

# OBSTETRICS & GYNECOLOGY



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**Date:** Jun 01, 2021  
**To:** "Roni Nitecki" [REDACTED]  
**From:** "The Green Journal" em@greenjournal.org  
**Subject:** Your Submission ONG-21-993

RE: Manuscript Number ONG-21-993

Outcomes of the first pregnancy following fertility-sparing surgery for early-stage cervical cancer: a population-based study

Dear Dr. Nitecki:

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 Jun 22, 2021, we will assume you wish to withdraw the manuscript from further consideration.

#### REVIEWER COMMENTS:

Reviewer #1:

The authors present a well written population based study on the pregnancy outcomes of women who undergo fertility sparing procedures for cervical cancer. Overall this is a well written paper. My main global issue is that it is far too long and verbose. Much of what the authors have written has come off as a book chapter rather than a study. This detracts from the data being presented. Specific comments:

Lines 113-114: While some of the data that is being presented is known, I do think this is the main reason why the data is novel. Since child bearing is being delayed increasingly, there is potential for increases risk of cervical cancer in women who desire fertility. I would expand on this concept more in the intro.

Line 122. I would disagree with the wording that it remains "Elusive" I think we have established that there is a risk.

Line 139- Large data bases are notorious for errors in data. How did you mitigate this in your work? You should at least comment on this as a weakness in your conclusion.

Line 150-152: I would explain the process of how you linked the data more thoroughly- perhaps in an appendix. I am concerned about how this was done and since your conclusion is based almost universally on the integrity of this linkage it would be prudent to explain this more.

Line 159-160: Why was the stage not available for the cohort? This calls into question the quality of your data set.

The methods section is far too verbose as written. Much of this should be moved an appendix.

Line 259: The magnitude of your odds ratio is not very impressive though statistically significant. Why do you think this is? In essence you should about double the risk of PTD- other studies have shown this to be higher. What is the difference?

The discussion is also far to verbose- please cut this down to an explanation of the clinical implications of your findings.

## Reviewer #2:

Nitecki and colleagues present a population-based study of women in California with AJCC Stage I cervical cancer evaluating the impact of fertility-sparing surgery on obstetric outcomes. Specifically, their objectives were to evaluate and characterize important obstetric outcomes (preterm birth, neonatal morbidity, maternal morbidity, etc) for the first pregnancy in women who underwent fertility-sparing surgery for early-stage cervical cancer. Their study used a case-control methodology to achieve its objectives. They report that rates of preterm birth (<37 weeks gestational age and <32 weeks gestational age) and neonatal morbidity were higher in patients who underwent fertility-sparing surgery for early-stage cervical cancer compared to controls. The manuscript is well written, the methodology is thoughtful and includes novel components (matched population and cervical cancer controls, focus on timing of conception and on first pregnancy post-treatment), and the study employs sound statistical methods. Importantly, the study addresses a very important clinical question and provides data that will help providers to counsel patients considering fertility-sparing surgery for early-stage cervical cancer. My main concern is in regards to the population of fertility-sparing surgery cervical cancer cases, which is 91.2% (n=103) LEEP/conization and 8.8% (n=10) trachelectomy. As the trachelectomy group has substantially higher rates of preterm birth, cesarean delivery, and neonatal morbidity, it is important to evaluate and compare the LEEP/conization group (excluding the trachelectomy cases) to the population controls and cancer controls, as this would provide additional essential information for providers in counseling patients.

## Major Comments:

## 1) Methodology

The authors do an excellent job of acknowledging the weakness of their study. One of the most impactful weakness is the number of trachelectomy cases included in the study population (n=10, 8.8% of cases), which the authors recognize. The authors admit that this low number of included trachelectomies "may underestimate the risk associated with a radical resection." They also evaluate and point out the difference in obstetrical outcomes between LEEP/conization procedures and trachelectomy, as shown in Table 3 and discussed in lines 268-271 and lines 318-329. However, the differences between these two procedures types need to be further evaluated and discussed. As touched in lines 318-329, a trachelectomy is a significantly more radical procedure than a LEEP or conization and therefore understandably has a higher "magnitude of risk of preterm birth." When evaluating Table 3, Figure 2A and 2B, it appears that this elevated magnitude of risk among trachelectomies may skew the risk of the entire fertility-sparing treatment group when compared to controls. For example, in Table 3, it is shown that the trachelectomy group has a 80.0% rate of PTB <37w and a 30.0% rate of PTB <32w, while the conization/LEEP group has a 20.4% and 1.9% rate, respectively. Figures 2A and 2B report the cervical cancer fertility-sparing cases (trachelectomy and conization/leeps) rates of PTB <37w and <32w as 26.5% and 5.1% which is statistically different in comparison to the population controls (15.0% and 0.8%, respectively) and the cervical cancer controls (13.5% and 0.6%, respectively). The rates of PTB in the conization/LEEP group are more numerically similar to the controls groups than when combined with the trachelectomies. Although these rates may still be statistically different, a comparison of the conization/LEEP group to the control groups needs to be done to evaluate for a difference in obstetrical outcomes. This comparison would provide important data for counseling patients. I believe a comparison of the trachelectomy group to control groups would be less relevant due to the low number of trachelectomies, which should be reiterated.

