

OBSTETRICS & GYNECOLOGY



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- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*

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obgyn@greenjournal.org.

Date: Aug 20, 2019
To: "Katie Propst" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-1384

RE: Manuscript Number ONG-19-1384

Extended Interval Pessary Care: A Randomized Trial

Dear Dr. Propst:

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 Sep 10, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: This is a well-designed and performed randomized controlled trial to explore if extending interval follow up for pessary care to 24 weeks was NOT INFERIOR to 12 weeks as determined by vaginal epithelial abnormalities. The authors determined that there was no difference in vaginal epithelial abnormalities at any study time point. I have few constructive comments as this was well done. However, the biggest flaws are those already identified by the authors including the use of a non-validated scale (Vaginal Epithelial Abnormalities [VEA]) for the primary outcome, an unmasked assessor, and an inability to completely assess the role of vaginal estrogen.

The authors discuss that given that the majority of patients were on vaginal estrogen they cannot make any conclusions regarding risk of vaginal epithelial abnormalities and pessary use. However, in this study approximately 30% of patients were not using vaginal estrogen. I would appreciate if the authors could report on the data of these 30% of women as that may provide helpful "real world" information for providers and patients.

Reviewer #2: Overall Comments: The authors present data from a randomized trial addressing interval pessary care in the setting of pelvic organ prolapse management. Guidelines exist for prolapse management in this setting reflecting typical follow-up time-points of 6 and 12 weeks for women not self-managing their pessary, however, there is no other level 1 data addressing this issue. The non-inferiority design is reasonable in this setting with the use of 12 weeks as somewhat of a standard. The statistical approach was ITT, but not sure how women dropping out of the study were addressed in the analysis as the primary outcome is assessment of vaginal epithelial abnormalities (VEA); also, there is a bias toward non-inferiority when assessed with ITT. Perhaps a per protocol approach would be of interest in this regard.

Specific Comments:

Title: Would consider removing "Extended"

Abstract: Clinicaltrials.gov notes that recruitment was performed in women using a ring or gellhorn-was incontinence dish added after the trial was initiated. Also, as noted here, one would think that perhaps women using a pessary for just stress urinary incontinence (SUI) were included-please clarify that all women had pessary use for prolapse. Please clarify primary outcome, was it at 24 or 48 weeks? Seems like as they randomized to 3 month vs 6 month f/u, the primary outcome would have been at 24 weeks (to ensure was safe to go to that time-point), with continued follow-up to 48 weeks-please clarify. What other expected adverse events were under surveillance?

Introduction: If primary outcome was at 48 weeks, would end current last sentence with "at 48 weeks". Please provide a

citation regarding suggested pessary follow-up in women receiving complete care in the office. (Does Palumbo et al, 2000 or the most recent UpToDate note a specific follow-up period for these patients?) Please provide a hypothesis.

Materials and Methods: Please see some of the comments regarding Methods in the Abstract section above. Please clarify the time-point of the primary outcome. Please also clarify discrepancy between the pessaries included here vs what is stated in clinicaltrials.gov. Typically, to minimize bias toward inferiority, only women treated per protocol- ie underwent the randomly assigned evaluation, should be considered in the outcome analysis-does this approach change your results? Did you consider using any existing vaginal epithelial assessment measures including the Vaginal Atrophy Index (VAI), the Genital Health Clinical Evaluation (GHCE), the Vaginal Physical Examination Scale, the Vaginal Health Index (VHI), or the Global Atrophy Score. Was intra/inter-rater reliability assessed with the currently used VEA measure? Would note secondary outcomes as exploratory as the trial was not specifically powered to assess.

Results: Table 1 reflects that 10% of subjects had vaginal erythema at baseline-was this not a study exclusion? It seems like the incontinence only (no prolapse) subjects introduces some heterogeneity into the population-please comment. Is the result different if you leave them out? Could you provide ORs and 95%CI's for the time-points in Table 3, perhaps stratifying by combining types 0-2 inclusive and types 3-4-this may be a more informative and interesting way to show the data. Did you collect the c/o vaginal discharge, pessary expulsion, vaginal spotting symptoms?

