

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: Feb 19, 2021
To: "Suketu M Mansuria" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-21-199

RE: Manuscript Number ONG-21-199

Does a Two-Layer Vaginal Cuff Closure at the Time of Total Laparoscopic Hysterectomy Reduce Complications Compared to a One-Layer Closure?

Dear Dr. Mansuria:

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 Mar 12, 2021, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

This is a retrospective cohort study of two layer closure versus one layer closure of the vaginal cuff at the time of total laparoscopic hysterectomy. I thank the authors for their valuable work in this field, and thank the editors for the chance to review this manuscript.

Strengths:

- * The authors explore patient characteristics and their effect upon vaginal cuff complications, which mitigates some of the confounders with exploring known confounders. The hysterectomies in this cohort were performed for a variety of indications in the benign gynecological spectrum, and this makes the findings applicable to most benign hysterectomies.
- * The primary outcome is clear and there is a sample size calculation provided.
- * This is a large cohort that is probably more than adequately powered to detect differences in the primary and secondary outcomes. (Of note, the authors do not take advantage of that by performing a post hoc power analysis or planning sample size before pulling records, but it appears that they had a large sample.)

Limitations:

- * All the surgeries were performed by minimally invasive gynecologists, who have more experience with laparoscopic suturing than some other gynecologists or those performing hysterectomies, so these results may not be generalizable to all surgeon pools.
- * As this is a retrospective cohort study, unknown confounders, selection or measurement bias, or surgical decision factors (like deciding to do more 2-layers closures on higher risk patients) cannot be accounted for in the analysis.
- * Mucosal separation versus dehiscence are subjective assessments sometimes, and I imagine not all of these patients with complications had the exact same workup to determine whether there was a cuff separation at all or cuff separation through to the abdomen (dehiscence). The authors do not even clearly define what was considered dehiscence and what verification in the record there had to be of this being present (versus a mucosal separation).

Comments for authors by section:

Abstract:

- * Line 55: As this is the primary outcome, I would like to see it briefly defined better in the abstract, such as listing all the complications that were considered part of this composite outcome.
- * Line 61: The abstract should include a brief sentence about the sample size or, if it is retrospective and only a certain number could be obtained, post hoc power calculation. As cuff complications are rare, as are postoperative complications

within 30 days, a power calculation goes a long way toward interpreting negative results.

* Line 73: Hospital readmissions within what time frame? 30 days? This should be clear from the abstract as well as in the manuscript.

Introduction:

* This is a clear and succinct introduction that explores the importance of the problem, but also reveals the complexity of the problem.

* Line 113: Please state a hypothesis that is to be tested. I assume it is that there will be less postoperative complications with 2 layer closure, but the authors should leave no questions at the last sentence of the introduction.

Methods:

* Line 118: Why was this time frame chosen in particular?

* Line 119-122: Why did you include only highly trained, higher volume MIGS surgeons, as opposed to everyone who performs hysterectomies in your institution. The latter would have made it a little more externally generalizable to the world.

* Line 120: Did all eleven surgeons perform the cuff closure, colpotomy, etc. the same way? I find that dubious, but perhaps they are very uniform at this institution.

* Line 151: What was considered a medical complication?

* Line 152: There should be some discussion here about how the difference between mucosal separation (which, by the way, should be epithelial separation if we are using proper terms) and dehiscence was assessed? Did there have to be bowel protrusion or imaging confirming air in the pelvis or exam verification of total separation to be called a dehiscence. It seems this could get subjective.

* Line 154-156: What was the time frame in which readmissions were assessed? 30 days out? Or up to 180 days?

* Line 157-159: This hypothesis belongs as the last sentence in the introduction.

* Line 162-166: You sort of skip a step of reasoning here. How many hysterectomies per year per group were you anticipating, making 6 years enough or more than enough?

Results:

* Line 186-189: Did these differences persist when corrected for BMI and for tobacco, specifically? As we know these are confounding factors and were not the same between the cohorts at baseline....

* Line 194: How was sexual activity determined, and the authors mean to say that the patients were specifically having insertive vaginal intercourse BETWEEN the surgery and the cuff complication? This should be discussed as being collected information in the Methods as well as appearing here.

* Line 205: Does this odds ration represent the difference between a high BMI cohort and a lower BMI cohort? And where was the cutoff, if this was the case? If it represents the OR for every 1 kg/m2 increase in BMI, be sure to clarify that here.

Discussion:

* Somewhere in the Discussion it should be pointed out that the extra OR time spent to do the second layer of closure was not sufficient to overcome the benefits and raise the postop complication rate overall (it was still lower). Some doubters may say "but you take the extra time to do it, and that raises risk of infection, pneumonia, cost, etc.)", but you can nip this in the bud by pointing out that your primary outcome was a composite of all 30-day complications.

* Good discussion of strengths and weaknesses of the study.

Reviewer #2:

Obstetrics & Gynecology

Does a Two-Layer Vaginal Cuff Closure at the Time of Total Laparoscopic Hysterectomy Reduce Complications Compared to a One-Layer Closure?

--Manuscript Draft--

Manuscript Number: ONG-21-199

Full Title: Does a Two-Layer Vaginal Cuff Closure at the Time of Total Laparoscopic Hysterectomy Reduce Complications Compared to a One-Layer Closure?

Article Type: Original Research

Manuscript Region of Origin: UNITED STATES

The authors should be congratulate on their work looking at 2 different cuff closure techniques following TLH. The following needs to be address prior to publication.

Precis:

1. Since the total complications include the cuff complication rate, and without including this this did not show a

significant difference, a more clear statement is needed.

Abstract:

1. Factors influencing cuff complications were not only examined, they were controlled for.
2. How many of these patients actually had a PE at the 6 month time period? How might this have affected your outcomes?
3. The wording here needs to be clear. Was the only difference between the groups cuff complications? As above, is the total complication rate only significant because of this or were there other complications that showed a difference? If not, the conclusion needs reworded to reflect this. Is it total complications at 30 days and only cuff complications at 180 days?

