4 (immediate surgery).

Reviewer 1, Comment 9
Discussion - Line 233-5 - Again these are sequential therapies which all include surgery so this statement needs to make it clear you are comparing to immediate surgery rather than a sequential management approach.

The manuscript was edited to clarify the language around the sequential medical then surgical treatment and to keep consistency with the edits throughout the revision.
Page 11, Line 253-254
"Our study found that all sequential medical then surgical treament pathways are cost-effective in the treatment of endometriosis when compared to proceeding immediately to surgery.

Reviewer 1, Comment 10
Line 236 - I would consider noting that "…while potentially cost-effective…" this is probably not the favored approach, although the caveats you provide are important ones.
Thank you for raising this important point. We address this issue in lines 255-260.

Reviewer 1, Comment 11
Line 251-3 - Clearly a limitation is what is meant by surgery and what are the range of outcomes.
Thank you for your feedback. We acknowledge in our limitations section the heterogenity of surgical management of endometriosis and how this confounds existing data on surgical care. To address this, we performed extensive sensitivity analyses on the reduction in pain from surgical management.

Reviewer 1, Comment 12
Figure 2 - Perhaps supplementary as you can reference this information in the manuscript (which you did).
We are happy to have Figure 2 as supplementary at the Editor's discretion.

Reviewer 1, Comment 13
Figure 3 - I think this is important for the reasons noted above - women that need a third therapy and either can't receive timely surgery or are concerned about surgery.
Thank you. We have expanded on the importance of this point in the discussion section in lines 255-260.

Reviewer 2, Comment 1
This is an interesting and useful manuscript that takes on the difficult task of assessing the cost effectiveness of various approaches to treating pelvic pain associated with endometriosis. This manuscript is somewhat unique and has many excellent attributes as an attempt to put a cost effectiveness lenses on treatment of a common disease. Linking it to clinical practice is a challenge.
Thank you for the review of our work.

Reviewer 2, Comment 2
One of the clinical difficulties encountered is how to approach the GnRH antagonist/Agonist drugs. Many will not use them without a surgical diagnosis due to the expense and side effect profiles. Others treat early feeling that the vast majority of those with endometriosis do respond well making surgery unnecessary. I wonder how the cost model might help guide clinical practice.
Thank you for this feedback. We agree that this is a challenging clinical scenario and difficult to approach timing of initiation of GnRH agonist and antagonist medications. We believe that this information helps to guide clinical practice as it showed that requiring trial of a third medication offered little comparative advantage prior to proceeding directly to surgery after the second therapy fails. As these medications were the most expensive they significantly impacted the model. When we examined strategy 2 and 3 with sensitivity analyses (as the difference in these strategies is the addition of a third medication, often a GnRH modulator), we found that this would result in an increased cost of $257 million dollars without a significant increase in QALYs. Also, with sensitivity analyses we found that if the GnRH medication was $7,408 or less, strategy 3 would be the dominant strategy. Yet, for the woman who is anxious to avoid surgical intervention, or when a prolonged wait for a surgical specialist occurs, trial of a GnRH modulator may be worthwhile.

Reviewer 2, Comment 3

The six month timeline for response is often what is reported in the literature for clinical studies yet a sequential approach of to get to 3 medications is not reasonable and would not be acceptable in most cases.

This is an important point. We acknowledge that setting a timeline for a cost-effectiveness model that allows for accurate statistical modeling while matching clinical practice is challenging. The timeline of six months was chosen as it was what was most frequently reported in the literature for clinical studies, and we wished to incorporate the highest level of evidence available. Additionally, it was felt to be a reasonable clinical timeline for several of the medications (LARCs, GnRH agonists, GnRH antagonists), however we do acknowledge that it would likely not be an acceptable length of time for all medications (primarily NSAIDs and SARCs.) The manuscript was edited to expand upon this limitation in the discussion section.

Page 12, line 285-288

"It was assumed that all therapies would be trialed for six months to allow adequate time to determine treatment failure, however many women will not tolerate side effects for that duration of time or find it to be an unacceptable length of time to trial a medication."

Reviewer 2, Comment 4

Another area not considered are the physical and radiology findings always used to guide practice. These results would likely change the approach and effect the model. Is there a bridge between the model's findings and practice. The discussion section might find some space for the makings of the bridge using Table 2 as an anchor.

We acknowledge that physical exam and radiology findings are used to tailor clinical treatments to the individual patient. Unfortunately, cost-effectiveness models are unable to model individual scenarios, which is an inherent limitation. We agree that it is important to acknowledge this and the manuscript has been updated to include this in the limitations section of the discussion.