Discussion: Reasonable discussion of the results in the context of the current literature.

Tables/Figures As above and Consort figure OK.

Reviewer #3: The authors present a randomized, non-inferiority trial of office-based pessary care comparing pessary checks every 12 weeks to pessary checks every 24 weeks. The primary outcome of this study was incidence of types 3 and 4 VEA at the final study visit.

This is an important area of research as it is very applicable to patient care and reducing patient burden from unnecessary office visits for pessary maintenance. This is a very clearly and well written manuscript reporting the results of a simple and elegant trial that addresses an important clinical topic and has high impact on clinical practice that is relevant to the readership of the green journal.

Questions for the authors:

- why exclude those women using something other than gel horn, ring or incontinence dish? How many patients were excluded because of this criteria?
- do you have information on reason for unscheduled visits? may be interesting to see why most patients re-present
- Discussion lines 205+, would specify for gel horn, ring or incontinence dish pessaries.
- was prolapse stage determine from a recent exam or baseline exam at initial presentation?

STATISTICAL EDITOR'S COMMENTS:

1. lines 45-46: Need to state the timing of the final study visit (appears to be 48 wks).
2. lines 53-54: Study underpowered to compare those interval differences, as expressed in Table 3.
3. Table 2: No need to statistically compare the two cohorts, since they were randomized and any difference is thought to be due to random chance. It is unfortunate, however, that patients were not allocated by block so that type/severity of prolapse, pessary type, duration of pessary use or history of prior epithelial abnormalities were not balanced.
4. Table 3: The study design was based on a test of non-inferiority, so that should be stated first and explicitly labelled as the primary outcome. For example, it could be shown as a figure showing the difference, the CIs and the zone of non-inferiority. The other differences shown in this Table are all secondary, were not specifically evaluated for power and are not generalizable, since they were all underpowered and NS. Also, need to explain the drop-out for the two treatment arms, since 54/64 among routine and 58/66 among the extended had evaluations at 48 wks. Were those unavailable for evaluation of epithelial abnormalities at 46 wks? If such information does exist, then it should be included as ITT outcomes.

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.

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

3. All studies should follow the principles set forth in the Helsinki Declaration of 1975, as revised in 2013, and manuscripts should be approved by the necessary authority before submission. Applicable original research studies should be reviewed by an institutional review board (IRB) or ethics committee. This review should be documented in your cover letter as well in the Materials and Methods section, with an explanation if the study was considered exempt. If your research is based on a publicly available data set approved by your IRB for exemption, please provide documentation of this in your cover letter by submitting the URL of the IRB website outlining the exempt data sets or a letter from a representative of the IRB. In addition, insert a sentence in the Materials and Methods section stating that the study was approved or exempt from approval. In all cases, the complete name of the IRB should be provided in the manuscript.

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5. 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.

6. 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.

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.

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10. 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.

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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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.

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 Sep 10, 2019, 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

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



August 23, 2019

To whom it may concern,

Thank you for your review of our manuscript. Please find our responses to the reviewers below and our updated manuscript attached.

There are very few clinical trials published on the use of vaginal pessaries. This study was highly regarded when it was presented at the American Urogynecologic Scientific Meeting in 2018. We feel that the findings in this study could improve the quality of life for women using a vaginal pessary. Pessaries are indicated as a first-line treatment measure for pelvic organ prolapse and incontinence and their use is widespread. There is currently a lack of Level I evidence regarding pessary care intervals for women undergoing office-based care. We have endeavored to provide evidence to guide care for these patients.

The Hartford Healthcare Institutional Review Board evaluated and approved this study (IRB # HHC-2014-0112) and it was registered at Clinicaltrials.gov (NCT02371083) prior to enrollment of any subjects. We have submitted this manuscript solely to *Obstetrics & Gynecology*, and the manuscript is not under consideration for any other journal.

I, the lead author, affirm that 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.

Sincerely,

Katie Propst, MD

Thank you for your thorough and thoughtful review of our work. Please see our responses to the reviewers' comments below with line numbers corresponding to the tracked changes version of our manuscript.