Introduction:

1. State what percentage of hysterectomies TLH now represents.
2. Are the factors listed all proven to be statistically significant? If so, please state this. Are these factors only referring to dehiscence or all cuff complications (separation, cellulitis, etc.,)? It seems that to be consistent throughout the paper, that this section should not be limited to cuff dehiscences.
3. What about early intercourse as a risk factor? What is the standard of care concerning return to intercourse following a routine hysterectomy?
4. Is there any data in the literature regarding open cases and cuff closure techniques?
5. As above, keep the wording consistent. If it is cuff dehiscence you are speaking about explain what you intend to study that would be included in vaginal cuff complications. If dehiscence is one of the complications, start your introduction with cuff complications.

Methods:

1. With rare complications, case controlled studies are the preferred methodology. Why was this methodology not used for this study?
2. How and why were the 2 different closure techniques chosen? This needs addressed in the conclusion as well as the possibility of a selection bias being present.
3. This is where you need to clearly define "total complications" and "cuff complications" and "postoperative complications" and then keep the wording consistent throughout the paper. I cannot tell if total complications were only measured at 30 days, whether cuff complications were reported at only 180 days, or what is meant by total and postoperative complications further worded as intraoperative complications. Once these are clearly defined and reported, the paper will be much more readable. Separating cuff complications and postop complications would also seem more reasonable given how the primary and secondary outcomes are described.
4. What was the time to cuff complications? The authors state that total complications are reported within 30 days, but by including cuff complications in these numbers, you are including complications up to 180 days. As in #2, clearly stating the definitions and then sticking to them is critical. Same for making a statement about ER visits and hospital admissions - were these only up to 30 days or did the time period extend to any ER visit or hospitalization within the 180 days?
5. The cuff angles were "tied extra-corporeally", not sutured this way.
6. There is no "fascia", it is vaginal muscularis.
7. Likewise, vaginal epithelium not mucosa.
8. Stating the needle does not pass through the first layer should be stated "an attempt was made to not pass through the first layer".
9. Is the 8-12 weeks standard? Could 4 weeks make a difference in the outcomes? Another confounder that should be mentioned.
10. Was 50% reduction in complications chosen to reduce the number of patient required to show significance? Usually clinical significance in surgery is reported in the 20-25% range.
11. Was time measured in surgery to perform the different closure methods?
12. Was vaginal length measured?
13. Was intercourse/ no intercourse reported for all patients?
14. How cuff cellulitis was or was not confirmed needs stated.
15. Was time to complication reported?

Results:

1. Table one - the groups are different. Using the word "slightly" is not appropriate. The groups were statistically significantly different in regard to BMI, obesity and tobacco use. This needs to be stated and its effect on the study discussed.
2. Table 2 - as asked above, if cuff complications are left out of postop complications, was there any difference between groups? It appears not and in fact, VTE was higher in the 2-layer group. As above, this seem misleading and why not report postop complications and cuff complications separately?
3. How many women actually had exams at the time periods reported? If only the ones that presented with complications are being reported, another selection bias is present.
4. Although the univariate and multivariate analysis account for the differences between groups, there still were differences (diabetes, obesity, and tobacco) that are recognized as risk factors for healing. This needs further addressed in the discussion and although statistically correct, clinically may be a different matter. .
5. As under the M+M, was intercourse reported for all subjects? Time to intercourse? Is intercourse the issue and not closure technique? Partner size and vaginal length?
6. What was the most common cause of ER/ hospitalization admission?
7. Providing an idea of what is included in Medical NOS would be helpful.

Discussion:

1. The first paragraph needs reworked to state the conclusion clearly. As pertaining to several comments already made, if total postoperative complications were only significant due to cuff complications, this point needs clarified. Stating there were no differences in intraop complications and ER/hospital admissions but then state that postop satisfaction (not measured in this study) and health care costs (also no reported on) could be substantially lowered is conjecture and not conclusion.
2. As the authors state, cuff complications are rare. Discuss why a case-control (2 or 3:1 match) was not chosen to study this.
3. Cost and time were not addressed and should not be part of the conclusion.
4. Intercourse was not reported for the 1-LVC group. All 16 who had cuff complications in the 1-LVC group were sexually active. As under the results, this needs discussed.
5. Selection bias needs discussed - why was one closure chosen over another?

Reviewer #3:

The authors present a retrospective chart review in a large cohort of patients who underwent laparoscopic closure of the vaginal cuff with one versus two layers of suture, I have the following questions/comments:

- 1) Four MIS fellowship trained surgeons who perform more than 40 hysterectomies each per year accounted for 97.4% of all the surgeries in this retrospective study. In the discussion, recommend addressing potential biases associated with retrospective studies and applicability of results to the larger gyn community based on the number of providers included. Does fellowship training and individual surgeon outcomes impact the results of this study?
- 2) Does use of a Pelosi uterine manipulator cup and 60 Watts energy potentially impact risk of vaginal cuff dehiscence? Would address in discussion section.
- 3) Is the average operative time available? A two layer closure versus one layer laparoscopic closure as outlined would have an impact on cost/utilization of resources which may be a consideration for providers with outcomes where differences are less than 2% depending on clinical significance (3.54 vs 5.62%)
- 4) Smoking does impact wound healing, lines 183-185 indicate the group with 2 layer closure was less likely to smoke. The discussion mentions obesity cancels out smoking, but supplemental figure 1 indicates only 5 of the 16 patients with vaginal cuff complication were both smokers and obese. Please address the potential impact of this in the discussion section.
- 5) Is mucosal separation a clinically significant outcome that would impact patient care compared to vaginal cuff dehiscence? Would address in discussion section

STATISTICS EDITOR COMMENTS:

Lines 64-66, 160-164: There were actually two primary outcomes: total post-op and vaginal cuff complication rates, so the 2-sided alpha is incorrect, it should be 0.025 in order to test both hypotheses. Also, the sample required for the smaller rates (vaginal cuff complication) is larger. Therefore only the total complication rate retains statistical significance. (however see comments re: Table 2, which enables both primary complication rates to be retained as having stats significance).

lines 186-187: The rates were similar for intraoperative complications, but the counts were small, limiting power and the study design was not powered to evaluate this factor. In any case, this is a secondary outcome.

