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)*

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Date: Nov 08, 2019
To: "Deanna Teoh" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-1907

RE: Manuscript Number ONG-19-1907

Diagnosis and Management of Adenocarcinoma in Situ: A Society of Gynecologic Oncology Evidence-based Review and Recommendations

Dear Dr. Teoh:

Your manuscript has been reviewed by the Editorial Board and by special expert referees. Although it is judged not acceptable for publication in Obstetrics & Gynecology in its present form, we would be willing to give further consideration to a revised version.

If you wish to consider revising your manuscript, you will first need to study carefully the enclosed reports submitted by the referees and editors. Each point raised requires a response, by either revising your manuscript or making a clear and convincing argument as to why no revision is needed. To facilitate our review, we prefer that the cover letter include the comments made by the reviewers and the editor followed by your response. The revised manuscript should indicate the position of all changes made. We suggest that you use the "track changes" feature in your word processing software to do so (rather than strikethrough or underline formatting).

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Nov 29, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: The review provides much needed clinical guidance which is evidence-based. Specific guidance for evaluation, treatment options and follow up with comprehensive documentation of literature review will assist the clinicians with AIS to provide the highest standard of medical care.

Reviewer #2: This is an extensive literature review to provide guidelines for the evaluation and management of cervical adenocarcinoma in situ (AIS). They have been reviewed and endorsed by ASCCP, harmonize with the ASCCP Risk Based Management Consensus Guidelines, and provide more specific guidance beyond that provided by the ASCCP guidelines.

Reviewer #3:

1. This is an important publication for OB/GYN providers, many of whom perform colposcopy and struggle with the AIS issues addressed. The paper is well written, systematic and has been reviewed by important stakeholders.

2. The recommendation for length of the conization is based on a reference paper which does not apply to the particulars of this paper. Reference number [20] Optimal cone size to predict positive surgical margins after cold knife conization (CKC) and the risk factors for residual disease - is a study which looked at CKC used to treat patients with squamous disease and not glandular disease (only about 1% of cases had glandular pathology), this is misleading and should not be used to support their recommendations. A better reference for the cone length is Bertrand M, Likrisch GM, Colgan TJ. The anatomic distribution of cervical adenocarcinoma in situ: implications for treatment. Am J Obstet Gynecol 1987;157:21-5.

3. It is important to highlight that the studies which showed no difference in residual disease or recurrence of AIS between LEEP vs CKC are all retrospective and the impact selection bias as to which patients to perform CKC on is not insignificant. Additionally in many instances LEEP was performed for squamous disease and AIS incidentally found in the LEEP specimen and then used in the study, an example is reference 39 (where 39 of the 44 the AIS was only detected on LEEP, yet the paper leads one to believe LEEP was prospectively performed in patient with AIS). It remains unclear if focal or coexistent AIS with CIN is different than someone with AIS only. The paper does emphasize that LEEPs for AIS is not optimal "except in the hands of a highly skilled LEEP surgeon..." but clarification of both the cone length data and limitations of the comparative CKC vs LEEP data are warranted. If a statement is made to clarify these limitations then an asterisk to this regards may be helpful next to LEEP in figure 1. Lastly a statement regarding incidental or coincident AIS on LEEPs for CIN might be useful.

4. Line 149, Consider making a comment regarding cytology review to confirm findings prior to excisional procedure in patient with AGC (favor neoplasia) with negative colposcopy/biopsies, especially if the experience of the pathologist is limited.

5. Line 166-168 Endocervical sampling in HPV-18 positive patients is a SGO specific statement which the authors should add to the recommendation 1.1 area and give a rating (appears the rating would be CIII). In the text of the article line 168 they call it "acceptable" to do the endocervical sampling but in Table 2 they recommend the sampling without also stating the alternative of no sampling (implying this is the only option ie "preferred"). For consistency sake and to stay true to the ASCCP terminology it makes sense to either state that ECC is "preferred" on line 168 or add that no sampling is an option to table 2.

6. Line 218 Again for consistency sake "acceptable" should be changed to "preferred" as that is what is in the recommendation 2.2 line 196.

7. Table 2 is a useful summary of the ASCCP colposcopy standards. But the bulleted minimum colposcopy standards on page 31 are not well presented or described and should either be elaborated on or removed.

8. Recommendation 3.3 line 229. As this recommendation is based on the low percentage of patients who might have micro invasive disease and it is unclear of any advantage to lymphadenectomy in micro invasive disease, it would seem reasonable to state that it is also acceptable not to do lymph nodes. To be clear that AIS, especially with negative margin may be managed by individual who are trained to do simple hysterectomies but are not trained at lymph node dissections.

9. Line 240 Recommendation for simple hysterectomy with bilateral salpingectomy (BS) - 1. Is the BS in this situation is for risk reduction of de novo fallopian tube cancer or is the BS is for concern of metastatic AIS? Clarification would be helpful.