## Minor Comments:

- 1) Delete "that" on line 296, Page 14
- 2) The statement made on page 15, line 332 that the study's population is "representative" of the US population is too strong of a statement. California's population has differing demographic characteristics compared to other areas of the country and, importantly, has a substantially lower preterm birth rate compared to other states in the nation (<https://www.usnews.com/news/best-states/articles/2017-11-06/10-states-with-highest-share-of-premature-births>). The time period of the study is also somewhat remote (2000-2012), which could impact current day generalizability as practice patterns have changed (Cui et al, Obstetrics & Gynecology 2018) and demographic characteristics have shifted. This statement should therefore be deleted or adjusted to reflect potential issues with generalizability.

## Reviewer #3:

The authors present a case control study evaluating the impact of fertility sparing surgery in the setting of suspected early stage cervical cancer. The authors present relevant data evaluating the risk of excisional procedures/cervical cancer on subsequent pregnancies. I have the following questions/comments:

- 1) Is there any ability with the database to delineate who underwent cold knife cone versus LEEP, as this would be insightful to understand potential differences in risk as outlined in existing literature
- 2) In the abstract would change conization in line 99 to indicate conization/LEEP to be consistent with manuscript
- 3) In the cervical cancer control group, the assumption indicated is a prior history of dysplasia and likelihood of excisional procedures for the group who delivered prior to their cervical cancer diagnosis. Is there any data that would support this in the existing data sets? If not, would indicate this is a potential limitation.
- 4) Table 3 includes 117 patients, would indicate the other 4 patients did not have data available for this table, or add the 4 patients for total of 117
- 5) Line 307-317 discusses the cancer control group, would identify limitations with the availability of data for prior dysplasia/excisional procedures in the actual control cohort.
- 6) Is there a reason for the 11 patients who were excluded having inconsistent DOB between the linked data sets? Was there a coding check with other data points for congruency beyond date of birth for the other patients included?
- 7) With only 10 patients undergoing trachelectomy, the authors indicate if anything the risk is underestimated with this procedure. Would add more to discussion regarding the limitation of 10 patients.

#### STATISTICS EDITOR COMMENTS:

Table 1: The cervical cancer patients appear well matched to both control groups, but the Authors need to provide p-values for the matching of cases vs each control group. Why were the groups also not matched by year of delivery, since those distributions are not randomly allocated, esp for the cervical cancer patients vs cervical cancer controls?

Table 2: The groups, esp 3-6 mo, and 6-12 mo. groups, are small and there is little power to have discerned a difference, for most of these outcomes, since they generally had small counts. For the first two columns (with N = 18 and 28), the %s and CIs should be rounded to nearest integer %, not cited to 0.1% precision.

Table 3: This Table is very revealing, since the outcomes of PTB and cesarean delivery occur so disproportionately among the trachelectomy group. As space permits, this should be included in the Abstract.

Figs 2 and 3: These should be replicated after omitting the trachelectomy cases. Assuming that the matching is valid after omitting the trachelectomy group, then there is no statistical difference in odds of PTB at either < 37 or < 32 wks vs each control group. Rather, the only statistical difference that is retained is the increased odds of neonatal morbidity.

General: Was there no data for the non-nulliparous women re: prior hx of PTB? That should be identified as a risk factor for PTB and either matched or separately analyzed.

#### EDITORS COMMENT:

Thank you for submitting this work to Obstetrics and Gynecology.

1. If you opt to submit a revision, please remove the patients with trachelectomy from the primary analysis. You can provide data for these 10 patients as supplemental material if you would like to do so, but the numbers are too small to draw conclusions and these patients are usually delivered at 36-37 weeks by physician choice/standard of care which is why you are seeing such a high rate of preterm birth in this group.
2. Please reduce the length of the manuscript by approximately 30%.

## EDITORIAL OFFICE COMMENTS:

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\*The manuscript's guarantor.

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- a. State which ICD-10-CM/PCS codes or algorithms were used as Supplemental Digital Content.
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- f. The journal does not require that the title include the name of the database, geographic region or dates, or use of database linkage, but this data should be included in the abstract.
- g. Include RECORD items 6.3 and 7.1, which relate to transparency about which codes, validation method, and linkage were used to identify participants and variables collected.

7. 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.

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Torri D. Metz, MD  
Associate Editor, Obstetrics

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

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