Table 1: Need to enumerate any missing data, esp for BMI or obesity.

Table 2: Need to clearly separate the primary from the secondary outcomes. Most of the components of post-op complications have small counts and there is insufficient power to generalize the NS findings. Should use Fisher's test for many of the comparisons. For example, for VTE 1:1759::4:1209, the p-value = 0.17, not 0.03, similarly for bladder complications, the correct p = 0.17. For comparison of cuff complication rates, the p-value should be < .01, since it is .002

Table 3: Need to state the referent for age, BMI. I presume age is per year and BMI is per kg/m². Need to include the adjusters retained in the final aOR model. line 206: states that aOR = 0.38 for multivariate analysis using characteristic =

vaginal cuff closure, but the text states 2-LVC closure as the characteristic. Need to clarify the outcome and characteristic. Should label the multivariate analysis as aOR, not OR. Immunosuppressant use clearly had some 0 entries for calculation of OR, so should just omit this entry.

EDITORIAL OFFICE COMMENTS:

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Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page.

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If the figure or table you want to reprint can be easily found on the internet from a reputable source, we recommend providing a link to the source in your text instead of trying to reprint it in your manuscript.

4. All submissions that are considered for potential publication are run through CrossCheck for originality. The following lines of text match too closely to previously published works.

Please be sure to cite or disclose <https://doi.org/10.1016/j.jmig.2020.08.603>, if not done already.

5. Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what

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

6. 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.

7. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 22 typed, double-spaced pages (5,500 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.

8. 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).

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

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16. 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.

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If the figures were created using a statistical program (eg, STATA, SPSS, SAS), please submit PDF or EPS files generated

directly from the statistical program.

Figures should be saved as high-resolution TIFF files. The minimum requirements for resolution are 300 dpi for color or black and white photographs, and 600 dpi for images containing a photograph with text labeling or thin lines.

Art that is low resolution, digitized, adapted from slides, or downloaded from the Internet may not reproduce.

17. Please cite the video in the text. Each supplemental file in your manuscript should be named an "Appendix," numbered, and ordered in the way they are first cited in the text. Do not order and number supplemental tables, figures, and text separately. References cited in appendixes should be added to a separate References list in the appendixes file.

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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. 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 Mar 12, 2021, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,
John O. Schorge, MD
Associate Editor, Gynecology

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

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: <https://www.editorialmanager.com/ong/login.asp?a=r>). Please contact the publication office if you have any questions.

Responses to Reviewer and Editor Comments: *Our responses are highlighted in Green Font and line numbers refer to the Track-changed manuscript.*

REVIEWER COMMENTS:

Reviewer #1:

This is a retrospective cohort study of two layer closure versus one layer closure of the vaginal cuff at the time of total laparoscopic hysterectomy. I thank the authors for their valuable work in this field, and thank the editors for the chance to review this manuscript.

Strengths:

- * The authors explore patient characteristics and their effect upon vaginal cuff complications, which mitigates some of the confounders with exploring known confounders. The hysterectomies in this cohort were performed for a variety of indications in the benign gynecological spectrum, and this makes the findings applicable to most benign hysterectomies.
- * The primary outcome is clear and there is a sample size calculation provided.
- * This is a large cohort that is probably more than adequately powered to detect differences in the primary and secondary outcomes. (Of note, the authors do not take advantage of that by performing a post hoc power analysis or planning sample size before pulling records, but it appears that they had a large sample.)

Limitations:

- * All the surgeries were performed by minimally invasive gynecologists, who have more experience with laparoscopic suturing than some other gynecologists or those performing hysterectomies, so these results may not be generalizable to all surgeon pools.
- * As this is a retrospective cohort study, unknown confounders, selection or measurement bias, or surgical decision factors (like deciding to do more 2-layers closures on higher risk patients) cannot be accounted for in the analysis.
- * Mucosal separation versus dehiscence are subjective assessments sometimes, and I imagine not all of these patients with complications had the exact same workup to determine whether there was a cuff separation at all or cuff separation through to the abdomen (dehiscence). The authors do not even clearly define what was considered dehiscence and what verification in the record there had to be of this being present (versus a mucosal separation).

Comments for authors by section:

Abstract:

- * Line 55: As this is the primary outcome, I would like to see it briefly defined better in the abstract, such as listing all the complications that were considered part of this composite outcome.

→ We clarified the primary outcome listed in the abstract (Line 55-57) as other reviewers also requested clarification on this.

- * Line 61: The abstract should include a brief sentence about the sample size or, if it is retrospective and only a certain number could be obtained, post hoc power calculation. As cuff complications are rare, as are postoperative complications within 30 days, a power calculation goes a long way toward interpreting negative results.

→ The Method section of the abstract (line 53) reports the retrospective nature of the study and the sample size is listed in (line 63-64). As per the reviewer's suggestion, we also performed a post hoc power calculation (line 61) and also added this in the method section (Line 198-214). A Post hoc power calculation with a sample size of 1760 women in the 1-LVC and 1213 women in the 2-LVC group achieved a 96.6% power to detect a difference between the group proportions of 0.016. The significance level of the test used was 0.05.

* Line 73: Hospital readmissions within what time frame? 30 days? This should be clear from the abstract as well as in the manuscript.

→ This was clarified in the abstract (Line 82) and method section.

Introduction:

* This is a clear and succinct introduction that explores the importance of the problem, but also reveals the complexity of the problem.

