OBSTETRICS & GYNECOLOGY

NOTICE: This document contains correspondence generated during peer review and subsequent revisions but before transmittal to production for composition and copyediting:

- 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: Dec 20, 2019
To: "Valerie Zaphiratos" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-2169

RE: Manuscript Number ONG-19-2169

Uterine Exteriorization Versus in Situ Repair for Elective Cesarean Delivery under Spinal Anesthesia using a Phenylephrine Infusion; a Randomized Controlled Trial

Dear Dr. Zaphiratos:

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 Jan 10, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: The purpose of this study was to compare the effect of exteriorized versus in situ uterine repair on intraoperative nausea and vomiting (IONV) during elective cesarean delivery under spinal anesthesia. It was hypothesized that in situ repair would cause less maternal discomfort as reflected by the frequency and severity of maternal nausea and vomiting intraoperatively. This study was a prospective, randomized, controlled, double-blinded trial with appropriate inclusion and exclusion criteria. The frequency of excluded after randomization subjects was similar in each group and did not raise black flags of concern. The primary outcome of the study was intraoperative nausea and vomiting. The authors appropriately evaluated other outcomes (blood loss, operative time) purported to be influenced by in situ repair. The statistical analysis appears appropriate. The tables and figures were appropriate and complimented the Methods and Results nicely. The results clearly demonstrated a reduction of nausea and vomiting intraoperatively by in situ repair without a concomitant increase in operative time or blood loss. The authors did note an increased need for peritoneal irrigation in the in situ group. They did not say whether they packed the gutters before the repair. The tradeoff might be increased nausea and vomiting if that was done, but one could argue that with more bleeding into the abdomen, there might be more adhesive disease that might occur with potential future ramifications. I think that the authors might want to comment about this potential issue. The authors conclude that exteriorization of the uterus for surgical repair during CD under spinal anesthesia associated with intravenous phenylephrine infusion is associated with a higher incidence and intensity of IONV, an increased incidence of tachycardia and hypotension requiring more interventions with phenylephrine boluses compared to in situ uterine repair. In this regard, the authors are guilty of a common error, in my opinion. A restating of the results is not a conclusion. What do the authors conclude? It seems obvious that the authors think that in situ repair is preferable to exteriorization and that, perhaps, it is time for a change. Why not say it?

Reviewer #2:

1) The study is a randomized double-blinded controlled trial comparing the effect that uterine exteriorization versus in-situ hysterotomy repair has on the incidence and severity of intraoperative nausea and vomiting (IONV) during elective cesarean section.

2) The study notes that fourteen staff Obstetricians participated in the study and all were (obviously) unblinded to the technique of uterine repair (Lines 245, 294-295). Information regarding these Obstetrician's unique and customary practice regarding uterine exteriorization (i.e., do they normally exteriorize the uterus to close the hysterotomy) is recommended in order to assist the reader in the interpretation of the results.

3) Hysterotomy closure techniques (suture choice, one-layer vs two layer, etc.), use of irrigation, bladder flap creation,

etc., are also widely variable and could clearly affect the results of this study. Given that the Obstetricians were unblinded, commentary on why these variables were not addressed or commented on is needed.

4) Previous studies clearly suggest that the uterus should be exteriorized during repair. This technique reportedly allows for better visualization and use of less suture without increasing blood loss, intraoperative nausea or pain, or rates of endometritis (Manuscript references 4,6,7; Lines 449, 455, 458). Although the authors discussed these studies (Lines 337-344), additional commentary regarding these studies and whether study design alone was responsible for these seemingly disparate results is warranted.

5) The authors mentioned peritoneal irrigation as a risk factor for IONV and references prior studies showing this effect during cesarean section (Lines 404-408). Notwithstanding, the current study reported a statistically significant reduction in IONV in the in-situ repair group despite an increased trend in peritoneal irrigation used on these patients. Although this trend was not statistically significant, this finding is nonetheless perplexing and underscores the need for all other portions of the Cesarean section to be standardized whenever possible.

Reviewer #3: This paper presents an RCT of exteriorization vs in situ repair with a primary outcome of maternal symptoms - post delivery intraoperative nausea/vomiting. Overall, I am very happy to read a paper where the primary outcome is a maternal experience outcome, and not EBL/QBL/Hb difference.

Introduction - well written - nicely motivated. A question - is there any data on the frequency of in situ vs exteriorized closures in a typical obstetric hospital? does teaching vs non teaching hospital matter, for instance, or other patient characteristics

Methods

1-line 195 - I will defer to the editors but do you think this truly counts as a double blinded trial, as the providers doing the surgery knew whether the uterus was in situ/exteriorized, as did the attending anesthesiologist? I agree the patient was blinded, as was the data collector, and I do think the results are valid, but not sure about using the terminology of "double blinded"

2-paragraph starting with line 228, BP assessment. is it standard to define hypotension as more than 20% away from the baseline MAP, and that this is the treatment threshold? Can you elaborate further why this was chosen and what this means?

3-paragraph starting with line 237. I could use some clarity as this is your primary outcome. Initially when I read this I thought, why are 4 of the 5 time points for determining intraoperative nausea not occurring at the time that the uterus could be either in situ or exteriorized? Then I see that ultimately, you defined you primary outcome using answers at 2 of these 5 time points. Why was done this way? Was it so that the patient wasn't primed to say yes/no at the actual time point you cared about? I would group the description of this variable with how you used it for your primary outcome in the same paragraph, for clarity. Also, I would move the sentences about blinding out of this paragraph - this information felt misplaced after learning about your primary outcome.

4-IONV scale - is this validated? Can you mention briefly something about its use either here, what this scale means, etc?

Results

5-consider presenting your Hb results in grams/deciliter

6-I am curious why you present the data on peritoneal irrigation. I did not expect this as you did not mention this as a secondary outcome in the methods section, and I am also not sure what it signifies and how it relates to the intervention. To me, it represents the "typical" practice of an obstetrician when closing in a prespecified way, rather than responsive to the clinical situation. Also, I am not sure how this may have affected the primary outcome - depends on how much manipulation/moving of bowels you do (which would cause n/v) - some people barely pour a little fluid in the belly, whereas others extensively irrigate/clear gutters/manipulate bowel. I am not sure what this variable means, even if it is nonsignificant, and would love some context about how peritoneal irrigation was performed, if it was standardized, etc, if you are reporting this data.

Discussion

7-lines 344-347 - this is stylistic but I would present the order of your results in a parallel fashion. Either present the result for in situ first for both outcomes, or exteriorization first for both outcomes, but not one of each. The direction of your findings is the same, but the way it is presented, if you are reading quickly, you may think incidence of IONV goes down with in situ repair but severity goes up.

8-lines 351-352 - from your introduction, I presumed that the use of phenylephrine for all patients would have overall decreased the incidence of n/v (due to decreasing incidence of hypotension overall), even if there is a relative difference

between in situ and exteriorization groups, but from the data you present in these lines, it does not appear that way. Essentially almost the same findings as you have. Are you surprised? Can you comment on this if so ?

