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.*

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:** Jan 14, 2020
**To:** "Kimberly Levinson" [redacted]
**From:** "The Green Journal" em@greenjournal.org
**Subject:** Your Submission ONG-19-2208

RE: Manuscript Number ONG-19-2208

Efficacy of adjuvant human papillomavirus vaccination for prevention of recurrent high-grade cervical intraepithelial neoplasia after surgical excision: a systematic review and meta-analysis

Dear Dr. Levinson:

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 Feb 03, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: Methodology of review: sensible clinical question posed. Appropriate databases queried with multiple search terms to maximize capture of relevant articles. 2 separate reviewers were used to reduce error and subjectivity with a 3rd used in the event of discrepancy. 4 total reviewers. Study authors contacted if questions arose. Included studies appropriate, exclusion criteria clearly delineated. Included studies quality assessment and potential bias via ROBINS-1 tool and summarized in fig 6. Confounding variables delineated both pre and post intervention. Primary and secondary outcomes expressed. Confidence levels depicted in figures

Question to authors: are the references properly attributed?? See 2 examples below

-Line 112: In fact, recent studies suggest that adjuvant HPV vaccination may help to prevent recurrence of CIN2+ (ref 12-14: these references do not address adjuvant HPV vaccination but general colposcopy and management of dysplasia)
-line 423 the link connects to a Spanish language version of the article

Materials and Methods: see above comments in methodology. 6 studies included. 2,984 women with 115 having the primary outcome

Results:
Line 206: studies found to have high bias (table 2) there is no table 2, I suspect they mean Fig 6. Please review/revise. Also listed incorrectly in legend
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Table 1: Good summary of each study included in the analysis and its results
Fig 4 &5 : Forest plots of the risk of CIN2+/CIN1 recurrence with comparison of HPV Vaccination (16/18) versus Control: moderate heterogeneity noted, but falls toward favoring vaccination

Reviewer #2:

1. Subject matter.

I consider it of very high importance. I wanted to personally thank you for embarking on this project, and here is why. I am clinician-educator, and I have been teaching ASCCP colpo curriculum for the past 10 years to residents and faculty and worked closely with ASCCP leaders and oncologists to make it evidence-based and provider focused. I would not be exaggerating if I say that literally every time we have a case conference to decide on management, someone will complain about lack of data on CIN recurance and regression in the setting of using HPV vaccine as adjuvant therapy. It is a burning question for clinicians because patients constantly ask about what they can do post-excision, and the only answer we can give them is a wishy washy one. We have been watching abstracts, posters, and occasional pilot work published on the topic, but nothing has been analyzed and complied together in a formal way. As a result of this preliminary limited work, I have been using HPV vaccine off-label for years as adjuvant therapy (as I am sure quite a few providers are doing), with disclosure about off-label use, and with financial hurdles. Not only do we not know what to say about efficacy, but we also have another big problem-insurance does not pay for it. Only recently did FDA approve vaccine for up to 45 (insurances are dragging their feet in paying for it, but they will eventually), and after 45 you are looking at $600-$1000 out of pocket cost. As one of my patients said, "I will pay, it's like not paying for another fancy bag this year! Maybe it will help", but most of them do not have the money to be able to direct their own care. I am hoping that publication of your work will make wheels turn and FDA will approve it for this indication as a result of this first step, which means my patients who can benefit from it will eventually get it, not just the ones who are over 45 or those who can afford to buy fancy bags they do not need.

I think it would be of use to emphasize those social factors/barriers to use in discussion and/or intro, to put it into perspective as to why showing evidence for efficacy is important-so that insurance would pay for it, and so that clinicians would pay attention and start using it, even if for now it would be off-label and out of pocket.

Intro

2.line 102. I would emphasize how many US women are not vaccinated and how low vaccination rates are among the underserved. It is not just a global problem; it is our American problem.

3.line 106-107
I would clarify that for CIN2 and CIN2/3 young women who are candidates can opt for conservative management (not excision) according to ASCCP guidelines. The way your sentence reads now it suggests excision which is not accurate. Moreover, this group of women can also benefit from HPV vaccine as an adjuvant treatment if you want to add a topic of potential treatment of persistent HPV infection/CIN1, or expectant management of CIN2.

4. line 109
I would re-write recurance rates in terms of CIN3+ in addition to CIN2+.

5. Lines 112-113.
References 12-14 are not studies, they are guidelines and review articles, and should be quoted as such.

Methods

6. Prospero registration is clear.

7. Data sources are appropriate.

8. Did you use a librarian to assist you with the search?

9. What word searches did you use?

10. Did 2 reviewers participate in each decision, or did you opt to only use 3rd reviewer in case of disagreement?

11. Lines 127-128.
I was not clear if you included abstracts in your review. From what is written it looks like you did authors sent you results in cases where articles to follow up on the abstract was not published. My understanding was the only published work and not abstracts would be included in reviews, and main reason being was that that was the only way to assure that it has gone through the proper peer-review process. Can you please clarify?