* Line 113: Please state a hypothesis that is to be tested. I assume it is that there will be less postoperative complications with 2 layer closure, but the authors should leave no questions at the last sentence of the introduction.

→ We added a hypothesis in the last sentence of the introduction (line 129-132).

Methods:

* Line 118: Why was this time frame chosen in particular?

→ The set dates were chosen as 2011 was the year that the first MIGS surgeon in the group decided to exclusively use two-layer laparoscopic vaginal cuff closures. Prior to this date all MIGS surgeons at our institution performed the traditional one-layer laparoscopic vaginal cuff closure. 2017 was chosen as the end date as this is the year that we started the collection of data use for this study.

* Line 119-122: Why did you include only highly trained, higher volume MIGS surgeons, as opposed to everyone who performs hysterectomies in your institution. The latter would have made it a little more externally generalizable to the world.

→ The reviewer is correct that the data may have been more generalizable to the OB/GYN community if non-MIGS surgeons had been included in the study. However, we specifically chose to only include MIGS surgeons because a) no non-MIGS surgeon currently performs a 2-layer vaginal cuff closure at our institution and b) we wanted to minimize the risk of confounding factors such as surgeon skill and variabilities in technique. The MIGS surgeons at our institution have all completed the same fellowship training at our institution and are extremely consistent in their hysterectomy technique, monopolar electrode setting for colpotomy performance, type of uterine manipulator used, and cuff closure suture used. Since our hypothesis specifically wanted to assess the total complications which also included cuff complications, we aimed to minimize any variables which could have influenced these complications including surgeon skill or techniques utilized other than how the cuff was closed. We highlight this point in our discussion (Line 329-331).

* Line 120: Did all eleven surgeons perform the cuff closure, colpotomy, etc. the same way? I find that dubious, but perhaps they are very uniform at this institution.

→ The eleven surgeons included in the study were all part of the MIGS division at our institution. They all completed their fellowship training at the same institution and utilized the same technique for the hysterectomy and colpotomy with the exception of the 1 vs. 2-LVC cuff closure technique. Other surgeons at our institution (ie. urogynecologists, oncologists, generalists, etc.) have significant variability in their technique but were not included in this study.

* Line 151: What was considered a medical complication?

→ This was elaborated on in figure 2. This term was used as an umbrella term to encompass any medical condition that did not fit into the other postoperative complication categories and occurred in the 30 postop periods (death (no cases occurred), TIA/stroke, arrhythmia, DKA, pneumonia).

* Line 152: There should be some discussion here about how the difference between mucosal separation (which, by the way, should be epithelial separation if we are using proper terms) and dehiscence was assessed? Did there have to be bowel protrusion or imaging confirming air in the pelvis or exam verification of total separation to be called a dehiscence. It seems this could get subjective.

→ We edited the paper to clearly define vaginal cuff dehiscence and vaginal mucosal separation. Vaginal mucosal separation was meant to describe separations including the superficial epithelium, but also the lamina propria. In these cases, the muscularis layer was still intact, and the peritoneal cavity was not entered. Dehiscence was defined as a defect in all three layers with the defect extending into the peritoneal cavity. This entry into the peritoneal cavity was confirmed in all cases by physical examination. A separation of the epithelium alone would likely not require intervention and heal spontaneously, but 50% of mucosal separation cases in our study required re-suturing in the operating room. We further elaborated on this in the methods section to clarify (Line 187-195)

* Line 154-156: What was the time frame in which readmissions were assessed? 30 days out? Or up to 180 days?

→ Readmissions for non-cuff related postoperative complications were only assessed up to 30 days postoperatively; however, cuff related readmissions were included up to 180 days given their delayed occurrence (Line 175-177).

* Line 157-159: This hypothesis belongs as the last sentence in the introduction.

→ The sentence was moved to the introduction section.

* Line 162-166: You sort of skip a step of reasoning here. How many hysterectomies per year per group were you anticipating, making 6 years enough or more than enough?

→ Based on our power analysis we only required 1049 patients per group which would have meant analyzing less than 6 years of data based on the number of hysterectomies performed per year in the MIGS group at our institution. We initiated the study in 2017 and hence decided to include all patients from when we began to utilize a two layer closure within our practice (2011) through 6 months before the study start date (to ensure we had adequate follow-up for any patients included in the study).

Results:

* Line 186-189: Did these differences persist when corrected for BMI and for tobacco, specifically? As we know these are confounding factors and were not the same between the cohorts at baseline....

→ We performed a univariate and multivariate analysis to adjust for the difference in the cohorts at baseline and only BMI and a 2-LVC closure had a protective impact on complications. This is demonstrated in Table 3.

* Line 194: How was sexual activity determined, and the authors mean to say that the patients were specifically having insertive vaginal intercourse BETWEEN the surgery and the cuff complication? This should be discussed as being collected information in the Methods as well as appearing here.

→ Unfortunately, due to the retrospective nature of this study, sexual activity (penetrative or otherwise) was not reliably recorded in 36% of all patient charts. All patients that did experience

a cuff dehiscence did so at the time of their first penetrative vaginal intercourse after surgery. We clarified this in the manuscript (line 336-342).

* Line 205: Does this odds ratio represent the difference between a high BMI cohort and a lower BMI cohort? And where was the cutoff, if this was the case? If it represents the OR for every 1 kg/m² increase in BMI, be sure to clarify that here.

→ The later is correct. The OR is represented for every 1kg/m² increase in BMI. This was included on the table format in Table 3.

Discussion:

* Somewhere in the Discussion it should be pointed out that the extra OR time spent to do the second layer of closure was not sufficient to overcome the benefits and raise the postop complication rate overall (it was still lower). Some doubters may say "but you take the extra time to do it, and that raises risk of infection, pneumonia, cost, etc.)", but you can nip this in the bud by pointing out that your primary outcome was a composite of all 30-day complications.