9-as I previously said, not sure why the 80% of MAP threshold was chosen, and this still does not make sense to me with this discussion. I understand this is the literature threshold but is this what practitioners are clinically using as treatment thresholds? Are proportions of baseline MAPs commonly calculated in the OR? Would you consider a secondary analysis calculating incidence of hypotension using a MAP threshold?

10-I am curious why you did not include women with unscheduled CD and what you think your findings would mean for these women. This is worth discussing, as most women having CD are unscheduled, they are the ones at "risk" of PPH (more than scheduled CD), but if there is benefit to leaving in situ, then this is the largest population of women who stand to be affected

11-the duration of surgery is impressive and I suspect will pose an issue with generalizability. The fact that these were on average <30 minute repeat cesarean deliveries suggest it is a highly efficient team with an attending primary surgeon and a trained primary assistant - as against a learning environment in which either the surgeon or the assistant is learning. In such cases, the argument exists for exteriorization, as limited experience slows down the exposure and poses concern for increased bleeding/Hb drop. Although I know your paper argues against this perspective, I am not sure it is applicable in all settings. Can you discuss this in your discussion section? You did mention this as a point in the introduction, so I believe the loop should be closed here.

12-one point you could make is that with less IONV/less discomfort, more women will be able to accomplish intraoperative skin to skin, which is important for new mothers and also beneficial to the baby (golden hour!)

13--lines 387-389 - I would say the larger argument for fewer interventions for hypotension is that women are likely to feel better, rather than unwell during their CD! Not decreasing the workload for the anesthesiology provider

14--lines 410-413 - if there is peritoneal irrigation, it is done after the closure of the hysterectomy to clear clots that are in the abdomen, since the blood had nowhere to go but intraabdominally in an in situ closure. It is unrelated to the exposure of the hysterectomy due to an in situ closure. Please revise this statement as I do not believe it is accurate. As I said earlier, I suspect this is surgeon preference

STATISTICAL EDITOR'S COMMENTS:

1. Abstract:Should conform to our RCT template.

2. Lines 118-120, 269-275, Table 2: The primary outcome (any none zero IONV score) should be clearly separated from all others. The others cited in Table 2 are all secondary outcomes. Should make consistent the rates of non-zero IONV (40 vs 21% in Table 2 and 40 vs 20 % in Abstract and 40.2% and 20.5% on lines 298-300. Given the sample sizes, the %s should be rounded to nearest integer %, not cited to nearest 0.1%. Therefore should consistently be cited as 40% and 21%.

3. lines 249-251: Should clarify how many times the nausea scale was applied (from the time point "beginning of uterine repair" and onward) and presumably, the score used was the highest.

4. Table 1: Since the groups were randomized, no need to compare the baseline characteristics with stats. Any difference is thought to be due to random chance.

5. Table 3: Should round the %s to nearest integer %. Why is there no p-value for the comparison of rates of reactive hypertension?

6. Table 4: Should round the % for endometritis to nearest integer % and include the p-value for comparing those rates.

Fig 2: Should clarify what groups are being compared with the * s and what significant differences are being applied.

Reviewer #4: The authors present their randomized controlled trial in which they compare the impact of uterine exteriorization vs in situ repair at the time of cesarean section on intraoperative nausea and vomiting as well as hypotension. They note that the patients in their study were undergoing elective cesarean delivery, and had spinal anesthesia as well as a phenylephrine infusion.

The following items should be addressed:

1. Abstract line 118-119 - the way these data are presented is confusing; it is not clear what the two comparison groups are in this context. Consider removing this comparison from the abstract and keeping it only within the text.

2. Methods - is the described phenylephrine infusion standard for cesarean sections at your institution? The reference

provided describes calculation of medication doses, but is not specific to the use of this medication in patients with spinal anesthesia. This is not a standard part of management at the time of cesarean in the US, and therefore it would be helpful to provide more context.

3. Methods - please describe the randomization scheme in more detail. Was the randomization done in blocks? How did the computer generate the randomization? Was there any differentiation by provider? Who was responsible for notifying the surgeon of the allocation, given that the study data collector and patient were blinded to the allocation?

4. Results and table 1 - how many prior cesarean sections did the patients with repeat cesarean have? Was there any notation of severity of adhesive disease among the participants? What about presence or absence of fibroids, or uterine anomalies, as these could also impact the amount of uterine manipulation required in exteriorization?

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

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. Clinical trials submitted to the journal as of July 1, 2018, must include a data sharing statement. The statement should indicate 1) whether individual deidentified participant data (including data dictionaries) will be shared; 2) what data in particular will be shared; 3) whether additional, related documents will be available (eg, study protocol, statistical analysis plan, etc.); 4) when the data will become available and for how long; and 5) by what access criteria data will be shared (including with whom, for what types of analyses, and by what mechanism). Responses to the five bullet points should be provided in a box at the end of the article (after the References section).

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

5. 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.

6. 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.

7. 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).

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. Abstracts for all randomized, controlled trials should be structured according to the journal's standard format. The Methods section should include the primary outcome and sample size justification. The Results section should begin with the dates of enrollment to the study, a description of demographics, and the primary outcome analysis. Please review the sample abstract that is located online here: http://edmgr.ovid.com/ong/accounts/sampleabstract_RCT.pdf. Please edit your abstract as needed.

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. 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 on the other hand, 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. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at http://links.lww.com/LWW-ES/A48. The cost for publishing an article as open access can be found at http://edmgr.ovid.com/acd/accounts/ifauth.htm.

Please note that if your article is accepted, you will receive an email from the editorial office asking you to choose a publication route (traditional or open access). Please keep an eye out for that future email and be sure to respond to it promptly.

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If you choose to revise your manuscript, please submit your revision through Editorial Manager at http://ong.editorialmanager.com. Your manuscript should be uploaded in a word processing format such as Microsoft Word. Your revision's cover letter should include the following:

* A confirmation that you have read the Instructions for Authors (http://edmgr.ovid.com/ong/accounts/authors.pdf), and
* A point-by-point response to each of the received comments in this letter.

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 Jan 10, 2020, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

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

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Hôpital Maisonneuve-Rosemont
Centre affilié à l'Université de Montréal

January 17th, 2020

Dr Nancy C. Chescheir, MD
Editor-in-Chief
Obstetrics & Gynecology

Dear Dr Chescheir,

We are pleased to submit our revised manuscript **"Exteriorization Versus in Situ Repair using a Phenylephrine Infusion; a Randomized Controlled Trial"** for consideration for publication as an original research article. (ClinicalTrial.gov, NCT02587013)

During cesarean delivery, the uterus can either be repaired in situ within the peritoneal cavity, or exteriorized from the abdomen. These two approaches have been studied with multiple RCTs and meta-analyses, but neither has been deemed clearly superior. Exteriorization has been reported as a risk factor for intraoperative nausea and vomiting (IONV) and the anesthetic technique can greatly influence its incidence. There is a paucity of literature addressing the issue with a standardized anesthetic technique and none with a phenylephrine infusion. Our objective was to compare the effect of exteriorized versus in situ uterine repair on maternal morbidities during elective cesarean delivery under spinal anesthesia with a phenylephrine infusion.