12. line 144
You included hysterectomy as a treatment in your search. Can you explain why?
Technically speaking, those studies should be excluded since assuming hysterectomy was total, it would be impossible for patients to get CIN2-no cervix. It is still of clinical relevance as post-hysterectomy patients are at risk for VIN and VAIN, but that is completely different topic. Not sure if that should be included in this review or not, but this issue of hysterectomy as treatment needs to be clarified.

13. It is not surprising that you were only able to identify 6 studies that met your inclusion criteria. This is a hot topic and publications are lagging.

In terms of combining systematic review and metanalysis, from the stylistic standpoint, it was hard to follow when you describe your results if you are talking about systematic review results or metanalysis results. For example, for secondary outcomes you say metanalysis was not performed for VIN/VAIN/genital warts, but systematic review results for same outcomes are discussed in paragraph above. Would it possible to organize in such a way that it is easy to follow and requires less back and forth when reading it to see which portion you are referring to?

14. You indicate that CIN2+ is the cut off used in vaccine studies, which is why you chose to use it as an endpoint. However, ASCCP chose to use CIN3+ for their guidelines because it is more clinically meaningful. Assuming that CIN3+ outcomes were scant in studies you pooled, would you still be able to run a sub-analysis on this, or at least comment on your attempt to do so, even if it was not fruitful in terms of N?

Results

15. line 232

Please correct to "incidence of cervical dysplasia" if that was the intent.

16. Table 1 is very helpful.

Would it be possible to include if study was industry-sponsored as one of the columns?
I was wondering if those trails were pharma trails which lead to FDA approval of bi- and quad- vaccines, or if those were conducted by independent clinicians in community setting. I know Future I and II are pharma studies, but general audience might want to know this. This info could also go into text if table seems crowded. I am asking because the way industry published quad vaccine articles was hard to read as they emphasized HPV-naïve outcomes, not outcomes in exposed women, which made it harder for clinicians to interpret.

Thank you for including a column which indicated if HPV vaccine was given before, after, or at the time of excision, and indicate how much time passed between HPV vaccine and excision before or after. It explains well why PATRICIA was excluded.

It is possible to include a column on what treatment consisted of. LEEP? CKC? Ablation? Cryo? This might have implications on result interpretation.

17. Could you comment on study 25? It is the only one that showed a higher risk of recurance for both CIN1+ and CIN2+, so it would be interesting for the reader to see what you think about the methodology of the study and how you should interpret their findings.

18. I think it is important to mention in the intro and/or discussion in terms of implications that HPV infection, low-grade cytology and CIN1 are all the same entity, which is the reason why it is basically treated the same clinically. While it does not require treatment, it requires closer follow up, which is burdensome to patients. To take it further, lines 243-252 discuss CIN1+ incidence, but I would argue that it is much use to separate CIN1 from CIN2+ in results and discussion. Hard to know how to clinically interpret CIN1+. Best to know CIN3+. Can live with CIN2+. Figures 2-5 should be redone with CIN2+ and CIN3+ as outcomes, not CIN1+ and CIN2+.

19. Lines 254-266. Please explain to the reader that lesions were tested for 16/18 in a research setting only (and why that info is of use) and that type of testing is not available in clinical practice. They may get confused with HPV 16/18 testing at the time of a screening cotest pap.

20. Mention intro that ASCCP and ACOG now favor LAST guidelines but that most of your studies still used CIN terminology. That would clarify it for the readers. Moreover, line 183-183 is problematic from methodology standpoint. You state that "studies reporting HGSIL were classified as CIN2+" but that is not in concordance with LAST guidelines. In order to classify CIN2 as HGSIL, you need to have positive p16. If you do not have it, then your CIN2 could be either LGSIL or HGSIL. It is especially problematic in the era when most of these studies were done, because most of them likely did not use p16 staining. I would strongly encourage you to leave CIN2 as CIN2, and HGSIL as HGSIL. If you chose to group them, you have to explain this issue to the reader.

21. Line 268. Incidence of VIN and Genital Warts section.
Neither VIN nor genital warts are mentioned in intro—it only appears under secondary outcomes in lines 186-188. It is a bit confusing to the reader. Please address.

22. Figures 2-5.
A. Can you pls add label to indicate which side favors control and which favors vaccine on the right hand side of the figure right under the column heading "Odds Ratio"?
B. In the column "study or subgroup" can you please add group low risk of bias and high risk of bias studies rows so that first low risk and then high risk studies are presented?

That way readers do not have to keep figure out which study is which from the text.
C. Please comment on I2 and P values and their significance, esp. given that it is 0 in Figure 2 and that P values are low.

23. I am wondering if results could be organized in such a way that systematic review findings are grouped together first, then meta-analysis data is presented. Using words such as "pooled" would draw attention to the meta-analysis component. I found myself toggling a bit when looking for findings for each part of this work.

24. Overall comments.

I think this review explicitly addressed a sensible clinical question; the search for relevant studies was exhaustive; selection and assessments of studies were reproducible; results are ready for clinical application.