REVIEWER COMMENTS:

Reviewer #1: This is a well-designed and performed randomized controlled trial to explore if extending interval follow up for pessary care to 24 weeks was NOT INFERIOR to 12 weeks as determined by vaginal epithelial abnormalities. The authors determined that there was no difference in vaginal epithelial

abnormalities at any study time point. I have few constructive comments as this was well done. However, the biggest flaws are those already identified by the authors including the use of a non-validated scale (Vaginal Epithelial Abnormalities [VEA]) for the primary outcome, an unmasked assessor, and an inability to completely assess the role of vaginal estrogen.

Thank you for the feedback.

The authors discuss that given that the majority of patients were on vaginal estrogen they cannot make any conclusions regarding risk of vaginal epithelial abnormalities and pessary use. However, in this study approximately 30% of patients were not using vaginal estrogen. I would appreciate if the authors could report on the data of these 30% of women as that may provide helpful "real world" information for providers and patients.

We thank the reviewer for raising this interesting question. We evaluated the question, and found no differences as a function of estrogen use among the overall sample or between the routine and extended arms, see line 206.

Reviewer #2: Overall Comments: The authors present data from a randomized trial addressing interval pessary care in the setting of pelvic organ prolapse management. Guidelines exist for prolapse management in this setting reflecting typical follow-up time-points of 6 and 12 weeks for women not self-managing their pessary, however, there is no other level 1 data addressing this issue. The non-inferiority design is reasonable in this setting with the use of 12 weeks as somewhat of a standard. The statistical approach was ITT, but not sure how women dropping out of the study were addressed in the analysis as the primary outcome is assessment of vaginal epithelial abnormalities (VEA); also, there is a bias toward non-inferiority when assessed with ITT. Perhaps a per protocol approach would be of interest in this regard.

Thank you for these comments. We have considered the suggestion to perform a per-protocol analysis and feel that it would lead to results that are significantly under-powered and not useful.

Specific Comments:

Title: Would consider removing "Extended"

Thank you for this suggestion, the title was changed: "Timing of Office-Based Pessary Care: A Randomized Trial"

Abstract: [Clinicaltrials.gov](https://clinicaltrials.gov) notes that recruitment was performed in women using a ring or gellhorn-was incontinence dish added after the trial was initiated. Also, as noted here, one would think that perhaps women using a pessary for just stress urinary incontinence (SUI) were included-please clarify that all women had pessary use for prolapse. Please clarify primary outcome, was it at 24 or 48 weeks? Seems like as they randomized to 3 month vs 6 month f/u, the primary outcome would have been at 24 weeks (to ensure was safe to go to that time-point), with continued follow-up to 48 weeks-please clarify. What other expected adverse events were under surveillance?

Thank you for your questions.

- 1. Incontinence dish pessary type was incorrectly not listed on clinicaltrials.gov, this has been corrected.**

2. Women were eligible for study participation if they were using a pessary to treat pelvic organ prolapse and/or incontinence, this detail was added to the abstract, see lines 43-44 and is noted in the materials and methods section, see lines 93-94.
3. Primary outcome was at 48 weeks (final study visit) see lines 47 and 53 for clarifications added to the manuscript. This was chosen to observe for longer-term impact of extended interval care on development of epithelial abnormalities. We agree with this point, patients needed assessment to ensure that they are safe to continue on the extended-interval schedule and this was conducted at 24 weeks with patient interview and exam at the 24 week visit.
4. Due to word limit constraints, information about adverse events was not included in the abstract. To clarify these details, additional information was added to the Materials and Methods section regarding adverse event monitoring, see lines 141-144.

Introduction: If primary outcome was at 48 weeks, would end current last sentence with "at 48 weeks". Please provide a citation regarding suggested pessary follow-up in women receiving complete care in the office. (Does Palumbo et al, 2000 or the most recent UpToDate note a specific follow-up period for these patients?) Please provide a hypothesis.

Thank you for these questions.

The authors feel that the final sentence of the introduction is accurate. Although the primary outcome is at 48 weeks, the intervals of pessary care studied in this trial are 12 and 24 weeks, not 48 weeks.