* Good discussion of strengths and weaknesses of the study.

→ While the operative times to close each vaginal cuff are not available, the time to close the vaginal cuff among the MIGS surgeons in our group is quite low (~ 3 minutes for a 1-LVC and approximately 6 min for a 2-LVC). The time to close the 2-LVC is demonstrated in the supplemental video. Hence, we do not think that other postoperative complications such as infections, pneumonia, etc. would be affected by such a small increase in added time. We elaborated on this in the discussion section.

Reviewer #2:

Obstetrics & Gynecology

Does a Two-Layer Vaginal Cuff Closure at the Time of Total Laparoscopic Hysterectomy Reduce Complications Compared to a One-Layer Closure?

--Manuscript Draft--

Manuscript Number: ONG-21-199

Full Title: Does a Two-Layer Vaginal Cuff Closure at the Time of Total Laparoscopic Hysterectomy Reduce Complications Compared to a One-Layer Closure?

Article Type: Original Research

Manuscript Region of Origin: UNITED STATES

The authors should be congratulate on their work looking at 2 different cuff closure techniques following TLH. The following needs to be address prior to publication.

Precis:

1. Since the total complications include the cuff complication rate, and without including this this did not show a significant difference, a more clear statement is needed.

→ The precis was edited (line 36-37) to reflect this composite outcome more clearly.

Abstract:

1. Factors influencing cuff complications were not only examined, they were controlled for.

→ This was added (Line 60).

2. How many of these patients actually had a PE at the 6-month time period? How might this have affected your outcomes?

→ We experienced a total of 5 VTE within the 30-day postoperative period. We did not assess medical post-operative complications past 30 days as it was felt that this would be unlikely to be attributable to surgery at a time point beyond 30 days as patients recover quickly after TLH and have resumed normal activity by the 30-day mark.

3. The wording here needs to be clear. Was the only difference between the groups cuff complications? As above, is the total complication rate only significant because of this or were there other complications that showed a difference? If not, the conclusion needs reworded to reflect this. Is it total complications at 30 days and only cuff complications at 180 days?

→ The wording in the method section was modified to reflect that complications comprised of total postoperative complications up to 30 days and cuff complications up to 180 days given their delayed nature. The conclusion was also modified to better reflect this. (Lines 56-58; Line 83-84).

Introduction:

1. State what percentage of hysterectomies TLH now represents.

→ We added this percentage to the introduction to reflect all laparoscopic hysterectomies (line 109)

2. Are the factors listed all proven to be statistically significant? If so, please state this. Are these factors only referring to dehiscence or all cuff complications (separation, cellulitis, etc.)? It seems that to be consistent throughout the paper, that this section should not be limited to cuff dehiscences.

→ We expanded our introduction to better reflect the content of our paper that addresses not only cuff complications but rather total post-operative complications including cuff complications. We focused more specifically on cuff complications in our introduction because we hypothesized that the difference between the 2 groups would primarily stem from differences in cuff complications. However, we felt a composite of all postoperative complications would be important to examine as we did not know if the use of a 2-LVC would also impact non cuff related postoperative complications. We focused specifically on cuff dehiscence compared to other postoperative complications (i.e. hematomas or infections) as many of those can be managed conservatively or without need for reoperation; whereas, cuff dehiscence can be more morbid and require reoperation. We elaborated on this in the second paragraph of the introduction.

3. What about early intercourse as a risk factor? What is the standard of care concerning return to intercourse following a routine hysterectomy?

→ We routinely instruct patients to wait 8-12 weeks prior to intercourse (line 160) and did mention precocious intercourse as a risk factor for cuff complications (Line 118). One patient who experienced a vaginal cuff dehiscence did have early intercourse at 6 weeks, but all other patient who experienced a cuff dehiscence did so after the instructed wait time and always with the first episode of intercourse after surgery. One cuff dehiscence even occurred at 5 months when the patient became first sexually active. Cuff dehiscence has been reported in the literature at varying time points following hysterectomy, so the ideal time to abstain from intercourse is not universally accepted.

4. Is there any data in the literature regarding open cases and cuff closure techniques?

→ We did not find any specific studies that looked at closure techniques for just TAH, likely as these dehiscence rates have traditionally been very low compared to laparoscopic procedures.

5. As above, keep the wording consistent. If it is cuff dehiscence you are speaking about explain what you intend to study that would be included in vaginal cuff complications. If dehiscence is one of the complications, start your introduction with cuff complications.

→ We made these adjustments in the second paragraph of the introduction to be more consistent that post-operative and cuff complications, not just dehiscence, were the factors examined in the study and expanded on this in the last introductory sentence as well (line 150-111-113)

Methods:

1. With rare complications, case controlled studies are the preferred methodology. Why was this methodology not used for this study?

→ The primary outcome selected in this study is total postoperative complications, which in the existing literature for TLH has been generally reported at 5-10%. While we also examined cuff dehiscence, which is a rare event, we specifically wanted to ensure that the use of a 2-layer closure did not impact other postoperative complication rates (cuff and non-cuff related complications such as infections, hematomas, etc.) and thus opted for a cohort study. We hypothesized that the difference between the 2 groups would primarily stem from differences in cuff complications; however, we felt a composite of all postoperative complications would be important to examine as we did not know if the use of a 2-LVC would also impact non cuff related postoperative complications. If only cuff dehiscence had been examined, a case-control study would likely have been more suitable. Furthermore, both groups experienced the outcome (complications) and our goal was not to retrospectively assess the rates of exposure to a one vs. two-layer closure as would be the design in a case-control study. In our cohort study the defined exposure was 1 vs. 2-layer cuff closure and we examined the differences in outcomes (complications).

2. How and why were the 2 different closure techniques chosen? This needs addressed in the conclusion as well as the possibility of a selection bias being present.