Questions below might need a bit more clarification in results and discussion:
a. Results not consistent across studies-one exception needs to be explained.
b. Is it possible to calculate absolute reduction risk and number needed to treat based on your metanalysis data?
c. What is your confidence in estimates of effect using GRADE, USPSPF, or Oxford?
d. Evidence summary table.
Given that you are looking at primary and secondary outcomes, this type of table would be of use. This way one column would list CIN2+, CIN1, VIN, VAIN, warts and then you can list N, confidence, RR, and risk difference per 100 patients if relevant.
e. Risk of bias estimate. Given that a few of the studies were RTCs, and risk bias tool used was for non-randomized interventions, why not use Cochrane Risk of Bias tool which is designed for RTCs?
f. How does your risk of bias influence your confidence in estimates of effect?
g. Given high risk of bias in a mix of retrospective analysis of RTCS and prospective cohort studies , how do we interpret results?
h. Given large reduction in incidence of CIN2, can that increase your confidence rating?
i. Do you consider your CI wide or narrow? How does that influence your interpretation of studies?

Reviewer #3: Overall - While the premise of the review is solid, combining studies of different designs strikes as unusual. Given the marked difference in methodologic quality both theoretically and as specifically documented in this paper between case-control, cohort and RCTs I would was surprised to see them combined into one meta-analysis. At the very least, the authors should have presented the data as subgroup analyses based on study type. I have included an excerpt from the Cochran handbook below:

"It is generally accepted that criteria should be set to limit the kinds of evidence included in a systematic review. The primary reason is that the risk of bias varies across studies. For this reason, many Cochrane reviews only include randomized trials (when available). For the same reason, it is argued that review authors should only include NRS that are least likely to be biased. It is not helpful to include primary studies in a review when the results of the studies are likely to be biased, even if there is no better evidence. This is because a misleading effect estimate may be more harmful to future patients than no estimate at all, particularly if the people using the evidence to make decisions are unaware of its limitations (Doll 1993, Peto 1995)."

Abstract:
Introduction: Clearly written and places the review in context. I would like to see a strong argument for the need for a meta-analysis.

Data sources: Clearly described and appropriate. Authors completed the PRISMA checklist and registered with PROSPERO.
Study selection: Described selection and exclusion criteria sufficiently well to replicate the trial. The tool used to evaluate the trials is one used for non-randomized trials, two of the six trials were RCTs. Was consideration given to assessing each of the different study types based on a specific tool appropriate for the design? This does not adequate assess Joura or Kim's trials.

Forest Plots-Figure 2
The studies should be separated by study-type/bias assessment so readers can better assess those of high versus low methodologic quality.

Discussion:
If the authors have an argument for combining study designs, this should be presented in the discussion section.
2 studies (of only 6) account for nearly 60% of the sample in this analysis, the implications should be described.
Also, the authors last conclusion about how this data advocates for implementation is a strong conclusion based on the quality of the data. An analysis that contains on RCTs after the 2 are published in 2020 would provide stronger evidence.

STATISTICAL EDITOR'S COMMENTS: General: Not all the studies analyzed were RCTs, and subanalysis by study type is likely unhelpful due to small numbers in each category. So, the meta-analysis represents an aggregation of randomized and non-randomized studies. As such, language that implies causation should be avoided and instead, the RR results should be described as showing associations, since there could be some variables besides vaccination status that could have influenced risk of cervical dysplasia.

ASSOC EDITOR - GYN
Please reduce language implying causation - as requested by STAT editor. Also, if all of the patients were previously unvaccinated please see whether there is a way to revise the manuscript title to reflect that is the population being studied.

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

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.

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. 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: Review articles should not exceed 25 typed, double-spaced pages (6,250 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.

5. Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). Do not structure the title as a declarative statement or a question. Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles. Abbreviations, jargon, trade names, formulas, and obsolete terminology also should not be used in the title. Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," or "A Systematic Review," as appropriate, in a subtitle. Otherwise, do not specify the type of manuscript in the title.

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).

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. 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."

9. 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: Reviews, 300 words. Please provide a word count.

10. 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.

11. 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.

12. 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%").

13. We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If on the other hand, it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

14. 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.

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

"Figure 1: Please check your n values as 3,708–4,665 does not equal 37
Figure 2–5: Please provide the original figure file (eps, tiff, jpeg, png, etc.) at a higher resolution.
Figure 6: We usually see risk of bias summaries with a second part. Did you want to provide this second part?"

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.

16. 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 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 21 days from the date of this letter. If we have not heard from you by Feb 03, 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

_____

[redacted]

JOHNS HOPKINS
MEDICINE

COVER LETTER FOR SUBMISSION OF MANUSCRUPT

February 3, 2020

Dear Editors,

Thank you for your review of our manuscript and the thoughtful comments. We have addressed the comments by the reviewers and editors. Please see our attached response.

Thank you again for considering our work. Given the timely and important impact of this data to help reduce the risk of recurrent cervical dysplasia, we hope this study can help inform clinicians and guide evidence-based treatment recommendations for women with cervical dysplasia.

Sincerely,

Kimberly Levinson, MD

**REVIEWER COMMENTS AND RESPONSES**

**Reviewer #1**

**Comment 1: Methodology of review: sensible clinical question posed. Appropriate databases queried with multiple search terms to maximize capture of relevant articles. 2 separate reviewers were used to reduce error and subjectivity with a 3rd used in the event of discrepancy. 4 total reviewers. Study authors contacted if questions arose. Included studies appropriate, exclusion criteria clearly delineated. Included studies quality assessment and potential bias via ROBINS-1 tool and summarized in fig 6. Confounding variables delineated both pre and post intervention. Primary and secondary outcomes expressed. Confidence levels depicted in figures**

Response 1: We appreciate the concise review of the methods. No changes requested.