Regarding our practice: "For patients to whom we provide complete pessary care, we typically remove the pessary every three months" (lines 80-81), we do not have a citation to support this comment, this practice is based on expert opinion of the physicians in our group. In the literature, recommendations for pessary care vary widely and are based on expert opinion. The current UpToDate review suggests a follow up interval after pessary fitting of "every three to six months thereafter for pessary cleaning and assessment by the clinician." The UpToDate article provides no citation for this recommendation as it is based on the opinion of the authors. These authors go on to cite Gorti et al, 2009 which demonstrates the widely varying practices of providers caring for pessaries as we have mentioned and cited in our introduction, see lines 71-74. We have reviewed the citation suggested (Palumbo et al, 2000). This paper is a guideline for pessary care and does cite a study where pessary care intervals were extended to six months in a patient population that included many women who removed their own pessary at home and represents a different patient type than we investigate in our work. We agree that this data is relevant to the current study but it does not change the motivation for our work- there is no level I evidence for pessary care interval.

Gorti M, Hudelist G, Simons A. Evaluation of vaginal pessary management: a UK-based survey. *J Obstet Gynaecol.* 2009;29(February):129-131.

Materials and Methods: Please see some of the comments regarding Methods in the Abstract section above. Please clarify the time-point of the primary outcome. Please also clarify discrepancy between the pessaries included here vs what is stated in clinicaltrials.gov. Typically, to minimize bias toward inferiority, only women treated per protocol- ie underwent the randomly assigned evaluation, should be considered in the outcome analysis-does this approach change your results? Did you consider using any

existing vaginal epithelial assessment measures including the Vaginal Atrophy Index (VAI), the Genital Health Clinical Evaluation (GHCE), the Vaginal Physical Examination Scale, the Vaginal Health Index (VHI), or the Global Atrophy Score. Was intra/inter-rater reliability assessed with the currently used VEA measure? Would note secondary outcomes as exploratory as the trial was not specifically powered to assess.

Thank you for these comments, please see above for comments regarding the time-point of the primary outcome.

The discrepancy on clinicaltrials.gov was corrected, thank you for pointing out this error.

The authors agree that the use of validated scales is ideal in research endeavors. However, the authors are not aware of any scales or rating systems describing epithelial abnormalities related to pessary use. The scales suggested are available and validated, however, they are related to atrophy of the vaginal epithelium which was not an outcome of the study. Atrophy of the vagina is a different pathology than discrete breaks in the vaginal epithelium related to pessary use. Many physicians believe that atrophy increases the risk of vaginal epithelial abnormalities and this is why many pessary patients are instructed to use vaginal estrogen. Although the link between atrophy and epithelial abnormalities seems intuitive, there is no data to support this association or the prevention of abnormalities by using topical estrogen. Additionally, description of atrophy of the vaginal tissues is beyond the scope of this investigation. For all of these reasons, we did not include any of the atrophy scales.

Intra/interrater reliability was not assessed for our VEA measure.

Results: Table 1 reflects that 10% of subjects had vaginal erythema at baseline-was this not a study exclusion? It seems like the incontinence only (no prolapse) subjects introduces some heterogeneity into the population-please comment. Is the result different if you leave them out? Could you provide ORs and 95%CI's for the time-points in Table 3, perhaps stratifying by combining types 0-2 inclusive and types 3-4-this may be a more informative and interesting way to show the data. Did you collect the c/o vaginal discharge, pessary expulsion, vaginal spotting symptoms?

Thank you for these comments.

Women were excluded for epithelial granulation tissue or breaks in the epithelium, women with erythema were allowed to participate, see lines 95-98.

The authors agree that allowing patients with incontinence only does increase heterogeneity into the sample. The authors considered this in study planning and made the decision to include all patients wearing the pessary types of ring, Gellhorn, and incontinence dish as to best approximate a realistic clinical population with our study sample. We are reluctant to perform a secondary analysis excluding patients who had incontinence only, this is a small group of only 5 patients.

Thank you for the suggestion to add confidence intervals for the values in table 3. Based on the comments by the statistical reviewer, table three was replaced with a figure to better illustrate the

primary outcome. As the statistical reviewer and others have pointed out, table 3 included only secondary outcomes that we were not powered to address. Therefore, this table was removed.

