OBSTETRICS & GYNECOLOGY

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

Date: Jul 19, 2019
To: "Alexander Berger" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-1010

RE: Manuscript Number ONG-19-1010

Long-Term Risk of Reoperation after Synthetic Mesh Midurethral Sling Surgery for Stress Urinary Incontinence

Dear Dr. Berger:

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 Aug 09, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: Overall: This is a review of women who received mid-urethral mesh surgery from a single health care entity. The cohort comprised 17,030 women. Overall there are some typos. There are other similar papers in the literature for instance the two stated below. How this paper fits in with existing literature; there are other papers. The paper would be stronger if there was more detailed comparing and contrasting to existing literature than currently is present in the manuscript.
Giusto LL, Zahner PM, Goldman HB
Management of the Exposed or Perforated Midurethral Sling.
Urol Clin North Am (United States), Feb 2019, 46(1) p31-40

Kurkijarvi K, Aaltonen R, Gissler M, et al.
Reoperations for Female Stress Urinary Incontinence: A Finnish National Register Study [epub ahead of print]
Eur Urol Focus (Netherlands), Jun 10 2017,

Author Conflicts: The authors acknowledge support but conflicts are not reported on the title page.
IRB/Ethics statement is buried and easy to overlook. Please make the statement of research ethics approval more clear.

Use the Green Journal's writing guide to assist with writing a good discussion. edmgr.ovid.com/ong/accounts/guidetowriting.pdf

Overall - overuse of terms short-term, medium-term, and long-term. The paper would be stronger if the authors used specific numbers. The Dictionary definition of medium-term is niether long nor short.

There is very liberal use of acronyms which require a reader to frequently look back and remind themselves of the meanings.

ABSTRACT

The abstract should match the manuscript. What is the long-term "risk" the authors set out to find? A risk ratio, an incidence. There is inconsistency in the abstract and throughout the manuscript regarding the primary outcome and measurements.

INTRODUCTION:

1. Line 93: Be specific - what is "a small portion"?

2. Line 97: Please provide more specifics regarding the safety communication the FDA put out. Readers of the Green journal come from many obgyn types of practice.

3. Line 108: Who had the concerns and who do the authors expect will use the findings reported in this manuscript?

4. If the primary objective was "long-term" outcome then please provide the number of years. This will allow readers to understand how many years of data the authors would have to report the outcome.The aims are clearly stated

MATERIALS AND METHODS:

5. The first paragraph in the Methods section packs too much information in and thus important statements like study design and ethics approval are buried.

6. The eligibility criteria included women who had surgery from 2005-2016 - this means that there was only two years worth of data for "long-term" outcomes. Please consider making and defining categories.

7. Line 139: What was the "overall reoperation rate?" Total number of reoperations within the cohort? Total number after 9-years? How does the years of the cohort in this paper match the number of years included in other studies. The authors state that a short coming of existing data is the lack of data for outcomes longer than 9 years.

RESULTS:

8. Line 169: How does the median follow up of 4.4 years fit into your short/medium/longterm groups?

9. Line 174-176 seems to have some typos and is confusing.

10. Line 178: A rate needs a numerator and a denominator - what is the time period?

DISCUSSION:

11. Overall the discussion would be stronger with more comparing and contrasting with existing literature.

12. The discussion should be about ½ shorter than it is.

13. Line 229: Low "risk" of reoperation - risk or risk ratio? Or rate?

14. Line 237: Do the authors mean political like Washington DC? This is a general statement and this paragraph needs a topic sentence.

15. Lines 283-289 - these comparison are confusing. The authors suggest a risk of 3.7% in a US study (citation 24) had a risk of complication at 9-years higher than the authors - yet the authors reported proporition was 6%.

16. Line 299-302: Do surgeons in the UK receive less training in sling use? What data do you have that MUS is performed by high-volume surgeons? Is there data/literature comparing Mesh outcomes of high and low volume surgeons?

17. An important bias not discussed is lack of follow up or some women never reporting their complications because of a desire to avoid another procedure.

TABLES AND FIGURES

18. Overall the tables are too busy and hard to read.

19. What is the numerator and denominator of the "cumulative incidence"?

Reviewer #2: Thank you for the opportunity to review your manuscript entitled, "Long-Term Risk of Reoperation after Synthetic Mesh Midurethral Sling Surgery for Stress Urinary Incontinence." In this retrospective cohort study, you conclude that midurethral slings have a low long-term risk of reoperation for mesh revision/removal and recurrent urinary incontinence. Your study design is logical, your statistical analysis appears appropriate, and your conclusions are supporting well by your findings. I believe that this work contributes well to the literature about the safety and efficacy of the use of midurethral slings.