**Comment 2: Question to authors: are the references properly attributed?? See 2 examples below**
**-Line 112: In fact, recent studies suggest that adjuvant HPV vaccination may help to prevent recurrence of CIN2+ (ref 12-14: these references do not address adjuvant HPV vaccination but general colposcopy and management of dysplasia)**
**-Line 423 the link connects to a Spanish language version of the article**

Response 2: We appreciate the reviewer catching this error, and these references have been corrected.

**Comment 3: Materials and Methods: see above comments in methodology. 6 studies included. 2,984 women with 115 having the primary outcome.**

Response 3: No changes requested.

**Comment 4: Results: Line 206: studies found to have high bias (table 2) there is no table 2, I suspect they mean Fig 6. Please review/revise. Also listed incorrectly in legend.**

Response 4: This reference did previously refer to Figure 6. Given the additional changes, this now refers to Figure 8 in the current version, and this has been changed in both the text and in the Legend.

**Comment 5: Line 207: consider adding " 1 or 2" in front of RCT to delineate how many there were - gives context to the reader (ie there were 2 RCT)**
Response 5: The risk of bias section of the paper, has now been split into 2 separate sections, 1 addressing the risk of bias in the RCTs, and 1 addressing the risk of bias in the non-RCTs. Therefore, this comment is no longer pertinent to the manuscript.

**Comment 6: Line 210: control trials were classified as high risk these? analyses were not intended upon initiation of the… (missing a word, sentence does not flow)**
Response 6: This sentence has been altered for readability and flow (now line 302-304 as this section has been moved further down in the manuscript).

**Comment 7: Lines 297 & 314: statement "our data suggest" rec change to our review of the available datasets suggest**
Response 7: We appreciate this suggestion, and the manuscript has been altered with this suggested change (line 352 & 375).

**Comment 8: Table 1: Good summary of each study included in the analysis and its results**
Response 8: No change requested

**Comment 9: Fig 4 & 5 : Forest plots of the risk of CIN2+/CIN1 recurrence with comparison of HPV Vaccination (16/18) versus Control: moderate heterogeneity noted, but falls toward favoring vaccination**
Response 9: No change requested

**Reviewer #2**
**Comment 1: Subject matter.**
**I consider it of very high importance. I wanted to personally thank you for embarking on this project, and here is why. I am clinician-educator, and I have been teaching ASCCP colpo curriculum for the past 10 years to residents and faculty and worked closely with ASCCP leaders and oncologists to make it evidence-based and provider focused. I would not be exaggerating if I say that literally every time we have a case conference to decide on management, someone will complain about lack of data on CIN recurance and regression in the setting of using HPV vaccine as adjuvant therapy. It is a burning question for clinicians because patients constantly ask about what they can do post-excision, and the only answer we can give them is a wishy washy one. We have been watching abstracts, posters, and occasional pilot work published on the topic, but nothing has been analyzed and complied together in a formal way. As a result of this preliminary limited work, I have been using HPV vaccine off-label for years as adjuvant therapy (as I am sure quite a few providers are doing), with disclosure about off-label use, and with financial hurdles. Not only do we not know what to say about efficacy, but we also have another big problem-insurance does not pay for it. Only recently did FDA approve vaccine for up to 45 (insurances are dragging their feet in paying for it, but they will eventually), and after 45 you are looking at $600-$1000 out of pocket cost. As one of my patients said, "I will pay, it's like not paying for another fancy bag this year! Maybe it will help", but most of them do not have the money to be able to direct their own care. I am hoping that publication of your work will make wheels turn and FDA will approve it for this indication as a result of this first step, which means my patients who can benefit from it will eventually get it, not just the ones who are over 45 or those who can afford to buy fancy bags they do not need.**
Response 1: We appreciate this comment and agree that this is why we initiated this type of analysis. We agree that this is of high importance both to clinicians and patients, and we hope that this will help to get the correct treatment to all patients who it could benefit.

**Comment 2: I think it would be of use to emphasize those social factors/barriers to use in discussion and/or intro, to put it into perspective as to why showing evidence for efficacy is important-so that insurance would pay for it, and so that clinicians would pay attention and start using it, even if for now it would be off-label and out of pocket.**
Response 2: We have added a sentence to the discussion (Lines 361-364) to emphasize the importance of the impact of social factors/barriers, as suggested

**Comment 3: Intro - line 102. I would emphasize how many US women are not vaccinated and how low vaccination rates are among the underserved. It is not just a global problem; it is our American problem.**
Response 3: We have added several lines in the introduction to further stress the importance of this issue both in the US and globally (Lines 87-91). A new citationwas also added (citation 8) to directly address current vaccination rates.