Yes, data was collected on patient complaint of vaginal discharge and vaginal spotting. These data are reported in the results section, see lines 186-189 and 197-198. Reason for some unscheduled visits was due to pessary expulsion for 5 unscheduled visits. As this information is not part of the primary outcome or likely related to the interval of care, it is not included in the results. If the editor feels that this should be added, we will add it but we prefer not to.

Discussion: Reasonable discussion of the results in the context of the current literature.

Tables/Figures As above and Consort figure OK.

Thank you for your feedback.

Reviewer #3: The authors present a randomized, non-inferiority trial of office-based pessary care comparing pessary checks every 12 weeks to pessary checks every 24 weeks. The primary outcome of this study was incidence of types 3 and 4 VEA at the final study visit.

This is an important area of research as it is very applicable to patient care and reducing patient burden from unnecessary office visits for pessary maintenance. This is a very clearly and well written manuscript reporting the results of a simple and elegant trial that addresses an important clinical topic and has high impact on clinical practice that is relevant to the readership of the green journal.

Thank you for the positive feedback.

Questions for the authors:

- why exclude those women using something other than gel horn, ring or incontinence dish? How many patients were excluded because of this criteria?

Thank you for this question. We made this decision as most patients in our practice wear these pessary types and we wanted to avoid having a variety of pessary types in very low numbers as we were concerned that this would bias our results. Additionally, we believe that these pessary types are the most commonly used and therefore, the results are applicable to a clinical population. As suggested, reasons for exclusion were included in the CONSORT diagram.

- do you have information on reason for unscheduled visits? may be interesting to see why most patients re-present

Thank you for this suggestion, please see additional information regarding most common reason for re-presenting, lines 196-198.

- Discussion lines 205+, would specify for gel horn, ring or incontinence dish pessaries.

Thank you for this suggestion, this clarification was added to the first sentence of the discussion, see lines 215-216.

- was prolapse stage determine from a recent exam or baseline exam at initial presentation?

Prolapse stage was determined based on POP-Q exam performed at the baseline study visit, not at the patient's initial visit to the office. This was clarified in the methods, see line 114.

STATISTICAL EDITOR'S COMMENTS:

1. lines 45-46: Need to state the timing of the final study visit (appears to be 48 wks).

Thank you, this was added, see line 47.

2. lines 53-54: Study underpowered to compare those interval differences, as expressed in Table 3.

Thank you for this comment. The authors have clarified timing of the primary outcome in the abstract, lines 47 and 53. Additionally, table 3 was replaced with a figure as suggested in number 4 below.

3. Table 2: No need to statistically compare the two cohorts, since they were randomized and any difference is thought to be due to random chance. It is unfortunate, however, that patients were not allocated by block so that type/severity of prolapse, pessary type, duration of pessary use or history of prior epithelial abnormalities were not balanced.

Thank you for this feedback. The authors prefer to leave the p value comparisons in table 2 as these demonstrate lack of baseline differences in the two arms of the sample with the exception of pessary type. We believe that this difference is relevant to the study findings. We are willing to remove these if the editor prefers.

4. Table 3: The study design was based on a test of non-inferiority, so that should be stated first and explicitly labelled as the primary outcome. For example, it could be shown as a figure showing the difference, the CIs and the zone of non-inferiority. The other differences shown in this Table are all secondary, were not specifically evaluated for power and are not generalizable, since they were all underpowered and NS. Also, need to explain the drop-out for the two treatment arms, since 54/64 among routine and 58/66 among the extended had evaluations at 48 wks. Were those unavailable for evaluation of epithelial abnormalities at 46 wks? If such information does exist, then it should be included as ITT outcomes.

Thank you for this comment. As the data in table 3 was secondary and NS, this table was removed and replaced with a figure better illustrating the primary outcome. In the revised manuscript we simply state that there were no differences in rates of VEA between the arms at any time point under secondary outcomes as these outcomes are not powered, lines 183-184.

Thank you for pointing out the discrepancy between the N analyzed for the primary outcome and the N analyzed in the CONSORT diagram, this discrepancy was corrected.