We conducted a double blind randomized controlled trial in 180 women undergoing elective cesarean delivery with a standardized anesthetic technique that included a phenylephrine infusion and a blood pressure management protocol. After approval by the Maisonneuve-Rosemont Hospital Research Center's Institutional Review Board (IRB #15056) and with written informed consent, patients were randomized to exteriorization or in situ uterine repair. Incidence of postdelivery IONV was significantly decreased in the in situ group compared to the exteriorization group (21% vs 40%; P = 0.01). The intensity of the IONV and the phenylephrine boluses requirements were also significantly increased in the exteriorization group. The duration of surgery, blood loss and postop hemoglobin were similar between both groups.

This study is the first double blind trial comparing both surgical techniques with a standardized anesthetic protocol that included a phenylephrine infusion. The findings strongly suggest that in situ uterine repair should be the uterine repair technique of choice by Obstetricians in elective cesarean section to minimize the maternal morbidities of nausea and vomiting and hemodynamic changes.

All of the authors certify that they will take public responsibility for the contents and have approved the final version. None of the authors has any conflicts of interest with the contents. This study was approved by Maisonneuve-Rosemont Hospital Research Committee and all of the authors attest that all applicable subject protection guidelines and regulations were followed in the conduct of this research. The work has not been published and is not under consideration elsewhere and does not duplicate other published work. However, some of the data from this work has been presented as an oral presentation in the Gertie Marx Research Competition at the 2019 SOAP 51st Annual Meeting in Phoenix, Arizona on May 2nd 2019.

[redacted]

Hôpital Maisonneuve-Rosemont
Centre affilié à l'Université de Montréal

The lead author affirms that she has read the Instructions for Author and this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained. The corresponding author attests to registering the trial and that the protocol reported to *Obstetrics & Gynecology* is identical to the posted trial.

Should this manuscript be accepted, we also agree that the editors and the publisher have the right to edit the manuscript and to modify it to comply with the *Obstetrics & Gynecology* standard punctuation, grammar and sentence structure. We will have the opportunity review final page proofs, and to insert corrections prior to publication, with the exception of published letters.

Finally, we accept that the corresponding author will be the sole author of further communication with the editorial office related to this manuscript, including any and all revisions, and he/she will have the authority to communicate on behalf of all authors in regards to further correspondence with the Editor and, if accepted, the publisher.

Thank you for reconsidering our manuscript and the reviewers' comments from December 20th 2019. We have carefully reviewed the comments and have revised the manuscript accordingly. Our point-by-point responses to each of the received comments are included below. Changes to the manuscript are shown in Track-changes. If you require further information, please do not hesitate to contact us.

Regards,

Danny Mireault, MD
Ste-Justine Hospital

Valerie Zaphiratos, MD, MSc
Maisonneuve-Rosemont Hospital

Philippe Richebé, MD, PhD
Maisonneuve-Rosemont Hospital

Pierre Drolet, MD
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Laurent Tordjman, MD
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Christian Loubert, MD
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Nadia Godin, RN
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[redacted]

Hôpital Maisonneuve-Rosemont
Centre affilié à l'Université de Montréal

REVIEWER COMMENTS:

Reviewer #1: The purpose of this study was to compare the effect of exteriorized versus in situ uterine repair on intraoperative nausea and vomiting (IONV) during elective cesarean delivery under spinal anesthesia. It was hypothesized that in situ repair would cause less maternal discomfort as reflected by the frequency and severity of maternal nausea and vomiting intraoperatively. This study was a prospective, randomized, controlled, double-blinded trial with appropriate inclusion and exclusion criteria. The frequency of excluded after randomization subjects was similar in each group and did not raise black flags of concern. The primary outcome of the study was intraoperative nausea and vomiting. The authors appropriately evaluated other outcomes (blood loss, operative time) purported to be influenced by in situ repair. The statistical analysis appears appropriate. The tables and figures were appropriate and complimented the Methods and Results nicely. The results
clearly demonstrated a reduction of nausea and vomiting intraoperatively by in situ repair without a concomitant increase in operative time or blood loss. The authors did note an increased need for peritoneal irrigation in the in situ group. They did not say whether they packed the gutters before the repair. The tradeoff might be increased nausea and vomiting if that was done, but one could argue that with more bleeding into the abdomen, there might be more adhesive disease that might occur with potential future ramifications. I think that the authors might want to comment about this potential issue. The authors conclude that exteriorization of the uterus for surgical repair during CD under spinal anesthesia associated with intravenous phenylephrine infusion is associated with a higher incidence and intensity of IONV, an increased incidence of tachycardia and hypotension requiring more interventions with phenylephrine boluses compared to in situ uterine repair. In this
regard, the authors are guilty of a common error, in my opinion. A restating of the results is not a conclusion. What do the authors conclude? It seems obvious that the authors think that in situ repair is preferable to exteriorization and that, perhaps, it is time for a change. Why not say it?

R: Thank you for your comments.

Peritoneal irrigation was a secondary outcome in our study, and we have modified the paragraph in our Methods to clarify this. We took note of this outcome on the suggestion of our Obstetrician (LT) because there are studies that report that peritoneal irrigation increases the risk of nausea and we wanted to ensure this was not a confounder. Although there were more patients who had peritoneal irrigation in the in situ group, this result is not significant with a p = 0.06. What is interesting is that the in situ group had statistically significant less nausea, despite having (non-significantly) more peritoneal irrigation. This increases the credibility of the fact that the increased nausea/vomiting in the exteriorization group is not due to peritoneal irrigation.

Moreover, it is not common practice for our Obstetricians to routinely pack the gutters. The Pelosi technique was the most common surgical approach; although there is some variability between obstetricians. We did not protocolize the surgical technique other than uterine repair (exteriorization vs in situ).

We did not find any evidence that there is more bleeding in the abdomen with either uterine closure technique since both the estimated intraoperative blood loss and the postoperative reduction in hemoglobin did not show a significant difference between groups, arguing against significant amounts of concealed blood that could increase future intraabdominal adhesions.

We have added this sentence at the end of our article as the Conclusion: "In situ uterine repair minimizes intraoperative maternal morbidity for elective CD and should be the preferred technique for uterine repair."

Reviewer #2:

1) The study is a randomized double-blinded controlled trial comparing the effect that uterine exteriorization versus in-situ hysterotomy repair has on the incidence and severity of intraoperative nausea and vomiting (IONV) during elective cesarean section.

2) The study notes that fourteen staff Obstetricians participated in the study and all were (obviously) unblinded to the technique of uterine repair (Lines 245, 294-295). Information regarding these Obstetrician's unique and customary practice regarding uterine exteriorization (i.e., do they normally exteriorize the uterus to close the hysterotomy) is recommended in order to assist the reader in the interpretation of the results.

R: Thank you for this point. It is important to understand the context at our center.

Although there is variability, the customary practice at our center for most obstetricians was to exteriorize the uterus prior to this study. Only two obstetricians would regularly use the in situ technique for the majority of their patients. However, only willing obstetricians proficient with both techniques participated in the study.

We added this sentence in the Methods section: "Although there is variability, the customary practice at our center is for most obstetricians to exteriorize the uterus."

3) Hysterotomy closure techniques (suture choice, one-layer vs two layer, etc.), use of irrigation, bladder flap creation, etc., are also widely variable and could clearly affect the results of this study. Given that the Obstetricians were unblinded, commentary on why these variables were not addressed or commented on is needed.