→ Whether a 1-LVC vs. a 2-LVC was utilized was not determined by patient characteristics. Rather, individual surgeons within the MIGS group decided to either exclusively perform a 1-LVC or 2-LVC closure on all of their patients. The decision was not based on surgeon consideration of a patient's risk for a cuff complication since the technique was performed on all patients within their individual practice. Also, all surgeons within the MIGS group have one common patient referral pool, further limiting selection bias.

3. This is where you need to clearly define "total complications" and "cuff complications" and "postoperative complications" and then keep the wording consistent throughout the paper. I cannot tell if total complications were only measured at 30 days, whether cuff complications were reported at only 180 days, or what is meant by total and postoperative complications further worded as intraoperative complications. Once these are clearly defined and reported, the paper will be much more readable. Separating cuff complications and postop complications would also seem more reasonable given how the primary and secondary outcomes are described.

→ We define these parameters more clearly in our methods section (Line 175-195) as well as the abstract and introduction.

4. What was the time to cuff complications? The authors state that total complications are reported within 30 days, but by including cuff complications in these numbers, you are including complications up to 180 days. As in #2, clearly stating the definitions and then sticking to them is critical. Same for making a statement about ER visits and hospital admissions - were these

only up to 30 days or did the time period extend to any ER visit or hospitalization within the 180 days?

→ This was addressed in the same section as mentioned in the last comment to help clarify this ambiguity.

5. The cuff angles were "tied extra-corporeally", not sutured this way.

→ This was corrected (line 147)

6. There is no "fascia", it is vaginal muscularis.

→ This was corrected.

7. Likewise, vaginal epithelium not mucosa.

→ We used mucosa to not only imply the superficial epithelium but also the lamina propria. Reviewer #1 also raised this concern. Vaginal mucosal separation was meant to describe separations including the superficial epithelium, but also the lamina propria. In these cases, the muscularis layer was still intact, and the peritoneal cavity was not entered. Dehiscence was defined as a defect in all three layers with the defect extending into the peritoneal cavity. A separation of the epithelium alone would likely not require intervention and heal spontaneously, but 50% of mucosal separation cases in our study required re-suturing in the operating room. We further elaborated on this in the methods section to clarify (Line 187-191)

8. Stating the needle does not pass through the first layer should be stated "an attempt was made to not pass through the first layer".

→ the statement was corrected (Line 158-159).

9. Is the 8-12 weeks standard? Could 4 weeks make a difference in the outcomes? Another confounder that should be mentioned.

→ The reviewer is correct that this could be a potential confounder and is based on individual surgeon preferences. However, to-date no universally agreed upon time point has been established that guarantees that it is absolutely safe for patients to resume intercourse without risk of dehiscence. This was seen in one of our patients who delayed sexual activity until 5 months postoperatively, yet still experienced a cuff dehiscence. On the other hand, at our institution most surgeons who perform abdominal hysterectomies generally only advocate for pelvic rest for 6 weeks and TAHs have generally be associated with one of the lowest dehiscence rates. (Lines 336-342)

10. Was 50% reduction in complications chosen to reduce the number of patient required to show significance? Usually clinical significance in surgery is reported in the 20-25% range.

→ A 50% reduction was arbitrarily chosen by the authors. We felt that a higher reduction in complications (50% rather than 25% as suggested by the reviewer), given the overall low complication rates, would lend more credibility to any statistically significant findings. If we had only wanted to demonstrate a 25% reduction in complications, we would actually have required a significantly smaller cohort.

11. Was time measured in surgery to perform the different closure methods?

→ Average operative time for cuff closures was unfortunately not collected, but as mentioned to Reviewer #1 and #3 the use of a second layer cuff added only approximately 3 minutes to the procedure beyond a 1-LVC closure. The 2-LVC closure takes approximately 6 minutes (versus 3 minutes for a 1-LVC) as demonstrated in our supplemental video. We do not think that postoperative outcomes are clinically significantly altered by this minor time difference. We included this in the discussion section in more detail (line 347-350)

12. Was vaginal length measured?

→ This was not examined in our study.

13. Was intercourse/ no intercourse reported for all patients?

→ Sexual activity unfortunately was not available for a large portion of the patient and hence was not utilized as a universal variable examined in this study (Line 336-337)

14. How cuff cellulitis was or was not confirmed needs stated.

→ This was included in line 185-189.

15. Was time to complication reported?

→ This question is difficult to answer without knowing which complication the reviewer is referring to. In our practice, patients are counseled extensively pre-operatively on symptoms of possible postoperative complications and are given details postoperative complications. If providers believe patients to be experiencing any postoperative complications, they are generally directed to present to the emergency room or the office immediately. Hence, patients are evaluated promptly without much delay from onset of a possible complication to the diagnosis.

Results:

1. Table one - the groups are different. Using the word "slightly" is not appropriate. The groups were statistically significantly different in regard to BMI, obesity and tobacco use. This needs to be stated and its effect on the study discussed.

→ The word was deleted. This was addressed by performing the uni- and multivariate analysis to account for this difference. We expanded on this in the discussion section (Lines 343-350).

2. Table 2 - as asked above, if cuff complications are left out of postop complications, was there any difference between groups? It appears not and in fact, VTE was higher in the 2-layer group. As above, this seem misleading and why not report postop complications and cuff complications separately?

→ Table 2 was restructured for ease of interpretation. Intraoperative complications and hospital/ER admission data was written in the text and the table meant to only focus on total postoperative complications. The primary outcome was total postoperative complications which included cuff and non-cuff related complications. We hypothesized that cuff complications would likely be the driving factor in difference in total postop complications, but we did not know whether utilizing a 2-LVC would impact other postoperative complication parameters such as infections, hematomas, VTE, or medical complications. Hence, we felt that it was important to demonstrate that there were no other post-operative parameters that changed as a result of utilizing a 2-LVC closure.