**Comment 4: line 106-107 - I would clarify that for CIN2 and CIN2/3 young women who are candidates can opt for conservative management (not excision) according to ASCCP guidelines. The way your sentence reads now it suggests excision which is not accurate. Moreover, this group of women can also benefit from HPV vaccine as an adjuvant treatment if you want to add a topic of potential treatment of persistent HPV infection/CIN1, or expectant management of CIN2**.
Response 4: We have added clarification to this sentence to indicate that for young women, <30, conservative management is an option (lines 97).

**Comment 5: line 109- I would re-write recurance rates in terms of CIN3+ in addition to CIN2+.**
Response 5: This sentence has been re-written to express recurrence rates broken down by CIN3+ and CIN2+ (line 98-99).

**Comment 6: Lines 112-113 - References 12-14 are not studies, they are guidelines and review articles, and should be quoted as such.**
Response 6: These references have been removed, as above (Reviewer 1 Comment 2).

**Comment 7: Methods. Prospero registration is clear.**
Response 7: No change requested

**Comment 8: Data sources are appropriate.**
Response 8: No change requested

**Comment 9: Did you use a librarian to assist you with the search?**
Response 9: A librarian did assist with this search. This was added to the methods section (line 116).

**Comment 10: What word searches did you use?**
Response 10: Various word searches were utilized in order to comprehensively gather appropriate studies. This has been added to the methods section (lines 118-120).

**Comment 11: Did 2 reviewers participate in each decision, or did you opt to only use 3rd reviewer in case of disagreement?**
Response 11: As stated in line 148-150, “Two reviewers independently screened titles and abstracts. When discrepancies arose between reviewers, a third team member served as a third adjudicator and a final decision.” and participated in each decision.

**Comment 12: Lines 127-128 - I was not clear if you included abstracts in your review. From what is written it looks like you did authors sent you results in cases where articles to follow up on the abstract was not published. My understanding was the only published work and not abstracts would be included in reviews, and main reason being was that that was the only way to assure that it has gone through the proper peer-review process. Can you please clarify?**
Response 12: We did not include abstracts in our review, and the text in line 123-124 was clarified to more clearly state that “Published abstracts alone were excluded if a related article by the authors could not be obtained.”

**Comment 13: Line 144 - You included hysterectomy as a treatment in your search. Can you explain why? Technically speaking, those studies should be excluded since assuming hysterectomy was total, it would be impossible for patients to get CIN2-no cervix. It is still of clinical relevance as post-hysterectomy patients are at risk for VIN and VAIN, but that is completely different topic. Not sure if that should be included in this review or not, but this issue of hysterectomy as treatment needs to be clarified.**
Response 13: We appreciate the reviewer’s attention to detail in this regard. This term had been added by the

librarian to ensure a broad range of search terms and to make sure that no study for secondary prevention or treatment for recurrent CIN was overlooked. However, upon running the search without the term “hysterectomy”, the same number of results arise. Therefore, we have excluded this term from the manuscript in order to simplify and clarify this issue (line 136).

**Comment 14: It is not surprising that you were only able to identify 6 studies that met your inclusion criteria. This is a hot topic and publications are lagging.**
Response 14: We agree that this is an important topic, and we are eager to see more evidence regarding this important subject. No change to the manuscript requested.

**Comment 15: In terms of combining systematic review and metanalysis, from the stylistic standpoint, it was hard to follow when you describe your results if you are talking about systematic review results or metanalysis results. For example, for secondary outcomes you say metanalysis was not performed for VIN/VAIN/genital warts, but systematic review results for same outcomes are discussed in paragraph above. Would it possible to organize in such a way that it is easy to follow and requires less back and forth when reading it to see which portion you are referring to?**
Response 15: We have altered the flow of the results section to reflect the systematic review findings first and then the meta-analysis. Additionally, these sections are labeled so that they do not require any back and forth when reading.

**Comment 16: You indicate that CIN2+ is the cut off used in vaccine studies, which is why you chose to use it as an endpoint. However, ASCCP chose to use CIN3+ for their guidelines because it is more clinically meaningful. Assuming that CIN3+ outcomes were scant in studies you pooled, would you still be able to run a sub-analysis on this, or at least comment on your attempt to do so, even if it was not fruitful in terms of N?**
Response 16: Lines 332-337 now specifically address the results for CIN3.

**Comment 17: Line 232 Please correct to "incidence of cervical dysplasia" if that was the intent.**
Response 17: The titles specific to cervical dysplasia have been re-labeled as such.

**Comment 18: Table 1 is very helpful.**
Response 18: We appreciate the positive feedback on this table.

**Comment 19: Would it be possible to include if study was industry-sponsored as one of the columns? I was wondering if those trails were pharma trails which lead to FDA approval of bi- and quad- vaccines, or if those were conducted by independent clinicians in community setting. I know Future I and II are pharma studies, but general audience might want to know this. This info could also go into text if table seems crowded. I am asking because the way industry published quad vaccine articles was hard to read as they emphasized HPV-naïve outcomes, not outcomes in exposed women, which made it harder for clinicians to interpret**.
Response 19: There were 2 trials that had industry support. Details are now included in the text in lines 259-261.

**Comment 20: Thank you for including a column which indicated if HPV vaccine was given before, after, or at the time of excision, and indicate how much time passed between HPV vaccine and excision before or after. It explains well why PATRICIA was excluded.**
Response 20: No change to the manuscript requested.