R: Although there is variability between obstetricians, we did not protocolize the surgical technique other than uterine repair. The most common surgical approach was the Pelosi, whereas the sutures choices and "the one-layer versus two-layer" hysterotomy closures are homogeneous. If the patient is a potential candidate for a VBAC, the two-layer technique is used, otherwise a one-layer technique is used. Bladder flap creation (which we understand this to mean separating the uterus from the bladder) is standard practice among all the surgeons in the study.

Among the technical surgical factors that you mention, only irrigation has been described as a potential risk factor for nausea and vomiting. The other factors (closure technique including suture choice, one vs two layer technique, bladder flap creation) have not been described as risk factors for nausea and vomiting in the literature, specifically the 16 RCT studies that looked at these outcomes included in the most recently published meta-analysis (Zaphiratos et al. 2016, reference 6). However, these factors may play a role in the duration of the procedure, and this outcome was not statistically significant between groups.

4) Previous studies clearly suggest that the uterus should be exteriorized during repair. This technique reportedly allows for better visualization and use of less suture without increasing blood loss, intraoperative nausea or pain, or rates of endometritis (Manuscript references 4,6,7; Lines 449, 455, 458). Although the authors discussed these studies (Lines 337-344), additional commentary regarding these studies and whether study design alone was responsible for these seemingly disparate results is warranted.

R: In our text, we describe what the proponents of uterine exteriorization describe as advantages. When looking at all published meta-analyses, including the most recent one (Zaphiratos et al. 2016, reference 6) which includes 16 RCT studies, they do not suggest the superiority of one technique over the other, and specifically not for the outcome of IONV. Study design greatly influences the results, especially our primary outcome of IONV. Having a heterogenous patient population that includes a mix of elective and urgent cesarean deliveries cannot be compared for IONV because there are too many confounding factors such as use of IV fluids, antiemetics, different comorbidities, length of labor, labour augmentation, urgency of procedure, etc. Moreover, the lack of a precise anesthetic protocol will also greatly influence the incidence of IONV by maintaining different blood pressure targets, using different vasopressors, opioid doses, and neuraxial block level and technique (epidural vs spinal anesthetic).

In the introduction, we describe that only one RCT (Siddiqui et al. 2007, reference 11) has evaluated nausea and vomiting as a primary outcome, and their study determined that exteriorization causes significantly more nausea and vomiting than in situ repair. Only 5 RCTs out of the 16 in the most recent meta-analysis reported nausea and vomiting as a secondary outcome, and the way it was reported was variable. What we see clinically, as anesthesiologists, is that exteriorization seems to increase the risk of nausea and vomiting, and this has been poorly studied in the literature. We have modified our paragraph as follows:

"To date, only five randomized controlled trials comparing uterine exteriorization versus in situ repair evaluated nausea and vomiting as an outcome. Of these, only one reported nausea and vomiting as a primary outcome with a standardized anesthetic technique. Their results demonstrated that uterine exteriorization significantly increases the risk of nausea and vomiting compared to in situ repair.(1) However, none of the past studies have used a standardized phenylephrine infusion for cesarean delivery under spinal anesthetic. A phenylephrine infusion has been shown to decrease the risk of hypotension and nausea when using a spinal anesthetic for caesarean delivery."

5) The authors mentioned peritoneal irrigation as a risk factor for IONV and references prior studies showing this effect during cesarean section (Lines 404-408). Notwithstanding, the current study reported a statistically significant reduction in IONV in the in-situ repair group despite an increased trend in peritoneal irrigation used on these patients. Although this trend was not statistically significant, this finding is nonetheless perplexing and underscores the need for all other portions of the Cesarean section to be standardized whenever possible.

R: Although there is some variability between obstetricians, we did not protocolize the surgical technique other than uterine repair. As we have mentioned in comment #3, the practice is quite homogeneous and therefore should not have influenced the results.

In prior studies, irrigation has been shown to increase the incidence of nausea and vomiting, as we describe in our manuscript. Other surgical portions of cesarean delivery, such as sutures and one or two layer closure has not been reported as a risk factor for nausea and vomiting in the literature. In our study, we took note of irrigation as a secondary outcome because of its potential impact on nausea and vomiting. Although there is a higher percentage of irrigation in the in situ group, this was not statistically significant between groups, and despite this, in situ repair still demonstrated less IONV.

Reviewer #3: This paper presents an RCT of exteriorization vs in situ repair with a primary outcome of maternal symptoms - post delivery intraoperative nausea/vomiting. Overall, I am very happy to read a paper where the primary outcome is a maternal experience outcome, and not EBL/QBL/Hb difference.

Introduction - well written - nicely motivated. A question - is there any data on the frequency of in situ vs exteriorized closures in a typical obstetric hospital? does teaching vs non teaching hospital matter, for instance, or other patient characteristics

R: Thank you for your comment; it would be very valuable to have this information to add more context to our study. Unfortunately, we could not find specific literature studying the frequency of in situ versus exteriorized closures in different hospitals.

From the most recent data we can find in the studies referenced in our manuscript, it seems that it varies significantly from one center to another. For example, in the study by George et al (reference 22), the incidence of uterine exteriorization was 88% at Duke University Health Centre versus 23% at IWK Health Centre. In the study by Viney et al (reference 28), the incidence at Virginia Commonwealth University Medical Center was 80.5%.

Methods

1-line 195 - I will defer to the editors but do you think this truly counts as a double blinded trial, as the providers doing the surgery knew whether the uterus was in situ/exteriorized, as did the attending anesthesiologist? I agree the patient was blinded, as was the data collector, and I do

think the results are valid, but not sure about using the terminology of "double blinded"

R: Thank you for this question. We also pondered this question for the same reasons. We referred to the dictionary (Merriam-Webster), which defines double blinded as: "of, relating to, or being an experimental procedure in which neither the subjects nor the experimenters know which subjects are in the test and control groups during the actual course of the experiments". In our study, the patients ("subjects") were blinded and our data collector ("experimenter") was also blinded and made sure the protocol was rigorously applied in all patients no matter the group in the operating room. Therefore, we feel that the study should maintain its "double blinded" label, although we are open to discussion on this point if the editors have another view regarding this.

2-paragraph starting with line 228, BP assessment. is it standard to define hypotension as more than 20% away from the baseline MAP, and that this is the treatment threshold? Can you elaborate further why this was chosen and what this means?

R: Thank you for this question. According to the International consensus statement on the management of hypotension with vasopressors during caesarean section under spinal anaesthesia, the most common definitions of hypotension used in research studies were either '< 80% baseline',or '< 100 mmHg OR < 80% baseline'. (Kinsella SM, et al. International consensus statement on the management of hypotension with vasopressors during caesarean section under spinal anaesthesia. Anaesthesia. 2018;73(1):71–92.)

The systolic BP is a less important variable than MAP as a determinant of organ perfusion. Commercially available automated non-invasive BP measurement devices are based on the oscillometric method, where pressure at maximum oscillation is equal to MAP. Systolic and diastolic BP are calculated using formulas based on proprietary algorithms not open to users, and it is unlikely that pregnant women are included in the process of developing these algorithms. We felt that using a percentage change (20%) from a measured value, in this instance MAP, would be more or at least as reliable than using a calculated value (systolic BP).