I do have the following questions:
1. Pg. 6, line 132-134. You indicate that you linked each patient's electronic, surgical, and implant records to create a record of primary MUS and reoperations and that you also included surgical implant logs with product names, product

numbers, and manufacturers.

Was a subset analysis performed to evaluate reoperation rates and other outcomes or complications by type and manufacturer / brand of MUS used? If you have this data, I recommend that you report it as it would be important information. If there was no difference between mesh types, manufacturers, or approaches to MUS, that too should be reported.

2. Pg. 15, line 318-319. Again you indicate that you examined women who received a wide range of MUS synthetic mesh implants and MUS approaches.

Again, the manuscript is absent further comment about whether or not the type of synthetic mesh had any impact on the primary or secondary outcome measures. This should be addressed in the manuscript.

Reviewer #3: This is a retrospective cohort study from an 11 year period within a large (median follow up 4.4 years), managed care organization investigating the long-term prevalence of reoperation among a population of women who have undergone a synthetic sling surgery for stress urinary incontinence. Thank you for allowing me to review this important paper.

Strengths

1* The size and scope of this study is rarely found in the literature (median follow up time 4.4 years which is very reasonable for an 11 year period), and only this volume and diversity of patients can really give us more accurate assessment of this clinical risk. The authors do review of individual records to validate data, which is rarely done in larger data studies.

2* Clearly stated aim which matches the primary outcome, and appropriate statistical analysis and correction is undertaken for the retrospective nature of the study (utilizing hazard ratios). Models with appropriately selected covariates for adjustment are performed.

3* Abstract and paper are well-written and clear regarding methods and interpretation.

Limitations

4* Retrospective database mining with CPT codes is not perfect, mostly for reasons that are not modifiable by the authors, such as inaccurate surgical coding. For example, some surgeons code a reoperation for a synthetic sling mesh exposure in the vagina where they do not remove part of the sling as a repair of a vaginal lesion as opposed to as a sling revision, and some would code that as a sling revision. Also, a sling revision could be excision of one fiber or a whole section/transection of the sling (no way to know from the code).

5* There needs to be more specific data and description of how the outcomes were assessed from the records, in particular provision of supplements that state the ICD 9/10 and CPT codes that correspond to the diagnosis and procedures searched by the authors (for both index surgery and reoperations), as well as the definitions used for complications other than reoperation. This is particularly important to define so that other large database studies can reproduce this trial design to validate the results in other settings/populations.

6* This study does a fair job assessing the prevalence of having A reoperation after a synthetic sling, but no way of accurately assessing the BURDEN of reoperation per individual after synthetic sling. In other words, in the Cox analyses, patients are censored once they have one reoperation for complications or stress incontinence, and if they had (say) 2-4 more operations after that synthetic sling to deal with complications or repeat symptoms. The authors DO address the issue of >1 surgery after synthetic sling (removal and then repeat SUI surgery) in the Results, but don't mention in the Methods they are going to do this.

Comments for the authors by section:

Introduction

7* Well outlines the extent of MUS use and its place in our surgical climate, as well as the need to accurately counsel women on true risks of reoperation with these materials over a longer term.

8* Line 105: It may be more diplomatic to say "several companies that formerly supplied…." and not list them specifically, as these companies have not historically enjoyed having clinicians assume or even state why they exited this space.

9* Line 109-111: Clearly stated objective that matches primary outcome, but it may be better to state that the main objective was reoperation for EITHER complications (safety) or persistent or recurrent stress incontinence (efficacy), as you study BOTH and the primary outcome is the OVERALL reoperation rate.

10* Line 111: Please state a hypotheses regarding both safety and efficacy outcomes just stated.

Methods

11* Line 128: "almost exclusively all" is a sort of awkward phrase; perhaps "receive nearly all their healthcare…" instead?

12* Line 132-137: Inclusion criteria and methods of search are clear. You may want to specify here that the INDEX (first surgery) for stress incontinence had to be a synthetic sling. In other words, if a woman had a Burch or a fascial sling (on or after 2005) and then later (before 2016) they ended up getting a mid-urethral synthetic sling for recurrent/persistent stress incontinence, I assume that individual would not be considered part of your study population, am I correct?

