Reviewer's report

Title: Hysteropexy in the treatment of uterine prolapse stage 2 or higher: a multicenter randomized controlled non-inferiority trial comparing laparoscopic sacrohysteropexy with vaginal sacrospinous hysteropexy (LAVA-trial)

Version: 2
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Reviewer: Robert E Gutman

Reviewer's report:

The authors are to be congratulated for undertaking a study with important implications. Hysteropexy is an important option for surgical treatment of uterovaginal prolapse with limited comparative studies regarding the types of hysteropexy. There are studies comparing hysteropexy to hysterectomy but not comparing vaginal and laparoscopic hysteropexy. It is important that the authors structure their study in such a way as to obtain results that will help guide future practice. The following are questions, concerns and recommendations regarding the protocol.

Abstract
1. Discretionary revision, last sentence of background paragraph: the trial hasn't been conducted yet, change to “plan to conduct the LAVA trial.”
2. Discretionary revision, methods: would add that validated outcome measures are being used.

Background
3. Discretionary revision, 1st paragraph: 1st reference is outdated. There is already a new ICI published on this topic.
4. Minor revision 4th paragraph, page 6: left off the word “intestines” after small when describing enterocele.
5. Major point, 2nd paragraph, page 7: While I agree that there is inconclusive evidence and similar results comparing sacrospinous hysteropexy (SSHP) and TVH, the only RCT by Dietz, 2010 (your reference #16) reported a higher rate of apical recurrences in the hysteropexy group 21% versus 3% hysterectomy group (p=0.03). Both groups had high rates of postoperative anterior vaginal wall prolapse (51% vs. 64%). The latter point is important because of how you structure your outcomes for this study and will be discussed later in this review.

Methods/Study design
6. Major point: I think it is appropriate to structure this as a non-inferiority result if only looking at the apical compartment (recurrent uterine prolapse), but my hypothesis would be that the laparoscopic results will be better based on anterior wall recurrence rates being much higher in the vaginal group resulting in overall more symptomatic prolapse that requires additional treatment with surgery or a
pessary.

7. Major revision, 1st paragraph study design page 9: The authors indicate that “follow-up after one year will be done by an physician not involved in the surgery.” Why not have 6 month and 1 year exams be done by someone other than the surgeon? The 1 year exam is the primary outcome and will contain significant bias if done by the surgeon. I strongly suggest that the 1 year exam be done by someone other than the surgeon.

8. Major revision recommended, 1st paragraph of primary and secondary outcomes, page10: The primary outcome is unclear throughout the paper. It sounds like POP-Q for uterine prolapse that is stage 2 (point C at or below -1) constitutes a failure. However it also mentions “symptoms or redo surgery in the case of uterine descent.” Do the authors mean that someone with recurrent stage 2 uterine prolapse that is not symptomatic or does not undergo reoperation would not be considered a failure? That is what this sentence implies. I would argue that the authors should have a composite outcome. Success should be those with anatomic descent of the apex at or above the mid-vagina (C < -TVL/2), no prolapse in any compartment (anterior or posterior walls) beyond the hymen (since that is where symptoms occur), and no reoperation for recurrent prolapse or pessary use. Failure of any one of these areas would constitute a failure. Since a woman could be included with the cervix 1cm internal to the hymen, I do not think her surgery would be considered successful if she ended up with the cervix 2cm internal to the hymen and the anterior wall 3 cm beyond the hymen. Yet, by the study criteria, that would not be considered a failure. Please reconsider how you define your primary outcome so that it is meaningful and relevant.