3-paragraph starting with line 237. I could use some clarity as this is your primary outcome. Initially when I read this I thought, why are 4 of the 5 time points for determining intraoperative nausea not occurring at the time that the uterus could be either in situ or exteriorized? Then I see that ultimately, you defined your primary outcome using answers at 2 of these 5 time points. Why was done this way? Was it so that the patient wasn't primed to say yes/no at the actual time point you cared about? I would group the description of this variable with how you used it for your primary outcome in the same paragraph, for clarity. Also, I would move the sentences about blinding out of this paragraph - this information felt misplaced after learning about your primary outcome.

R: Thank you for this question, as it raises important points.
We used 5 time points for a few reasons;

- *As you allude in your question, it was done so the patient was not primed to answer only at the actual time point we cared about.*
- *We defined the primary outcome using the last 2 time points because exteriorization could still have an impact on IONV in the moments after the uterus is reinserted into the abdomen.*
- *It was also to be able to protocolize which patients had severe nausea/vomiting (≥2 on IONV scale) requiring antiemetics prior to actual application of randomization (exteriorization or in situ uterine repair). It was designed to maintain patients' comfort at all time during the procedure and withdraw these patients from analysis (Figure 1: Flow diagram).*
- *It was also a way to prime and remind the surgeons to mention out loud the different steps of the surgery and not only at the actual time point we cared about.*

We have modified the paragraph as follows:
"The patients were questioned at 5 pre-determined surgical time points (skin incision, hysterotomy, placental delivery, beginning of uterine repair, beginning of fascia repair) during the procedure and were asked to verbalize any nausea at any time. Only the last two time points until the last skin staple were used for the primary outcome because we deemed that nausea occurring any time after beginning uterine repair was likely due to the repair rather than other factors. Asking at these 5 time points aimed to maintain patients' comfort throughout surgery, prevented priming, and allowed the withdrawal of patients who required antiemetics prior to the application of randomization (Figure 1). The time points were expressed verbally by the Obstetrician performing the surgery to blind the data collector from the surgical technique. The attending Anesthesiologist and the Obstetrician were not blinded whereas the patient and the data collector, who remained seated behind the surgical drape at the head of the patient and could not see the surgical technique, were blinded. The nausea was quantified on a scale of 0 to 3; 0 being no nausea, 1 being light nausea, 2 being severe nausea, and 3 being nausea accompanied with vomiting. Vomiting was defined as the expulsion of gastric contents and retching was considered equivalent to vomiting."

4-IONV scale - is this validated? Can you mention briefly something about its use either here, what this scale means, etc?

R: During the development of the protocol, we reviewed the literature looking for a validated IONV scale; there was none that we could find. Therefore, we developed this scale for its ease of use and simplicity for patients. It was not the goal of this study to validate an IONV scale.

We would question the patient as follows:
"Do you have any nausea?"
If the answer was "no", we would rate it 0.
If the answer was "yes", we would follow with: "Is your nausea mild or severe?"
If the answer was "mild", we would rate it 1 and if the answer was "severe", we would rate it 2.
If the patient had obvious retching or vomiting defined as the expulsion of gastric contents, we would rate it as 3.

Results

5-consider presenting your Hb results in grams/deciliter

R: This has been corrected.

6-I am curious why you present the data on peritoneal irrigation. I did not expect this as you did not mention this as a secondary outcome in the methods section, and I am also not sure what it signifies and how it relates to the intervention. To me, it represents the "typical" practice of an obstetrician when closing in a prespecified way, rather than responsive to the clinical situation. Also, I am not sure how this may have affected the primary outcome - depends on how much manipulation/moving of bowels you do (which would cause n/v) - some people barely pour a little fluid in the belly, whereas others extensively irrigate/clear gutters/manipulate bowel. I am not sure what this variable means, even if it is nonsignificant, and would love some context about how peritoneal irrigation was performed, if it was standardized, etc, if you are reporting this data.

R: Thank you for pointing this out. We have added irrigation amongst the secondary outcomes in the Methods section. The paragraph has now been modified as such: "The timing of the nausea, vomiting, hypotensive episodes, tachycardia and vasopressor boluses were noted. The duration of uterine repair (from the moment the obstetrician verbalized "beginning of uterine repair" to "beginning of aponeurosis repair"), total duration of surgery (from skin incision to last skin staple) and use of peritoneal irrigation were noted. Hemoglobin was recorded before surgery and within 24 hours after surgery. The estimated blood loss was assessed by measuring the blood in the suction unit and weighing lap pads."

We present data on peritoneal irrigation because it has been described as a risk factor for IONV in cesarean deliveries in a randomized controlled trial by Viney at al (reference 28); although the uterus was exteriorized >80% of the time in their study. We felt that omitting to discuss this risk factor would show a lack of rigor on our part. Since there is a paucity of literature on this topic, we felt that our data may be interesting and may question the previous conclusions whether peritoneal irrigation actually causes more IONV and if it has the same effect when the uterus is not exteriorized.

However, this was not the main focus of our study, therefore we cannot make definitive conclusions especially because bowel irrigation was not standardized, and was at the discretion of each Obstetrician. In our center, irrigation usually consists of the Obstetrician instilling the abdominal cavity with approximately 100 to 200 mL of warm water after closure of the hysterotomy and minimizing bowel manipulation. The decision to irrigate depended on their evaluation of the bleeding after uterine closure. The type of surgical repair did not influence their decision to irrigate. Half the patients did not receive any irrigation at all.

Discussion

7-lines 344-347 - this is stylistic but I would present the order of your results in a parallel fashion. Either present the result for in situ first for both outcomes, or exteriorization first for both

outcomes, but not one of each. The direction of your findings is the same, but the way it is presented, if you are reading quickly, you may think incidence of IONV goes down with in situ repair but severity goes up.

R: Thank you for this helpful comment. We have made the corrections in the article accordingly: "In our trial, the incidence of postdelivery IONV was statistically higher in the exteriorization group compared to in situ (40% vs 21%; p = 0.01). Interestingly, the severity of IONV was also greater in the exteriorization group with a significant difference in the distribution of results on the 4-point IONV scale. The exteriorization group suffered from vomiting or retching (IONV score 3/3) over three times more (17%) compared to the in situ group (5%)."

8-lines 351-352 - from your introduction, I presumed that the use of phenylephrine for all patients would have overall decreased the incidence of n/v (due to decreasing incidence of hypotension overall), even if there is a relative difference between in situ and exteriorization groups, but from the data you present in these lines, it does not appear that way. Essentially almost the same findings as you have. Are you surprised? Can you comment on this if so ?

R: We were also somewhat surprised with the rate IONV in our study reaching an incidence as high as without the phenylephrine infusion in the Siddiqui et al study (reference 11).