Page 12, line 291-293

"Lastly, this model cannot account for individual physical exam and radiology findings that would be used to guide clinical care, nor can it be applied to women seeking fertility, as hormonal contraceptives are counterproductive to this goal."

Reviewer 3, Comment 1

Thank you for the opportunity to review this paper about a stepwise approach to the management of endometriosis-related dysmenorrhea. Although it has many ideas that go in a correct direction for the treatment of this disease today in 2021, it also leaves me a lot of perplexity. I agree with the idea from which this study starts (we must make it clear that medical treatments can be the way of recovery for many patients with endometriosis today and very costs effective) but the study design seems to me too theoretical and not very applicable for many reasons in our gynecological practice.

Thank you for your review of our work. We appreciate your thoughtful feedback.

Reviewer 3, Comment 2

Ok for many possible strategies but NSAIDs are not a suitable treatment for endometriosis, but they are only a mask of the problems, so I would cancel this path/proposal. All pathways must include a role for hormonal treatments, the ethiopathogenetic treatements for this estrogens dependent disease.

We acknowledge the validity of this point, and the importance of hormonal therapy. However, a trial of NSAIDs is common first-line treatment for dysmenorrhea, especially upon first presentation of symptoms. In our experience, many times the initial complaint of dysmenorrhea is made to a primary care provider, while awaiting GYN referral. We include this arm as a bit of a "straw man" to demonstrate

the importance of hormonal therapy when history and physical are highly suggestive of endometriosis as the underlying origin for dysmenorrhea.

Reviewer 3, Comment 3
For SARCs, model inputs were based on combined hormonal contraceptives: why not progestin only pills?
We reviewed a wide range of literature on various SARCs and their treatment efficacy. CHCs were ultimately chosen because they are what is most commonly prescribed. When deciding which SARC to base the model inputs on, we reviewed clinical studies that examined the efficacy of OCPs, Ortho Evra, Nuvaring, progesterone only pills, and depo provera. Between these different methods, CHCs were found to improve endometriosis-related dysmenorrhea the most, therefore the decision was made to choose from one of these three methods. OCPs are most commonly used by women in the US, therefore the model inputs were based on OCPs.

Reviewer 3, Comment 4
For LARCs, model inputs were based on the 52 mg levonorgestrel intrauterine system: why not etonogestrel implant? It works very well in this disease.
On our review of the literature, both the levonorgestrel intrauterine device and the etonogestrel implant had very similar rates of improvement in dysmenorrhea, therefore either could be used in the model. They are also similar in cost. Results for the IUD can be extrapolated reasonably to the implant. Based on expert opinion, it was decided that of those two methods, IUDs are more commonly placed, therefore the model inputs were based on the IUD.

Reviewer 3, Comment 5
Followed by surgery if no improvement…what surgery are you talking about for dysmenorrhea? hysterectomy? what solution do you propose in patients who want to maintain fertility? For young women?
We have clarified the text as requested. The manuscript was edited to define the surgical technique: laparoscopic ablation or excision, resection of deep infiltrating endometriosis, and resection of endometrioma by cystectomy. These were the described techniques utilized in the publication used as the basis for the probability of improvement with surgery. Regarding patients desiring fertility, this model doesn't account for that population, and this is incorporated into the discussion section of the manuscript. Page 6, Line 123-125; Page 12 Line 291-293
"Surgical management included laparoscopic ablation or excision of endometriosis, resection of deep infiltrating endometriosis and resection of endometrioma by cystectomy."
"*Lastly, this model cannot account for individual physical exam and radiology findings that would be used to guide clinical care, nor can it be applied to women seeking fertility, as hormonal contraceptives are counterproductive to this goal."*

Reviewer 3, Comment 6
Strategy 2 (NSAID, SARC/LARC, surgery) vs. Strategy 3 (NSAID, SARC/LARC, LARC or trial of GnRH modulators, surgery), I think that the first decision between SARC or LARC…is not just a model, this choice depends directly and completely on the will of the patient who must be compliant with the treatment for a long time. In this disease setting, the most important aspect is to promote the woman's compliance to medical treatments with all the necessary means!!!
We agree with this sentiment completely and appreciate the comment. Cost-effectiveness models are limited by their inability to take into account individual preferences of each patient which we must do in our clinical practice.