The reviewer is correct that it appears that the main driving factor for a significant change in the 2-layer closure is due to cuff complications rather than any other postop complications.

When we separate the cuff vs. non-cuff complications in a secondary analysis – cuff complications retain statistical significance between the groups ($p=0.04$) vs. non-cuff complications does not ($P=0.78$). This supports that a reduction in post-op complications is largely driven by changes in cuff complications.

3. How many women actually had exams at the time periods reported? If only the ones that presented with complications are being reported, another selection bias is present.

→ Routine postoperative examinations of the vaginal cuff in our practice are based on surgeon preference. Approximately half of the surgeons elect to routinely examine the vaginal cuff at the

postoperative visit while the rest do not. While the reviewer is correct that this could introduce a confounding factor, in our experience most cuff complications generally are not an asymptomatic event. If cuff dehiscence occurs, patients generally will present with bleeding or pain, and infections generally will have some degree of abnormal discharge, fever or pain that would trigger the patient to present for evaluation. In cases of complaints, all physicians in our practice perform a vaginal examination to be thorough in their evaluation.

4. Although the univariate and multivariate analysis account for the differences between groups, there still were differences (diabetes, obesity, and tobacco) that are recognized as risk factors for healing. This needs further addressed in the discussion and although statistically correct, clinically may be a different matter. .

→ This was further clarified in the discussion section (Line 342-350)

5. As under the M+M, was intercourse reported for all subjects? Time to intercourse? Is intercourse the issue and not closure technique? Partner size and vaginal length?

→ We clarified this in the methods section and addressed the other concerns above. Data for sexual activity unfortunately was incomplete and not available for a large portion of patients and hence could not be used as a reliable variable. Partner size and vaginal length information was also not available. Patients were instructed to refrain from intercourse for 8-12 weeks which is standard practice for most gynecologic surgeons.

6. What was the most common cause of ER/ hospitalization admission?

→ In our cohort, the most common reason for presentation was postoperative pain and nausea and vomiting, given that a majority of our cases are performed as outpatient surgeries. With the introduction of ERAS in our practice, these rates improved as previously reported (Peters, et al. AJOG 2019). Incision check was the next most common reason for evaluation in the ED.

7. Providing an idea of what is included in Medical NOS would be helpful.

→ This was detailed in figure 2. This term was used as an umbrella term to encompass any medical condition that did not fit into the other postoperative complication categories and occurred in the 30 postop periods (death (no cases occurred), TIA/stroke, arrhythmia, DKA, pneumonia).

Discussion:

1. The first paragraph needs reworked to state the conclusion clearly. As pertaining to several comments already made, if total postoperative complications were only significant due to cuff complications, this point needs clarified. Stating there were no differences in intraop complications and ER/hospital admissions but then state that postop satisfaction (not measured in this study) and health care costs (also no reported on) could be substantially lowered is conjecture and not conclusion.

→ The reviewer is correct that we did not specifically study postop satisfaction and health care cost in our study and that this statement is conjecture. The sentence was reworded (Line 282)

2. As the authors state, cuff complications are rare. Discuss why a case-control (2 or 3:1 match) was not chosen to study this.

→ Please see comment #1 in the Methods section of this reviewer's comments where we discussed this question.

3. Cost and time were not addressed and should not be part of the conclusion.

→ This point was addressed in Discussion point #1.

4. Intercourse was not reported for the 1-LVC group. All 16 who had cuff complications in the 1-LVC group were sexually active. As under the results, this needs discussed.

→ A statement about why sexual activity/intercourse was not reported as a variable was added in the discussion section (Line 315). Chart review of the 16 cases of dehiscence/mucosal separation did have data available regarding sexual activity, especially since all patients presented to the emergency room/office with complaints following their first episode of intercourse.

5. Selection bias needs discussed - why was one closure chosen over another?

→ This point was further addressed in the methods section to explain that this was not a selection bias for this study. Surgeons either universally performed a 1-LVC or a 2-LVC closure for all their patients. Surgeons did not decide whether to perform a 1-LVC vs. a 2-LVC closure based on the patients' risk factors or the appearance of the cuff at the time of surgery. (Line 161-163).

Reviewer #3:

The authors present a retrospective chart review in a large cohort of patients who underwent laparoscopic closure of the vaginal cuff with one versus two layers of suture, I have the following questions/comments:

1) Four MIS fellowship trained surgeons who perform more than 40 hysterectomies each per year accounted for 97.4% of all the surgeries in this retrospective study. In the discussion, recommend addressing potential biases associated with retrospective studies and applicability of results to the larger gyn community based on the number of providers included. Does fellowship training and individual surgeon outcomes impact the results of this study?

→ Hysterectomies included in this study were limited to MIGS trained surgeons at our institution to specifically focus on the cuff closure technique and to minimize others confounding factors such as high vs. low surgeon volumes (which have shown to favor high volume surgeons; Mowat, et al., AJOG 2016), surgical technique, uterine manipulator used, and colpotomy technique. An increasing number of general OB/GYN providers now feel comfortable suturing laparoscopically. A 2-LVC closure technique, as demonstrated in our supplemental video, is easy to learn. Furthermore, OB/GYN residents are now required to pass 'fundamentals of laparoscopic surgery' (FLS) training and hence should feel comfortable with the techniques demonstrated in the video.

In regard to individual surgeon outcomes, the cuff dehiscence rates in the 1-LVC closure were the same across the surgeons who utilized this closure technique and hence it is less likely that individual surgical skills among already highly trained MIGS surgeons contributes significantly. We added this data in the result section (Line 250-252) and discussion (Line 329-331).

2) Does use of a Pelosi uterine manipulator cup and 60 Watts energy potentially impact risk of vaginal cuff dehiscence? Would address in discussion section.