10. Line 321- ASCCP recommends "long term" follow up after treatment for AIS, they do not specify a duration as far I have found. They do specify 20 years surveillance after treatment for high grade squamous disease. Please give a more specific reference for the 25 years follow up as I could not find the 25 years on the ASCCP website.

11. Line 535 For follow up after hysterectomy references the Khan MJ paper [reference 42], which acknowledges there is no specific data for glandular disease follow up after hysterectomy. The SGO has different guidelines for vaginal cytology management after hysterectomy for cervical cancer. It is interesting that more aggressive follow up and use of a non FDA approved HPV test is being recommended for follow up in this situation yet SGO does not recommend it after treatment for invasive disease . Ritu Salani, et al. An update on post-treatment surveillance and diagnosis of recurrence in Women with gynecologic malignancies: Society of Gynecologic Oncology (SGO) recommendations Gynecologic Oncology 146 (2017) 3-10.

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4. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric 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.

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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. 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: Original Research articles, 300 words; Guidelines, 250 words. Please provide a word count.

8. Only standard abbreviations and acronyms are allowed. A selected list is available online at http://edmgr.ovid.com/ong/accounts/abbreviations.pdf. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

9. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

10. 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%").

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* 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 Nov 29, 2019, 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]

12 November 2019

Re: Diagnosis and management of adenocarcinoma in situ: A Society of Gynecologic Oncology evidence-based review and recommendations

Dear Dr. Chesheir,

On behalf of our research group, I wish to thank you for the thoughtful review of our manuscript entitled “Diagnosis and management of adenocarcinoma in situ: A Society of Gynecologic Oncology evidence-based review and recommendations.” We appreciate the time and effort and have responded to the requested revisions.

Reviewer 3:

2. The recommendation for length of the conization is based on a reference paper which does not apply to the particulars of this paper. Reference number [20] Optimal cone size to predict positive surgical margins after cold knife conization (CKC) and the risk factors for residual disease—is a study which looked at CKC used to treat patients with squamous disease and not glandular disease (only about 1% of cases had glandular pathology), this is misleading and should not be used to support their recommendations. A better reference for the cone length is Bertrand M, Likrisch GM, Colgan TJ. The anatomic distribution of cervical adenocarcinoma in situ: implications for treatment. Am J Obstet Gynecol 1987;157:21-5.

We appreciate this recommendation. This reference has been added.

3. It is important to highlight that the studies which showed no difference in residual disease or recurrence of AIS between LEEP vs CKC are all retrospective and the impact selection bias as to which patients to perform CKC on is not insignificant. Additionally in many instances LEEP was performed for squamous disease and AIS incidentally found in the LEEP specimen and then used in the study, an example is reference 39 (where 39 of the 44 AIS was only detected on LEEP, yet the paper leads one to believe LEEP was prospectively performed in patient with AIS). It remains unclear if focal or coexistent AIS with CIN is different than someone with AIS only. The paper does emphasize that LEEPs for AIS is not optimal “except in the hands of a highly skilled LEEP surgeon…” but clarification of both the cone length data and limitations of the comparative CKC vs LEEP data are warranted. If a statement is made to clarify these limitations then an asterisk to this regards may be helpful next to LEEP in figure 1. Lastly a statement regarding incidental or conincident AIS on LEEPs for CIN might be useful.

-We agree that the data on LEEP vs CKC are all retrospective. This clarification has been added to the manuscript (Line 202). While there are potential biases of retrospective studies, the meta-analysis cited showed no difference in residual disease or recurrence risk despite a

[redacted]

higher risk of positive margins. The language regarding acceptability of CKC or LEEP is taken from the ASCCP management guidelines.
-We agree that there are not data to determine if coexistent AIS and CIN is different than AIS alone. Given that AIS and CIN are frequent diagnosed simultaneously, we have specified that when both AIS and CIN are diagnosed, management should proceed per the recommendations for management of AIS (Lines 173-174).
-We have included criteria for an “adequate specimen” in the manuscript (Lines 209-215).
-We have added the criteria for an adequate excisional specimen to Figure 1.

4. Line 149, consider making a comment regarding cytology review to confirm findings prior to excisional procedure in patient with AGC (favor neoplasia) with negative colposcopy/biopsies, especially if the experience of the pathologist is limited.

While we always encourage clinicians to review and discuss results with the pathologist/cytopathologist, especially in cases of cytologic/histologic discrepancies, the purpose of this manuscript is to provide general recommendations for management of confirmed atypical glandular findings. The 2001 Bethesda System includes specific designations of AGC-NOS and AGC-favor dysplasia. While cytology review can be requested in specific circumstances by clinicians, in general risk of AIS or cancer is >90% when AGC-favor dysplasia is designated. Therefore, in general additional evaluation with a diagnostic excisional procedure is recommended in the setting of a negative colposcopy/biopsies. These recommendations are concordant with the ASCCP risk-based management guidelines.