According to our group, this discrepancy can be explained by 2 main factors:
1- The treatment threshold for hypotension in our study was 80% of baseline BP whereas it was 90-100% in the Siddiqui et al study. A study by Ngan Kee (reference 21) demonstrated that there is a distinct association of nausea and vomiting with the degree of maternal hypotension, and strict control of blood pressure can significantly reduce IONV.
2- The fact that we used a nausea and vomiting scale that included a "mild nausea" category (scored as 1 in our study) may have caused a Hawthorne effect. Indeed, some of the patients may have answered they had mild nausea when asked the question, but may not have spontaneously told us they were nauseous if not asked. This was obviously the case for both groups.

We have added comments on this issue in the first paragraph of the discussion as follows:
"[…] These numbers are consistent with the only other randomized trial in the literature which reported IONV as a primary outcome and used a standardized anesthetic technique, which showed an IONV incidence of 38% for uterine exteriorization and 18% for in situ repair.[11] The similar incidence of IONV despite a phenylephrine infusion might be explained by the different treatment thresholds for hypotension (80% versus 90-100% of baseline BP) and by the "mild nausea" category on our IONV scale causing a Hawthorne effect. Rescue antiemetic use was consistent with our protocol which stipulated that patients with IONV ≥2/3 should receive an antiemetic. Its use was significantly reduced in the in situ group (18% vs 34%; p = 0.03)."

9-as I previously said, not sure why the 80% of MAP threshold was chosen, and this still does not make sense to me with this discussion. I understand this is the literature threshold but is this what practitioners are clinically using as treatment thresholds? Are proportions of baseline MAPs

commonly calculated in the OR? Would you consider a secondary analysis calculating incidence of hypotension using a MAP threshold?

R: As we alluded to in our response to your second comment; 80% threshold or decrease of 20% from baseline blood pressure is both very common in the literature and in clinical practice as well. Although practitioners usually don't calculate with a calculator as precisely as what is done in the scientific literature, a "ballpark" estimation of this threshold is often used in a clinical setting.

By reviewing this paragraph in the Discussion, we understand that there might be some confusion as to what represents clinical practice. We changed the "80% of baseline MAP" to "80% of baseline BP" and we added clarifications as to why we used MAP instead of systolic BP:
"Anesthetic and non-anesthetic factors influence the incidence of IONV. Hypotension is one of the most preventable and measurable factors.(2) We performed volume co-loading, left uterine displacement, and used a prophylactic phenylephrine infusion as well as phenylephrine boluses to treat hypotensive episodes. A phenylephrine infusion is associated with less hypotension and greater accuracy for maintaining BP near baseline compared to a bolus only regimen, and it is associated with less IONV and physician interventions.(3–7) Despite the finding that keeping maternal BP at 100% of baseline minimizes IONV,(3) we used a treatment threshold of 80% of baseline BP because it is the most commonly used threshold in the literature(4,5,8) and better represents clinical practice. Unlike previous studies, we used MAP instead of systolic BP as the treatment parameter because the MAP is a more important variable as a determinant of organ perfusion than systolic BP and it is more precisely measured. This is due to the fact that commercially available automated non-invasive BP measurement devices are based on the oscillometric method, where pressure at maximum oscillation is equal to MAP. Systolic BP and diastolic BP are calculated using formulas based on proprietary algorithms not open to users, and it is unlikely that pregnant women are included in the process of developing these algorithms.(9)"
We are uncertain of what is meant by a secondary analysis calculating incidence of hypotension using a MAP threshold since this is what we have used in our study. To calculate the incidence of hypotension, we defined a hypotensive episode as reaching MAP less than 80% of baseline.

10-I am curious why you did not include women with unscheduled CD and what you think your findings would mean for these women. This is worth discussing, as most women having CD are unscheduled, they are the ones at "risk" of PPH (more than scheduled CD), but if there is benefit to leaving in situ, then this is the largest population of women who stand to be affected

R: Having a heterogenous patient population that includes a mix of elective and urgent/unplanned cesarean deliveries cannot be compared for IONV because there are too many confounding factors such as use of IV fluids, antiemetics, different comorbidities, length of labor, labour augmentation, urgency of procedure, etc.
A lot of the unscheduled deliveries are done under epidural anesthesia that does not influence blood pressure the same way a spinal does and does not have the same block density; both of these factors greatly influence the incidence of IONV.

However, we agree that the largest population that might benefit from the findings of our study are unscheduled CD. With the results we have, we think more studies are needed to look more specifically at this patient population.

11-the duration of surgery is impressive and I suspect will pose an issue with generalizability. The fact that these were on average <30 minute repeat cesarean deliveries suggest it is a highly efficient team with an attending primary surgeon and a trained primary assistant - as against a learning environment in which either the surgeon or the assistant is learning. In such cases, the argument exists for exteriorization, as limited experience slows down the exposure and poses concern for increased bleeding/Hb drop. Although I know your paper argues against this perspective, I am not sure it is applicable in all settings. Can you discuss this in your discussion section? You did mention this as a point in the introduction, so I believe the loop should be closed here.

R: This is a very interesting point. Our centre was an academic center. As you mention in your comment, the primary surgeon was always an attending but the primary assistant would vary significantly in experience since it was a senior resident at times but it could be a medical student at other times.

We incorporated your comment in the discussion within the "Limitations" paragraph as follows: " […] However, the use of metoclopramide as IONV prophylaxis may have in fact helped single out the effect of uterine exteriorization on IONV by preventing nausea from other causes. Although this study was conducted in an academic center, the short duration of the CD (<30 minutes) with a majority of repeat procedures may not represent the reality of all centers. In cases where the operator has limited experience, such as a resident in an academic setting, the argument may exist for exteriorization, in order to ensure adequate closure to prevent the risk of bleeding. Finally, this study was conducted in a single center and was not powered for variables other than nausea and vomiting, which was our primary outcome."

12-one point you could make is that with less IONV/less discomfort, more women will be able to accomplish intraoperative skin to skin, which is important for new mothers and also beneficial to the baby (golden hour!)

R: Thank you for this point. This has been added in our Discussion in the ERAS paragraph as follows:
"With the advent of enhanced recovery after surgery (ERAS) where perioperative care should accelerate patient recovery,(10–12) our data suggests that the in situ uterine repair technique for elective caesarean deliveries may enhance recovery. Nausea and vomiting is a patient-important outcome that has been described as worse than postoperative pain,(13,14) and is the most common complication in the recovery room.(15) In addition, with less IONV, more women will be able to accomplish early intraoperative skin-to-skin contact, which is important for new mothers and also beneficial to the newborns."

13--lines 387-389 - I would say the larger argument for fewer interventions for hypotension is that women are likely to feel better, rather than unwell during their CD! Not decreasing the workload for the anesthesiology provider

R: Good point. We included this anesthesiologists' number of interventions comment as it is often reported in the Anesthesiology literature.
This has been modified as follows:
"There was also a statistically significant difference in the number of phenylephrine bolus requirements with a median of 4 boluses for the exteriorization group and 1.5 for the in situ group (p = 0.001). Less hypotension and tachycardia are likely to make the parturient feel better during surgery and this reduction in interventions is desirable when caring for an awake parturient under regional anesthesia. In addition, it also decreases the workload for the anesthesiologist providing care.(4)"

14--lines 410-413 - if there is peritoneal irrigation, it is done after the closure of the hysterectomy to clear clots that are in the abdomen, since the blood had nowhere to go but intraabdominally in an in situ closure. It is unrelated to the exposure of the hysterectomy due to an in situ closure. Please revise this statement as I do not believe it is accurate. As I said earlier, I suspect this is surgeon preference

R: Thank you for this comment. We deleted the last sentence of the paragraph in which these lines were contained.