**Comment 21: It is possible to include a column on what treatment consisted of. LEEP? CKC? Ablation? Cryo? This might have implications on result interpretation.**
Response 21: An additional column has been added to Table 1 to indicate the treatment.

**Comment 22: Could you comment on study 25? It is the only one that showed a higher risk of recurance for both CIN1+ and CIN2+, so it would be interesting for the reader to see what you think about the methodology of the study and how you should interpret their findings.**
Response 22: The analysis in this paper is a subgroup of the cohort who had a LEEP and those who received a LEEP were not randomized separately. This analysis was underpowered to detect a difference in recurrence, as the authors state in their conclusion, and likely this methodology introduced bias. A short explanation has been added to the

discussion (lines 422-429).

**Comment 23: I think it is important to mention in the intro and/or discussion in terms of implications that HPV infection, low-grade cytology and CIN1 are all the same entity, which is the reason why it is basically treated the same clinically. While it does not require treatment, it requires closer follow up, which is burdensome to patients. To take it further, lines 243-252 discuss CIN1+ incidence, but I would argue that it is much use to separate CIN1 from CIN2+ in results and discussion. Hard to know how to clinically interpret CIN1+. Best to know CIN3+. Can live with CIN2+. Figures 2-5 should be redone with CIN2+ and CIN3+ as outcomes, not CIN1+ and CIN2+.**
Response 23: The important point about the impact of reducing CIN1 as well as CIN2+ is taken, and we added lines 355-357) to address this in the discussion. We did also add the section on CIN3 (lines 332-337) in the results section of the paper, and Figure 4 was added to include a figure specific to CIN3 in order to be comprehensive in this regard.

**Comment 24: Lines 254-266. Please explain to the reader that lesions were tested for 16/18 in a research setting only (and why that info is of use) and that type of testing is not available in clinical practice. They may get confused with HPV 16/18 testing at the time of a screening cotest pap.**
Response: A footnote was added to line 257 to address this concern and to ensure that the reader understands that this testing was done for research purposes.

**Comment 25: Mention intro that ASCCP and ACOG now favor LAST guidelines but that most of your studies still used CIN terminology. That would clarify it for the readers. Moreover, line 183-183 is problematic from methodology standpoint. You state that "studies reporting HGSIL were classified as CIN2+" but that is not in concordance with LAST guidelines. In order to classify CIN2 as HGSIL, you need to have positive p16. If you do not have it, then your CIN2 could be either LGSIL or HGSIL. It is especially problematic in the era when most of these studies were done, because most of them likely did not use p16 staining. I would strongly encourage you to leave CIN2 as CIN2, and HGSIL as HGSIL. If you chose to group them, you have to explain this issue to the reader.**
Response 25: We appreciate this important note regarding terminology. We included this in the methods section as this was felt to be the more appropriate location for this detail regarding terminology (lines 212-215). While we agree with the comment that CIN2+ lesions require p16 positivity to be classified as HSIL, the opposite is not precisely true (p16 positivity is NOT required to call a HSIL lesion CIN2+). In fact, the definition of HSIL per LAST guidelines is “A proliferation of squamous or metaplastic squamous cells with abnormal nuclear features including increased nuclear size, irregular nuclear membranes, and increased nuclear to cytoplasmic ratios accompanied by mitotic figures. There is little or no cytoplasmic differentiation in the middle third and superficial thirds of the epithelium. Mitotic figures are not confined to the lower third of the epithelium and may be found in the middle and/or superficial thirds of the epithelium.”[1] Therefore, we feel that this classification is reasonable. We have included this, however, in the limitations of the study (line 413-416) to draw the reader’s attention to the fact that this change in terminology does have the potential to impact the analysis.

**Comment 26: Line 268 - Incidence of VIN and Genital Warts section.**
**Neither VIN nor genital warts are mentioned in intro—it only appears under secondary outcomes in lines 186-188. It is a bit confusing to the reader. Please address.**
Response 26: We have added to the introduction that HPV not only causes cervical dysplasia, but also vulvar dysplasia and genital warts (line 85-86).

**Comment 27: Figures 2-5. A. Can you pls add label to indicate which side favors control and which favors vaccine on the right hand side of the figure right under the column heading "Odds Ratio"?**
Response 27: Under each of the figures, there is a label which states this. It is directly under the numerals on the

[1] Darragh TM, Colgan TJ, Thomas Cox J, Heller DS, Henry MR, Luff RD, McCalmont T, Nayar R, Palefsky JM, Stoler MH, Wilkinson EJ, Zaino RJ, Wilbur DC, Members of the LAST Project Work Groups. The Lower Anogenital Squamous Terminology Standardization project for HPV-associated lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. Int J Gynecol Pathol 2013 Jan;32(1):76-115.

x-axis.

**Comment 28: Figures 2-5. B. In the column "study or subgroup" can you please add group low risk of bias and high risk of bias studies rows so that first low risk and then high risk studies are presented? That way readers do not have to keep figure out which study is which from the text.**
Response 28: Thank you for the suggestion. We have included the risk of bias tool on our forest plots.