13* Line 134-135: Please provide a supplement that lists the particular products that you considered synthetic slings, and how these were sorted into RMUS, TOT, and SIS as per the breakdown in the results and tables below. As the authors did an individual review of the records, it should not be hard to list the products implanted in the index surgeries of the study patients. I ask for this because it helps to give our readers an idea of how many of the products being studied here are actually no longer commercially available, both underscoring the points made by the authors in the introduction about companies leaving this space and so the reader can attached appropriate external validity to their patients using a different range of products now.

14* Line 135: Please provide a supplement that lists the particular ICD 9/10 codes used in the search that indicated the placement of a sling to the authors. For CPT codes searched, was only 57288 code used or were other codes screened to see if the surgeon perhaps incorrectly coded a synthetic sling for incontinence an aberrant way?

15* Line 141-143: Again, please supply the ICD 9/10 codes that you considered to correspond to these diagnoses and the CPT code (or codes if you used more than CPT 57287) that you included or considered legitimate for a reoperation for complications. You can include these as supplemental Tables and reference them here, but you have to be very specific.

16* Line 145-146: Same request: provide a Table of the CPT codes for these procedures you considered legitimate and reference that Table here.

17* Line 147-149: In what time frame after the surgery were these assessed? Any time in the study period. For some of these complications, like recurrent UTI or de novo urgency, it makes sense to collect them from as far from the index surgery as you have data, but a UTI 10 years after a sling seems a bit meaningless in the context of assessing safety of a former sling. What were your criteria for "UTI" as a complication (non-recurrent)? In what time frame after the surgery? In line 202 below, you clarify that you were interested in UTIs within 1 year, but that seems a little far away from the surgery to be blaming the surgery exclusively.

18* Line 151-158: Appropriate survival analysis with hazard ratios generated.

19* Line 151-158: Just curious….was there any secondary analyses regarding if patients had TWO or THREE surgeries in the follow up period after the index synthetic sling. If, for example, a patient got a revision for mesh exposure, had persistent or repeat mesh exposure, and then later had to get sling removed, and then LATER had to get repeat stress incontinence procedure (all very possible in an 11 year period!), then was this accounted for somehow IN THE SURVIVAL ANALYSIS? Or would the patient just be censored when they got the first of the 3 follow-up procedures as a "complication" reoperation and then no more analysis of that patient? I see in line 207-210 below you address the 2-3 surgeries after synthetic sling issue, but I assume that has no impact on the HR analyses.

20* Figure: In the Flow Chart it is indicated that n=119 patients did not have demographic information and were excluded. How much demographic information had to be missing for them to be excluded? And why, in this large managed care organization, would demographics be missing? It is amazing to me that someone could have a surgery and be insured for that surgery with the same organization and not have, say, any information on their age, race, etc. You cannot get Kaiser insurance without offering this information, so perhaps were these patients under a special security protection that the authors could not access their information?

Results

21* Line 168-176: The median follow up of 4.4 years seems very reasonable for an 11 year span of synthetic sling follow up. As there is follow up bias to reoperation (people less likely to need reoperation don't necessarily follow up for a long time), is there any data available on the number of patients for whom data out to 9 years was present? Was there any patient characteristic(s) associated with length of follow up? (I ask because it may be that the characteristics of patients getting slings changed from 2005-2016, so there may be bias to the type of patients with longer follow up in this large population). This should be analyzed and discussed, at the very least comparing characteristics of 5 year patients to 9 year patients that generate the two hazard ratios discussed in line 179.

22* Line 192: "reoperation" typo

23* Line 195: I don't really feel that I know what "cystourethroplasty" means in this context. For that one patient, how did the surgeon define this procedure? Technically, many of the other procedures for stress incontinence listed here could be called cystourethroplasties (including slings!), although I admit the terminology is poorly regulated in most databases.

24* Line 198: I think you mean to say that the "prevalence of reoperation for recurrent SUI was 9.8%". Is that correct? If so, please clarify that.

25* Line 199-200: Please put "%" sign after numbers here, so the readers know these are percentiles of patients having this occur as opposed to time to occurrence or some other unit (like time to reoperation or rate per 1000, etc). If you fear confusion with the "95% CI", I assure you the readers will figure it out.

26* Line 202-205: Do you change here from discussing UTIs within a year of surgery to discussing de novo urgency ANYTIME after the surgery? If so, this could confuse readers. Clarify the time frame of surveillance you are indicating.