Reviewer 3, Comment 7

I am a doctor who focuses on medical treatments for endometriosis, but you can never talk about the weight of the possible side effects that these treatments can give to our patients. In most cases it's not a question of ineffectiveness, it's a question of side effects. So these models are quite useless, counseling is the first aspect to consider.
Thank you for this important comment. We acknowledge that cost-effectiveness analyses can never be a substitution for counseling and individualized patient care. We highlight in the discussion the importance of providing patient centered counseling and individualized care. These analyses are one of many adjuncts that can be utilized to help the physician consider the benefits/risks of different approaches. The side effects of these medications is not to be underestimated and the manuscript was edited to further discuss this importance in the discussion section.
Page 12, Line 284-285
"This model does not account for side effects of medical management which may influence the acceptability of the strategy and lead a patient to elect early discontinuation."

STATISTICS EDITOR COMMENTS:

Statistic editor, Comment 1:
Lines 169-170, 204-205: Need to include the tornado diagrams, either in main text or in supplemental material.
We have included the tornado diagram as a supplemental figure.

Statistic editor, Comment 2
Lines 170-172, 179-181: As pointed out by the Authors, one cannot assume a normal distribution when sampling the costs or probabilities in the model. The Authors acknowledge a right skewing of costs since the range is from 1/2 to 2x the point estimate. Likely higher costs would have a strong influence on willingness to pay or on cost of QALYs. What shape parameters were used for the beta and gamma distributions to assure that the higher end of costs were adequately represented in the model? What sensitivity analyses were done to show that the conclusions were robust to an underestimate of costs or their distribution?
Multivariable sensitivity analysis was performed using a Monte Carlo simulation with 10,000 iterations. To achieve the multivariate sensitivity analysis, the probability and cost inputs were varied simultaneously by sampling their distributions. Fundamentally, probabilities cannot have normal distributions because the tails extend beyond 0 and 1 violating one of the rules of a probability distribution. A way to approximate a symmetric distribution that is kept between 0 and 1 is the beta distribution which was the shape utilized for the probabilities. For costs, the distribution is not symmetric and has a long right-sided tail to account for the few rare extremes in the upper range of cost. Thus, the gamma distribution is used for costs as it is right skewed to account for the upper outliers in cost. We used inputs from the literature (study size, and costs of the treatments) to determine the standard deviation of the beta and gamma distributions. We conducted one way and two way sensitivity analyses to assess for threshold values on all costs (and other) inputs. We performed a Monte Carlo simulation to assess for how all multivariate change might affect model outcomes.

EDITORIAL OFFICE COMMENTS:

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A.OPT-IN: Yes, please publish my point-by-point response letter.
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Response: We are happy to opt-in and have our point-by-point response published.

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Response: The disclosures have been double checked and are correct on the manuscript's title page.

3. Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), observational studies using ICD-10 data (ie, RECORD), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluations of health interventions (ie, CHEERS), quality improvement in health care studies (ie, SQUIRE 2.0), and studies reporting results of Internet e-surveys (CHERRIES). Include the appropriate checklist for your manuscript type upon submission. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at http://ong.editorialmanager.com. In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, RECORD, CHEERS, SQUIRE 2.0, or CHERRIES guidelines, as appropriate.

Response: The above comment was reviewed.

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.

Response: The above comment was reviewed and our manuscript is consistent with the revitalize definitions.

5. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 5,500 words. Stated word limits include the title page, précis, abstract, text, tables, boxes, and figure legends, but exclude references.

Response: Our revised manuscript does not exceed the word limitation.

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

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*** Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.**
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Response: Our manuscript adheres to the rules governing the use of acknowledgements.

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

Response: A cost-effectiveness analysis for endometriosis

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 limit for Original Research articles is 300 words. Please provide a word count.

Response: The abstract was reviewed closely and edited to reflect the revisions in the manuscript. Word count: 300

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.

Response: There are no abbreviations or acronyms in the title or precis. If an abbreviation is used, it is spelled out for the first time.

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.

Response: The manuscript has been reviewed and does not contain the virgule symbol in sentences with words.

11. In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone. If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts. Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1%").

Response: Our manuscript has been reviewed to reflect the above comment.

12. 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.

Response: The table checklist has been reviewed and the tables conform to the journal style.

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Response: The reference style and has been edited and updated in the manuscript.

14. Figures 1-2: okay
Figure 3: Is this available at a higher resolution?
Figure 4: okay

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Response: Figure 3 has been resubmitted with higher resolution.

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Response: Thank you for the information regarding open access.

Thank you for the opportunity to revise and resubmit our manuscript.

Sincerely,

Jacqueline Bohn, MD
OHSU Department of OB/Gyn
[redacted]