**Comment 29: Figures 2-5. C. Please comment on I2 and P values and their significance, esp. given that it is 0 in Figure 2 and that P values are low**.
Response 29: We have added a footnote to these figures which states "the $I^2$ statistic, which showed the inter-study heterogeneity as a proportion of the total heterogeneity, ranged between 0-46% which indicates a low level of heterogeneity between the studies in each of the meta-analyses"

**Comment 30: I am wondering if results could be organized in such a way that systematic review findings are grouped together first, then meta-analysis data is presented. Using words such as "pooled" would draw attention to the meta-analysis component. I found myself toggling a bit when looking for findings for each part of this work.**
Response 30: The results section has been reorganized with additional headings to help clarify the Systematic review findings from the meta-analysis findings. We also added the wording "pooled", as suggested, to help further clarify.

**Comment 31: Overall comments. I think this review explicitly addressed a sensible clinical question; the search for relevant studies was exhaustive; selection and assessments of studies were reproducible; results are ready for clinical application.**
Response 31: We appreciate this positive feedback on our manuscript. No change requested.

**Comment 32: Questions below might need a bit more clarification in results and discussion:**
**a. Results not consistent across studies-one exception needs to be explained**.
Response 32: please see above response to Comment #22.

**Comment 33: Questions below might need a bit more clarification in results and discussion:**
**b. Is it possible to calculate absolute reduction risk and number needed to treat based on your metanalysis data?**
Response 33: Table 2 has been added which describes both of these findings for each outcome.

**Comment 34: Questions below might need a bit more clarification in results and discussion:**
**c. What is your confidence in estimates of effect using GRADE, USPSPF, or Oxford?**
Response 34: GRADE was utilized to describe the confidence in estimates in Table 2. We have outlined this in the methods section as well (lines 201-207).

**Comment 35: Questions below might need a bit more clarification in results and discussion:**
**d. Evidence summary table. Given that you are looking at primary and secondary outcomes, this type of table would be of use. This way one column would list CIN2+, CIN1, VIN, VAIN, warts and then you can list N, confidence, RR, and risk difference per 100 patients if relevant.**
Response 35: We appreciate this suggestion and have included Table 2 to address this.

**Comment 36: Questions below might need a bit more clarification in results and discussion:**
**e. Risk of bias estimate. Given that a few of the studies were RTCs, and risk bias tool used was for non-randomized interventions, why not use Cochrane Risk of Bias tool which is designed for RTCs?**
Response 36: We appreciate this suggestion and have now used both the Cochrane Risk of Bias tool for RCTs and the ROBBINS-I tool to evaluate the non-RCTs which are displayed in Figures 7a and b and 8a and b respectively and also described in the Methods (lines 170-200) and Results (lines 291-299) sections.

**Comment 37: Questions below might need a bit more clarification in results and discussion:**
**f. How does your risk of bias influence your confidence in estimates of effect?**
Response 37: We appreciate this suggestion and have clarified this in our discussion lines 418-422. In the results

section, we have included an analysis of the quality of results which factors in both bias and confidence intervals (lines 291-305)

**Comment 38: Questions below might need a bit more clarification in results and discussion:**
**g. Given high risk of bias in a mix of retrospective analysis of RTCS and prospective cohort studies, how do we interpret results?**
Response 38: We have discussed this issue further in our discussion as a limitation. Lines 417-430 address how best to interpret the results based on the quality of the evidence.

**Comment 39: Questions below might need a bit more clarification in results and discussion:**
**h. Given large reduction in incidence of CIN2, can that increase your confidence rating?**
Response 39: Yes, this does increase the confidence rating, as addressed in lines 418-421.

**Comment 40: Questions below might need a bit more clarification in results and discussion:**
**i. Do you consider your CI wide or narrow? How does that influence your interpretation of studies?**
Response 40: Please see lines 418-421 of the discussion where this is addressed.

**Reviewer #3**
**Comment 1: Overall - While the premise of the review is solid, combining studies of different designs strikes as unusual. Given the marked difference in methodologic quality both theoretically and as specifically documented in this paper between case-control, cohort and RCTs I would was surprised to see them combined into one meta-analysis. At the very least, the authors should have presented the data as subgroup analyses based on study type. I have included an excerpt from the Cochran handbook below:**
**"It is generally accepted that criteria should be set to limit the kinds of evidence included in a systematic review. The primary reason is that the risk of bias varies across studies. For this reason, many Cochrane reviews only include randomized trials (when available). For the same reason, it is argued that review authors should only include NRS that are least likely to be biased. It is not helpful to include primary studies in a review when the results of the studies are likely to be biased, even if there is no better evidence. This is because a misleading effect estimate may be more harmful to future patients than no estimate at all, particularly if the people using the evidence to make decisions are unaware of its limitations (Doll 1993, Peto 1995)."**
Response 1: While we understand that it would be ideal to only include randomized studies in a review, as per the statistical editor's comment below, a subgroup analysis would not be helpful in this setting given the small numbers. Therefore, the available evidence is utilized in this review in order to best inform current practice.

**Comment 2: Introduction - Clearly written and places the review in context. I would like to see a strong argument for the need for a meta-analysis.**
Response 2: We appreciate the positive feedback on the introduction. We have added lines 109-111 to further stress the importance of this meta-analysis not only with regards to changing guidelines and practice patterns, but also with regards to disparities in treatment.