27* Line 207-210: Now I see you are addressing the "repeat repeat surgery" issue; you may want to add in the Methods that you were planning this analysis so the reader knows it was done.

Discussion

28* Line 229-230: This is where it is useful to say the number of the 9 year population, so the readers know how good that follow up actually was.

29* Line 237-281: This could be shortened a lot. I see the agenda that the authors are trying to put forth (slings work well and are not as high risk as other SUI procedures), and I think the readers can see this point and be convinced without rehashing quite this much SUI surgical history.

30* Line 285-291: Please put into context how large these studies were and if the follow up was as extensive and exclusive as in a Kaiser setting. This helps for comparison to the present study.

31* Line 300: I would be cautious about criticizing an entire country's worth of sling surgeons in this paper....lots of readers of this journal in the UK! It may be that the time frame of this study was happening when more surgeons are more frequently placing slings, so the former studies (from anywhere!) reflect a more trained population of surgeons worldwide, as opposed to the present study's setting versus the UK or Canada.

32* Line 304-317: The authors perform a good discussion of the limitations; the one thing I would suggest adding is the fact that the Cox proportional hazard only accounts for the first reoperation (survival analysis), and cannot account for the BURDEN of reoperation (patients that get 2-4 operations after their synthetic sling like revision, then removal, then repeat SUI, etc).

STATISTICAL EDITOR'S COMMENTS:

1. lines 151-153, Table 1: This is a large series, but the population studied was within a managed care system with follow-up ranging up to more than 10 years. For example, although > 15K women were at risk for > 1 year, only 7.5K were at risk for > 5 years. Need to inform the reader as to the number of women who left the managed care within 1, 5 or 9 years of their initial operation. If there were a large fraction of turnover, then there would be greater potential for selection bias of incidence of re-operation or other complications among those remaining within the system. Then, the reported hazard rate ratios could be inaccurate. This requires more data, more analysis and potentially, a much stronger statement re: limitations than currently in lines 304-307.

2. Lines 156-157: Were the re-operation counts vs time tested as to whether they conformed to the model's assumption of proportional hazards, rather than some other distribution of outcomes? Need to provide such analysis.

3. Tables: Need to state units for age and BMI. The study has large samples, but some subsets are relatively small (eg, age > 80 or Asian/Pacific ethnicity. For those specific subsets, the counts of re-operation are still smaller. The use of adjusted HR with 10 variables likely results in over fitting. Thus, the aHR for Asian/Pacific re-operation rates is likely imprecise and may not be replicable. This problem is compounded for the re-operation for mesh revision/removal since the risks are much smaller (generally < 1%) and the chances of over fitting much greater.

4. General: The Wald chi-square test used in the Tables is a test for all categories compared to the referent, so it is only applicable to a particular subset when there is only one subset being compared to the referent. So, the p = .04 in Table 1 is comparing all other ethnicities vs the White referent, not specifically to the Asian/Pacific cohort. Likewise the p = .03 in Table 3 does not specifically refer to the SIS cohort, but rather whether TOT and SIS collectively differ from RMUS.

5. The other issue with the Tables is the number of comparisons made, with no adjustment for multiple hypothesis testing. Likely the few significant associations could be due to chance alone when testing 19 comparisons at p < .05 level. There is

~ 62% risk that at least one comparison out of 19 would have p < .05

6. Therefore, need to modify lines 58-59 and 62-64 in Abstract and lines 195-197, first, regarding misuse of the p-values and second, because of potential for over fitting in the case of Asian/Pacific ethnicity.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:
A. OPT-IN: Yes, please publish my point-by-point response letter.
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2. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

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

3. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric and gynecology data definitions at https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

4. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: 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.

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

6. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

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* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.
* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

7. Provide a 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."

8. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows:

Original Research articles, 300 words. Please provide a word count.

9. 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.

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11. 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%").

12. 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.

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* A point-by-point response to each of the received comments in this letter.

If you submit a revision, we will assume that it has been developed in consultation with your co-authors and that each author has given approval to the final form of the revision.

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Aug 09, 2019, we will assume you wish to withdraw the manuscript from further consideration.

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The Editors of Obstetrics & Gynecology

2018 IMPACT FACTOR: 4.965
2018 IMPACT FACTOR RANKING: 7th out of 83 ob/gyn journals

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