OBSTETRICS & GYNECOLOGY

NOTICE: This document contains comments from the reviewers and editors generated during peer review of the initial manuscript submission and sent to the author via email.

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

Date: Jun 11, 2021
To: "thomas lorey" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-21-1149

RE: Manuscript Number ONG-21-1149

Invasive Cervical Cancer Following a Pap-Positive/HPV-Negative Cotest: A Clinician's Perspective

Dear Dr. lorey:

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 Jul 02, 2021, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: This is an important clinical topic that addresses how to manage women with +pap but -HPV result and highlights a hole in current ASCCP guidelines that recommend HPV only screening as triage. Though the outcome of invasive cancer is rare in women with -HPV paps, one could make the argument that any woman who consents to undergo cervical cancer screening but whose cancer is missed is a failure of our screening program. At the same time, current pap guidelines represent a course correction from penultimate guidelines, which led to increased invasive testing, biopsies and created anxiety for patients.

General feedback:

Strengths:
-Importance of this topic, as above
-ICC after +pap -HPV, albeit rare, is something ObGyns want and need to know
-It is critical to maintaining best practices in cervical ca screening for us as obstetrician-gynecologists to continually evaluate our screening & mgmt algorithms
-Methods appear correct and appropriate

Weaknesses:
-Guidance on pap results is nuanced and while the authors did an excellent job contextualizing their findings, I would have appreciated a more in-depth review of literature as an accompaniment to their work
-I am not aware that a research letter is a form of submission to the Green Journal. If it is not and authors prefer not to submit an original research article, they could consider reframing their findings to possibly work as a Clinical practice & quality article

Reviewer #2: Thank you for the opportunity to review your work. In this research letter, the authors describe a retrospective cohort study looking at patients with positive pap smear results but negative HPV cotesting who developed cervical cancer within 12 months of their cervical cancer screening.

My comments and questions are below:

Title:
- Would it be possible to clarify "pap-positive" in the title?

Intro:
- Line 6-7: Would consider rewording objective to clarify meaning of "actually help individuals."

Methods:
- How was Pap positive defined? Based on the table it looks as though ASCUS/LSIL was included. Could consider including this in the methods section and title.
- Please refer reader to other publications from KPNC which describes methods in detail. Many readers have not been looking at this closely in the last 10 years and might not know that it has been published extensively.
- How was symptomatic defined. If the primary objective is does abnormal pap smear and HPV negative contesting result in underdiagnosing of cervical cancer, I'm unsure if all symptomatic patients should be included since they would be triaged to biopsy regardless of cytology/HPV testing.
- The FIGO staging for cervical cancer was updated during the study period. Would clarify, which staging was used. The reference (#5) is from an article in 1995. Would update this reference.
- Did the authors look at previous paps/hpv testing or biopsies for patients and how this influenced their current testing?

Discussion:
- In line 34-35, it suggests that 1 individual per year in a population of 3.5 to 4 million were tested over a 17-year study period. Over this time period, many patients likely had more than one pap test and therefore I am unsure about this claim. I would clarify if the study included 4 million paps with cotesting or if it included 4 million individual patients' paps with cotesting.

Reviewer #3: The authors present a single institution analysis of how useful co-testing is for diagnosing ICC, they found that in 20 out of 54 with a Pap+/HIV- test, cancer was inapparent on exam in 20 patients. I am not sure that a research letter is a suitable format to present this topic. The authors conclude that there may be an overestimation of the benefit of a + Pap test with negative HPV testing, however this is without context. In those patients with clinically undetectable cancer picked up only on pap test there may be substantial benefit, and indeed all of them had earlier stages of cancer amenable to curative treatment. This has to be weighed against the potential harms and costs of Pap+/HPV- screens in individuals who are not subsequently diagnosed with cancer or high grade dysplasia. They also omit the number of patients in whom a pap+/hpv- test reveals a high grade dysplasia. The Pap test is one of the few useful screening tests available to a population for cancer prevention, I do not recommend being so quick to discard it. The KNPC database has enough patient information to conduct a full risk-benefit analysis looking at the harms and benefits of pap+/hpv-.

line 7: change " the fundamental question..." to "the objective of this study was to..."

line 10: this is redundant as it restates the objective, additionally, this information would be of value to gynecologists outside of KNPC as well, since the institutional datasets are quite robust

line 23: why did you only compare to distribution of histological types of ICC in 2018

line 25: how were ICC diagnosed in patients with abnormal pap but no clinical evidence of cancer

line 33-38: I am not sure I understand this conclusion, the result seem to suggest that 20 patients would have had their cancer missed, but I do not see anywhere in the article that over-estimation of clinical benefit is a concern, perhaps highlighting this as a potential impetus for the study would be helpful

STATISTICAL EDITOR COMMENTS:

The Statistical Editor makes the following points that need to be addressed:

Should include overall prevalence and CIs. Based on 54 cases among 4055057 tests, that would be ~ 1:75,000 cases with 95% CIs of from 1:58,000 to 1:100,000.

Methods: Were all types of HPV co-tested? Could these cases still represent (+) HPV, just not the types tested? Should concisely mention the stats tests used in the Table.

Table 1: The counts by subset are mostly very small, so the NS (p-trend = 0.4) result of stage distributions vs symptomatic or asymptomatic is likely underpowered and cannot be generalized.

EDITOR COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:
A. OPT-IN: Yes, please publish my point-by-point response letter.

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

2. 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.

3. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Research Letters articles should not exceed 600 words. Stated word limits include the title page, précis, abstract, text, tables, boxes, and figure legends, but exclude references.

4. 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]."

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

6. 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."

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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 Jul 02, 2021, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

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

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