STATISTICAL EDITOR'S COMMENTS:

1. Abstract:Should conform to our RCT template.

R: This has been modified accordingly.

2. Lines 118-120, 269-275, Table 2: The primary outcome (any none zero IONV score) should be clearly separated from all others. The others cited in Table 2 are all secondary outcomes. Should make consistent the rates of non-zero IONV (40 vs 21% in Table 2 and 40 vs 20 % in Abstract and 40.2% and 20.5% on lines 298-300. Given the sample sizes, the %s should be rounded to nearest integer %, not cited to nearest 0.1%. Therefore should consistently be cited as 40% and 21%.

R: This has been modified accordingly.

3. lines 249-251: Should clarify how many times the nausea scale was applied (from the time point "beginning of uterine repair" and onward) and presumably, the score used was the highest.

R: We added more details to the previous paragraph to clarify our primary outcome as follows:
"The patients were questioned at 5 pre-determined surgical time points (skin incision, hysterotomy, placental delivery, beginning of uterine repair, beginning of fascia repair) during the procedure

and were asked to verbalize any nausea at any time. Only the last two time points until the last skin staple were used for the primary outcome because we deemed that nausea occurring any time after beginning uterine repair was likely due to the repair rather than other factors. Asking at these 5 time points aimed to maintain patients' comfort throughout surgery, prevented priming, and allowed the withdrawal of patients who required antiemetics prior to the application of randomization (Figure 1). The time points were expressed verbally by the Obstetrician performing the surgery to blind the data collector from the surgical technique. The attending Anesthesiologist and the Obstetrician were not blinded whereas the patient and the data collector, who remained seated behind the surgical drape at the head of the patient and could not see the surgical technique, were blinded. The nausea was quantified on a scale of 0 to 3; 0 being no nausea, 1 being light nausea, 2 being severe nausea, and 3 being nausea accompanied with vomiting. Vomiting was defined as the expulsion of gastric contents and retching was considered equivalent to vomiting.

Nausea evaluated at 1 or more on the nausea scale from the time point "beginning of uterine repair" and onward was considered as positive for IONV due to uterine exteriorization or uterine repair (for in situ patients). A predetermined algorithm was also used to treat nausea and vomiting. A score of 2 or more on the nausea scale was treated with ondansetron 4 mg intravenously and a bolus of phenylephrine 2.0 mcg.kg^{-1} of LBW IV, or a bolus of ephedrine 5 mg IV if the heart rate was < 50 beats per minute. Nausea and vomiting refractory to the previous treatment was treated with metoclopramide 10 mg IV."

4. Table 1: Since the groups were randomized, no need to compare the baseline characteristics with stats. Any difference is thought to be due to random chance.

R: The "P value" column has been deleted from table 1.

5. Table 3: Should round the %s to nearest integer %. Why is there no p-value for the comparison of rates of reactive hypertension?

R: This has been modified accordingly. We added the p-value for reactive hypertension.

6. Table 4: Should round the % for endometritis to nearest integer % and include the p-value for comparing those rates.

R: This has been modified accordingly. We added the p-value for the endometritis.

Fig 2: Should clarify what groups are being compared with the * s and what significant differences are being applied.

We have added clarifications for Figure 2 and deleted one of the "" to avoid confusion. The changes are the following:*

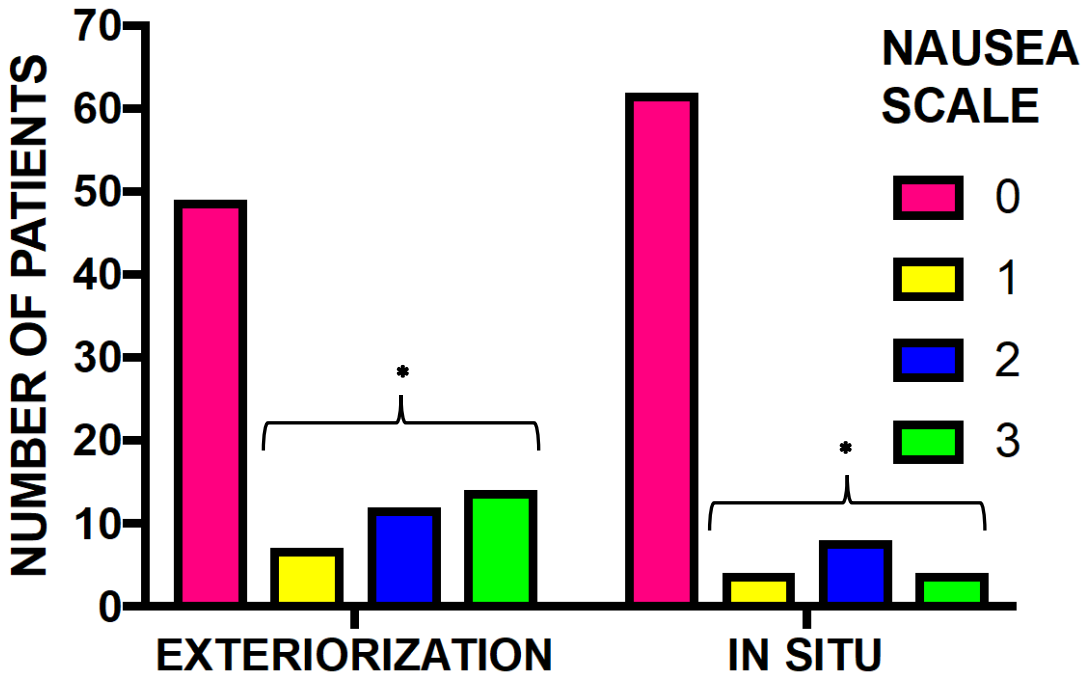

Figure 2. Distribution of postdelivery intraoperative nausea and/or vomiting (IONV) on the nausea and vomiting scale in each group. Nausea scale: 0 = no nausea, 1 = mild nausea, 2 = severe nausea, and 3 = vomiting and/or retching. Asterisks (*) represents statistically significant differences between in situ and exteriorization group for IONV ≥1. Chi-square test for trend between group is also statistically significant.

Reviewer #4: The authors present their randomized controlled trial in which they compare the impact of uterine exteriorization vs in situ repair at the time of cesarean section on intraoperative nausea and vomiting as well as hypotension. They note that the patients in their study were undergoing elective cesarean delivery, and had spinal anesthesia as well as a phenylephrine infusion.

The following items should be addressed:

1. Abstract line 118-119 - the way these data are presented is confusing; it is not clear what the two comparison groups are in this context. Consider removing this comparison from the abstract and keeping it only within the text.

R: We removed the sentence "When present, the severity of IONV was significantly less in the in situ group (IONV 3/3 42% vs 25%; p = 0.005)" from the abstract.

2. Methods - is the described phenylephrine infusion standard for cesarean sections at your

institution? The reference provided describes calculation of medication doses, but is not specific to the use of this medication in patients with spinal anesthesia. This is not a standard part of management at the time of cesarean in the US, and therefore it would be helpful to provide more context.