→ To our knowledge the use of coagulation vs. cutting energy for colpotomy use has been assessed in limited studies. Taskin et. al. 2019 EJOG examined the use of 35-40W cutting vs. coagulation current energy for colpotomy and did not find differences in dehiscence rates in a small RCT. The impact of electrosurgical energy on the tissue is difficult to study, as the amount of energy applied to the tissue is not only dependent on the power setting but also the duration of energy application to the tissue and the tissue thickness. The tissue effect can be variable,

even with identical settings. In terms of uterine manipulators, Van den Haak, et al. (2015 Arch Gynecol Obstet.) published a review that found no difference in safety between different manipulators. The Pelosi manipulator was used in this study as it is the standard manipulator used by the MIGS surgeon at our institution as they were all trained using this manipulator. Furthermore, our dehiscence rates for the 1-LVC closure are similar to those reported by other studies investigating dehiscence; thus, it is less likely that varying these two variables made a significant impact. This was added to the text (Line 352-365)

3) Is the average operative time available? A two layer closure versus one layer laparoscopic closure as outlined would have an impact on cost/utilization of resources which may be a consideration for providers with outcomes where differences are less than 2% depending on clinical significance (3.54 vs 5.62%)

→ Average operative times difference with respect to cuff closures were unfortunately not collected, but as mentioned to Reviewer #1 the use of a second layer cuff added only approximately 3 minutes to the procedure beyond a 1-LVC closure. The 2-LVC closure take approximately 6 minutes as demonstrated in our supplemental video. We do not think that postoperative outcomes are clinically significantly altered by this minor time difference. We included this in the discussion section in more detail (lines 299-303)

4) Smoking does impact wound healing, lines 183-185 indicate the group with 2 layer closure was less likely to smoke. The discussion mentions obesity cancels out smoking, but supplemental figure 1 indicates only 5 of the 16 patients with vaginal cuff complication were both smokers and obese. Please address the potential impact of this in the discussion section.

→ We adjusted the statement in the discussion section. We meant to imply that previous studies have shown smoking to be a factor that negatively impacts wound healing and in terms increases cuff dehiscence. On the other hand, a higher BMI has generally been found to be protective of cuff dehiscence, possible due to an increased estrogenic state which aids in cuff healing. We modified this statement in the text to better reflect this statement. (line 342-350).

5) Is mucosal separation a clinically significant outcome that would impact patient care compared to vaginal cuff dehiscence? Would address in discussion section

→ We included mucosal separation, which is defined as a non-full thickness separation of the vaginal cuff, as a clinically significant outcome in our study because 50% of the four cases of mucosal separation in the 1-LVC group required re-suturing of the cuff in the operating room. Mucosal separation was not meant to just represent the superficial epithelium which we agree would likely be less of a clinically significant patient care factor. We defined these factors more clearly in (Line 189-191).

STATISTICS EDITOR COMMENTS:

Lines 64-66, 160-164: There were actually two primary outcomes: total post-op and vaginal cuff complication rates, so the 2-sided alpha is incorrect, it should be 0.025 in order to test both hypotheses. Also, the sample required for the smaller rates (vaginal cuff complication) is larger. Therefore only the total complication rate retains statistical significance. (however see comments re: Table 2, which enables both primary complication rates to be retained as having stats significance).

→ The editor, as did some of the reviewers, point out that the primary outcome of the study may have been ambiguous. The primary outcomes of the study were total postoperative

complications. This included both 30 days non-cuff complications and 180-day vaginal cuff complications. The vaginal cuff complications are included in the “total” postoperative complications and were not selected as a second primary outcomes separate from postop complications. We further elaborated on this in the methods section to make it more clearly.

lines 186-187: The rates were similar for intraoperative complications, but the counts were small, limiting power and the study design was not powered to evaluate this factor. In any case, this is a secondary outcome.

→ We agree with the editors that the rates of intraoperative complications were small, likely in part due to high-volume surgeons performing the hysterectomies examined in this study. Hence, it would be difficult to obtain adequate power analysis to assess intraoperative complications as a primary outcome and hence it was selected as a secondary outcome. We chose to include the results in the study to demonstrate that there is no statistical difference between the one and two layer closure, which would be expected as a 1- vs. 2-layer closure should only impact postoperative complications rather than intraoperative complications.

This was better outlined in the methods section (Line 193-196).

Table 1: Need to enumerate any missing data, esp for BMI or obesity.

→ We added this in Table 1. We had no missing data for BMI/Obesity. 21 cases in total did not have any recorded information on tobacco use. Postmenopausal status was not known in 28 cases/n=2973). This data was added to Table 1.

Table 2: Need to clearly separate the primary from the secondary outcomes. Most of the components of post-op complications have small counts and there is insufficient power to generalize the NS findings. Should use Fisher's test for many of the comparisons. For example, for VTE 1:1759::4:1209, the p-value = 0.17, not 0.03, similarly for bladder complications, the correct p = 0.17. For comparison of cuff complication rates, the p-value should be < .01, since it is .002

→ This table was adjusted by our statistician as recommended by the reviewer using Fisher's exact tests. Previous analysis had only used patient with complications as denominator for analysis rather than the entire sample which we believe caused the confusion.

Table 3: Need to state the referent for age, BMI. I presume age is per year and BMI is per kg/m². Need to include the adjustors retained in the final aOR model. line 206: states that aOR = 0.38 for multivariate analysis using characteristic = vaginal cuff closure, but the text states 2-LVC closure as the characteristic. Need to clarify the outcome and characteristic. Should label the multivariate analysis as aOR, not OR. Immunosuppressant use clearly had some 0 entries for calculation of OR, so should just omit this entry.

→ Referent for age, BMI were added in Table 3. aOR label was modified. Immunosuppressant use was omitted. The table was revised to better reflect the referent for the model.

The reference for the vaginal cuff closure was indeed the 1-LVC closure hence the aOR =0.38 refers to the reduced OR of experiencing a cuff complication with a 2-LVC closure. We have adjusted Table 3 to better reflect this.