9. Major revision recommended for inclusion/exclusion criteria of 3rd and 4th paragraphs, study population page 10: Is any abnormal cervical smear considered an exclusion criteria (ASCUS with high risk HPV negative) or those with cervical dysplasia? What about those with high risk HPV but normal cervical smears? The authors need to be more specific about what abnormal ultrasound findings of the uterus and ovaries will be excluded. Will a small asymptomatic fibroid that is 2cm be excluded? The authors specify abnormal uterine bleeding. Does this mean menorrhagia, menometrorrhagia, and dysmenorrhea? What about postmenopausal bleeding? I would suggest that any recent postmenopausal bleeding even with a negative workup in the past year be excluded since Frick’s article suggests a high rate of unanticipated abnormal pathology in this population. Will the authors include or exclude those women with cervical elongation? There is a study by Lin et al indicating a 10 fold increased risk of failure in women with cervical elongation undergoing SSHP. While it is difficult to quantify cervical elongation, I would suggest that the authors leave this to the discretion of the enrolling surgeon but exclude those felt to have elongation or the need for cervical shortening/partial tracheectomy. Those patients may be better served with a TVH. Alternative is to mandate surgical shortening but not as clean for the study.

10. Minor revision, first paragraph of randomization, page 11: I agree with stratifying or block randomization according to centre but wouldn’t do this for
severity of prolapse/POP-Q stage as there should be no difference between groups in a RCT that is adequately powered and done correctly.

11. Major revision, first paragraph of randomization, page 11: The authors need to add details here about when the randomization will take place. Implied in the discussion regarding sample size that randomization is done before the operating room so that 10% will likely drop out because they are not happy with their assignment. Please state when randomization will be done, by whom, and how subjects that withdraw after randomization will treated.

12. Minor revision, data collection, 2nd paragraph of this section, page 11: who will administer validated quality of life questionnaires at baseline and postop visits.

13. Discretionary revision, major point to be considered but does not necessarily require revision, last paragraph page 11: Collection of a postop pain diary by VAS is a great idea. How will the authors make sure that the patients are completing the pain diary regularly rather than just filling it out the day before the 6 week visit. There will be significant recall bias if the patients are not completing them on a regular basis. The authors should consider a way to collect this at shorter intervals. Maybe mail in the daily diary at 2 weeks and then collect pain scores once a week for 2-6 weeks that is submitted at 6 weeks. Do you really need a daily pain diary after 2 weeks?

14. Minor revision suggested, paragraph 1, page 12: Be specific regarding the exam data (POP-Q) and validated questionnaires that will be collected at each time interval.

15. Discretionary revision/question, paragraph 2 of interventions section page 12: It is a good idea to have all investigators perform at least 20 of “each” to eliminate the learning curve. Will a participating surgeon be required to perform both of the procedures or could they partner with another surgeon so that one does the laparoscopic and the other does the vaginal procedure?

16. Discretionary revision, paragraph 1, page 13 in section on laparoscopic sacrohysteropexy: Will the surgeon be able to run the graft further down the anterior and posterior walls of the vagina into the vesicovaginal and rectovaginal space? I suggest the authors consider dissecting the bladder further off the anterior wall and running the grafts down further to decrease the risk of anterior vaginal wall recurrences. We use a slightly different technique similar to that shown in a video published by Dr. Paraiso at the Cleveland clinic. This technique allows better proximal anterior vaginal wall support similar to that observed with laparoscopic sacrocolpopexy.

17. Minor revision suggested, end of paragraph 1, page 13: I suggest making an anterior and/or posterior colporrhaphy mandatory if there is any prolapse of the anterior or posterior vaginal walls at or beyond the hymen after the study procedure is completed. This is the most likely location of failures in this study.

18. Discretionary revision suggested, 1st paragraph statistical analysis section for sample size, page 14: I believe that they will have at least a 10% attrition from being unhappy with the treatment allocation with more lost to follow up over the 1 and 5 year study period. Maybe there is better follow-up in a European
population because of the health care system.

19. Major revision, last paragraph page 14, data analysis: This again concerns the primary outcome. Be specific. Sounds like a purely anatomic outcome. However, again states with symptoms. If using symptoms, need to specify what validated measure. No symptoms of vaginal bulging and protrusion on a validated questionnaire would be recommended, such as the Pelvic Floor Distress Inventory 20 question #3.

20. Discretionary revision: I suggest that the authors also add another secondary outcome to track. They should follow uterine issues such as bleeding, cervical dysplasia, etc and the need for a subsequent hysterectomy.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

No conflicts of interest.