R: Phenylephrine infusion is standard for cesarean sections under spinal anesthesia at our institution. We do not generally program the infusion based on a lean body weight, but we did for the purpose of a clinical trial. The starting phenylephrine infusion dose for most patients was around 25 mcg/min which is supported by the Obstetrical anesthesia literature. (1-5)

We firmly believe that for cesarean sections under spinal anesthesia a vasopressor, mainly phenylephrine, should be part of the standard management and it has been heavily supported by the literature for over a decade, including the 2018 "International consensus statement on the management of hypotension with vasopressors during caesarean section under spinal anaesthesia." (1)

Moreover, as we mention in our cover letter, we presented our results at the 2019 SOAP annual meeting in Phoenix, AZ. From multiple discussions and polls during the conference, the vast majority of American obstetrical anesthesiologists do in fact use a phenylephrine infusion during cesarean sections.

1. Kinsella SM, Carvalho B, Dyer RA, Fernando R, McDonnell N, Mercier FJ, et al. International consensus statement on the management of hypotension with vasopressors during caesarean section under spinal anaesthesia. Anaesthesia. 2018;73(1):71–92.
2. Allen TK, George RB, White WD, Muir HA, Habib AS. A double-blind, placebo-controlled trial of four fixed rate infusion regimens of phenylephrine for hemodynamic support during spinal anesthesia for cesarean delivery. Anesth Analg. 2010;111(5):1221–9.
3. Ngan Kee WD, Khaw KS, Ng FF. Comparison of phenylephrine infusion regimens for maintaining maternal blood pressure during spinal anaesthesia for Caesarean section. Br J Anaesth. 2004;92(4):469–74.
4. Heesen M, Klöhr S, Rossaint R, Straube S. Prophylactic phenylephrine for caesarean section under spinal anaesthesia: Systematic review and meta-analysis. Anaesthesia. 2014;69(2):143–65.
5. Siddik-Sayyid SM, Taha SK, Kanazi GE, Aouad MT. A randomized controlled trial of variable rate phenylephrine infusion with rescue phenylephrine boluses versus rescue boluses alone on physician interventions during spinal anesthesia for elective cesarean delivery. Anesth Analg. 2014 Mar;118(3):611–8.

3. Methods - please describe the randomization scheme in more detail. Was the randomization done in blocks? How did the computer generate the randomization? Was there any differentiation by provider? Who was responsible for notifying the surgeon of the allocation, given that the study data collector and patient were blinded to the allocation?

R: The randomization scheme was computer-generated by 'randomization.com' in blocks of 20 patients.

The Obstetrician was given a sealed envelope by the research nurse prior to the surgery.

There was no differentiation by provider since all obstetricians who agreed to participate were proficient with both techniques. We did not calculate if there was a difference in IONV by provider because our study was not powered for this outcome and with the high number of obstetricians (14) who participated in the study.

We added the details about the randomization as follows:
"Upon arrival in the operating room, the patients were randomly assigned by means of a computer-generated randomization scheme in blocks of 20 patients into one of the two study groups: exteriorized repair or in situ repair. The group allocation was blinded by the use of sealed envelopes until that moment. Staff Obstetricians proficient with both methods of uterine repair performed the surgery."

4. Results and table 1 - how many prior cesarean sections did the patients with repeat cesarean have? Was there any notation of severity of adhesive disease among the participants? What about presence or absence of fibroids, or uterine anomalies, as these could also impact the amount of uterine manipulation required in exteriorization?

R: The number of prior cesarean sections was a maximum of three and it was similar between both groups.

The severity of adhesive disease among the participants was not noted. Because of the randomized controlled design of the study, this characteristic should be similar between both groups therefore not influencing the results that we have.

Significant leiomyomata or uterine anomalies were among the exclusion criteria because they were considered "medical or obstetric conditions with a risk of uterine atony and postpartum hemorrhage" that we mention in our Methods section.

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:

R: A. OPT-IN: Yes, please publish my point-by-point response letter.

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. Clinical trials submitted to the journal as of July 1, 2018, must include a data sharing statement. The statement should indicate 1) whether individual deidentified participant data (including data dictionaries) will be shared; 2) what data in particular will be shared; 3) whether additional, related documents will be available (eg, study protocol, statistical analysis plan, etc.); 4) when the data will become available and for how long; and 5) by what access criteria data will be shared (including with whom, for what types of analyses, and by what mechanism). Responses to the five bullet points should be provided in a box at the end of the article (after the References section).

R: This was already included on the last page of the manuscript that we submitted and is on this resubmission.

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

5. 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.

R: This has been modified accordingly.

6. 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.

R: The title has been changed to : "Exteriorization Versus in Situ Repair using a Phenylephrine Infusion; a Randomized Controlled Trial" which is 99 characters long including spaces.

7. 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).

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.

R: The abstract has been revised and there are no more inconsistencies between the Abstract and the manuscript.

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.

R: The word count is now 300 words and is included in the manuscript.

9. Abstracts for all randomized, controlled trials should be structured according to the journal's standard format. The Methods section should include the primary outcome and sample size justification. The Results section should begin with the dates of enrollment to the study, a description of demographics, and the primary outcome analysis. Please review the sample abstract that is located online here: http://edmgr.ovid.com/ong/accounts/sampleabstract_RCT.pdf. Please edit your abstract as needed.

R: Abstract has been modified to fit the journal's standard format.

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.

R: We were wondering if it was acceptable to retain this symbol when discussing different IONV scores as we think it pertains to a measurement or data. For example, when we use it in the following sentence:
"Rescue antiemetic use was consistent with our protocol which stipulated that patients with IONV ≥2/3 should receive an antiemetic."

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%").

R: We have standardized the presentation of our data, mainly for P values and for percentages. We added the effect size to our data in Tables 2-3-4 by adding columns for relative risk with 95% CI and difference between means or medians with 95 % CI of difference. Please note that only the 95% CI without the RR was reported for the "endometritis" in Table 4 because there was no case of endometritis in the exteriorization group.

13. 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 on the other hand, it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

R: This claim of first report was based on a systematic search of the literature that is included in the manuscript: (MEDLINE; 1966–April 2019; English language; search terms:

"exteriorization," "nausea," "vomiting," and "cesarean section").

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.

R: The Table Checklist has been reviewed and we have made appropriate changes to our tables including labelling all columns and reporting standard deviations with the plus/minus sign.

15. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at http://links.lww.com/LWW-ES/A48. The cost for publishing an article as open access can be found at http://edmgr.ovid.com/acd/accounts/ifauth.htm.

Please note that if your article is accepted, you will receive an email from the editorial office asking you to choose a publication route (traditional or open access). Please keep an eye out for that future email and be sure to respond to it promptly.

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If you choose to revise your manuscript, please submit your revision through Editorial Manager at http://ong.editorialmanager.com. Your manuscript should be uploaded in a word processing format such as Microsoft Word. Your revision's cover letter should include the following:

* A confirmation that you have read the Instructions for Authors (http://edmgr.ovid.com/ong/accounts/authors.pdf), and
* A point-by-point response to each of the received comments in this letter.

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 Jan 10, 2020, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

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