5. Line 166-168 Endocervical sampling in HPV18+ patients is a SGO specific statement which the authors should add to the recommendation 1.1 area and give a rating (appears the rating would be CIII). In the text of the article line 168 they call it “acceptable” to do the endocervical sampling but in Table 2 they recommend the sampling without also stating the alternative of no sampling (implying this is the only option ie “preferred”). For consistency sake and to stay true to the ASCCP terminology it makes sense to either state that ECC is “preferred” on line 168 or add that no sampling is an option to table 2.

Thank you for identifying this inconsistency.
-Endocervical sampling in the setting of an HPV-18+ test regardless of colposcopy findings has been added to Recommendation 1.1 (Lines 144-146).
-Added “acceptable” to table 2, which by the defined terminology means that not performing endocervical sampling is also acceptable. The remainder of the table details results/findings for which endocervical sampling is indicated.

6. Line 218 Again for consistency sake “acceptable” should be changed to “preferred” as that is what is in the recommendation 2.2 line 196.

[redacted]

We appreciate identification of this inconsistency, and have changed the terminology in the "literature review" section (Lines 218-222).

7. Table 2 is a useful summary of the ASCCP colposcopy standards. But the bulleted minimum colposcopy standards on page 31 are not well-presented or described and should either be elaborated on or removed.

Full description of the ASCCP colposcopy standards is beyond the scope of this paper. We refer the reader to the ASCCP manuscript by Wentzensen *et al.* (full citation in the footnote of the table) for additional details.

8. Recommendation 3.3 line 229. As this recommendation is based on the low percentage of patients who might have micro invasive disease and it is unclear of any advantage to lymphadenectomy in micro invasive disease, it would seem reasonable to state it is also acceptable not to do lymph nodes. To be clear that AIS, especially with negative margins may be managed by individuals who are trained to do simple hysterectomies but are not trained at lymph node dissection.

We agree that lymph node assessment is not required and thus the term "acceptable" was intentionally used rather than "preferred" or "recommended." Since surgical evaluation of lymph nodes is a dichotomous decision, the natural alternative is not to perform surgical lymph node assessment. Reasons to consider surgical lymph node assessment is further detailed in the accompanying section literature review.

9. Line 240. Recommendation for simple hysterectomy with bilateral salpingectomy (BS)-1. Is the BS in this situation for risk-reduction of de novo fallopian tube cancer or is the BS for concern of metastatic AIS? Clarification would be helpful.

This has been clarified (Lines 278-282).

10. Line 321—ASCCP recommends "long term" follow-up after treatment for AIS, they do not specify a duration as far as I have found. They do specify 20 years surveillance after treatment for high-grade squamous disease. Please give a more specific reference for the 25 years follow-up as I could not find the 25 years on the ASCCP website.

We acknowledge that the ASCCP does not define "long term" follow-up in their guidelines. Our manuscript provides surveillance recommendations for patients undergoing fertility-sparing management based on a review of the literature.
The 25 year surveillance after treatment for high-grade squamous disease has not yet been published, but are part of the upcoming ASCCP Risk-Based Management Guidelines which will be published in 2020. Our intent is for this manuscript and the ASCCP Risk-Based Management Guidelines to be published concurrently.

[redacted]

11. Line 535 For follow-up after hysterectomy references the Khan MJ paper (reference 42), which acknowledges there is no specific data for glandular disease follow-up after hysterectomy. The SGO has different guidelines for vaginal cytology management after hysterectomy for cervical cancer. It is interesting that more aggressive follow-up and use of a non-FDA approved HPV test is being recommended for follow-up in this situation yet SGO does not recommend it after treatment for invasive disease. Ritu Salani, et al. An update on the post-treatment surveillance and diagnosis of recurrence in Women with gynecologic malignancies: Society of Gynecologic Oncology (SGO) recommendations. Gynecologic Oncology 146 (2017) 3-10.

We acknowledge the discrepancies between the SGO and ASCCP guidelines. The SGO guidelines by Salani *et al*. provide surveillance recommendations following cancer treatment, and the goal is to identify recurrent disease. In contrast, the ASCCP provides recommendations for surveillance following dysplasia, and the goal is to diagnose high-grade vaginal dysplasia. Since AIS is categorized as dysplasia rather than an invasive cancer, we recommend surveillance per the ASCCP Risk-Based Management Guidelines, and do not make a separate recommendation regarding HPV testing in this setting. We do acknowledge in the manuscript that the HPV test is not FDA-approved for vaginal screening/surveillance, but also include the rationale for considering inclusion of HPV testing post-hysterectomy.

If you have any questions or need additional information, please do not hesitate to contact me:

[redacted]

We look forward to a favorable review of our manuscript.

Sincerely,

Deanna Teoh, MD, MS, FACOG, FACS

[redacted]

[redacted] Discover℠