**Comment 3: Data sources - Clearly described and appropriate. Authors completed the PRISMA checklist and registered with PROSPERO.**
Response 3: We appreciate the positive feedback in this regard. No change requested.

**Comment 4: Study selection - Described selection and exclusion criteria sufficiently well to replicate the trial. The tool used to evaluate the trials is one used for non-randomized trials, two of the six trials were RCTs. Was consideration given to assessing each of the different study types based on a specific tool appropriate for the design? This does not adequate assess Joura or Kim's trials**.
Response 4: We appreciate this suggestion and have now used both the Cochrane Risk of Bias tool for RCTs and the ROBBINS-I tool to evaluate the non-RCTs (Methods lines 170-200, Results lines 291-305)

**Comment 5: Forest Plots-Figure 2 The studies should be separated by study-type/bias assessment so readers can better assess those of high versus low methodologic quality.**
Response 5: We appreciate this suggestion and have separated the forest plots by study-type and included the bias

assessments.

**Comment 6: Discussion - If the authors have an argument for combining study designs, this should be presented in the discussion section. 2 studies (of only 6) account for nearly 60% of the sample in this analysis, the implications should be described. Also, the authors last conclusion about how this data advocates for implementation is a strong conclusion based on the quality of the data. An analysis that contains on RCTs after the 2 are published in 2020 would provide stronger evidence.**
Response 6: We have added a section in the limitations portion of the discussion to address the fact that 60% of the sample is from two studies (lines 404-406). Furthermore, we have changed the language in the last concluding paragraph to better match the implications of the data (lines 443-445)

**STATISTICAL EDITOR'S COMMENTS**
**Comment 1: General - Not all the studies analyzed were RCTs, and subanalysis by study type is likely unhelpful due to small numbers in each category. So, the meta-analysis represents an aggregation of randomized and non-randomized studies.**
Response 1: We appreciate this response and acknowledgement that utilizing the available data is reasonable in this setting.

**Comment 2: As such, language that implies causation should be avoided and instead, the RR results should be described as showing associations, since there could be some variables besides vaccination status that could have influenced risk of cervical dysplasia.**
Response 2: The language in the text has been changed in multiple locations to describe the association with a reduced risk of recurrence rather than causation.

**ASSOC EDITOR - GYN**
**Comment 1: Please reduce language implying causation - as requested by STAT editor. Also, if all of the patients were previously unvaccinated please see whether there is a way to revise the manuscript title to reflect that is the population being studied.**
Response 1: As above, the language has been changed in multiple areas of the text to avoid language of causation. Additionally, the title has been changed to reflect that this is in previously unvaccinated women.

**EDITORIAL OFFICE COMMENTS**
**Comment 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:**
Response 1: A. OPT-IN: Yes, please publish my point-by-point response letter.

**Comment 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.**
**Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page.**
Response 2: All disclosures have been checked to ensure that they are correct

**Comment 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.**
Response 3: Use of these definitions is not problematic

**Comment 4: Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Review articles should not exceed 25 typed, double-spaced pages (6,250 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.**
Response 4: Our studies meets these restrictions.

**Comment 5: Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). Do not structure the title as a declarative statement or a question. Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles. Abbreviations, jargon, trade names, formulas, and obsolete terminology also should not be used in the title. Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," or "A Systematic Review," as appropriate, in a subtitle. Otherwise, do not specify the type of manuscript in the title.**
Response 5: The title has been reduced to <100 characters including spaces, the sub-title is not included

**Comment 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).**
Response 6: We have adhered to the guidelines. Poster presentations at 2 meetings are noted on the title page.

**Comment 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 7: A short title, <45 characters has been added to the Title page.

**Comment 8: 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."**
Response 8: A précis has been added to page 2 which is <25 words as specified.

**Comment 9: 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: Reviews, 300 words. Please provide a word count.**
Response 9: The abstract has been checked for accuracy. The abstract adheres to word limit guidelines and is 300 words.

**Comment 10: 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 10: Only standard abbreviations are utilized and are spelled out the first time. Abbreviations are not used in the title or précis.

**Comment 11: 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 11: We have not utilized this symbol in the text, except to express data.

**Comment 12: 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 data has been reported in the above desired fashion.

**Comment 13: We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If on the other hand, it is not based on a systematic search but only on your level of awareness, it is not a claim we permit**.
Response 13: We have taken out this claim of “first” in line 397 to comply with this request.

**Comment 14: 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 14: We have checked with the table checklist, and both of our tables conform to this style.

**Comment 15: The Journal's Production Editor had the following to say about the figures in this manuscript:**
**"Figure 1: Please check your n values as 3,708–4,665 does not equal 37**
**Figure 2–5: Please provide the original figure file (eps, tiff, jpeg, png, etc.) at a higher resolution.**
**Figure 6: We usually see risk of bias summaries with a second part. Did you want to provide this second part?"**
Response 15: The numbers in Figure 1 have been corrected to account for all records. The original figure files have now been uploaded with the higher resolution. We have provided the second part for what is now figure 7.