


BMJ Open Preoperative POPQ versus Simulated Apical Support as a Guideline for Anterior or Posterior Repair at the Time of Transvaginal Apical Suspension (PREPARE trial): study protocol for a randomised controlled trial

Myung Jae Jeon ,¹ Chul Hong Kim,² Hyun-Hee Cho,³ Dong Hoon Suh,⁴ Soo Rim Kim⁵

To cite: Jeon MJ, Kim CH, Cho H-H, *et al.* Preoperative POPQ versus Simulated Apical Support as a Guideline for Anterior or Posterior Repair at the Time of Transvaginal Apical Suspension (PREPARE trial): study protocol for a randomised controlled trial. *BMJ Open* 2020;**10**:e034170. doi:10.1136/bmjopen-2019-034170

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2019-034170>).

Received 08 September 2019
Revised 12 December 2019
Accepted 16 December 2019



© Author(s) (or their employer(s)) 2020. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Professor Myung Jae Jeon; jeonmj@snu.ac.kr

ABSTRACT

Introduction Transvaginal reconstructive surgery is the mainstay of treatment for symptomatic pelvic organ prolapse. Although adequate support for the vaginal apex is considered essential for durable surgical repair, the optimal management of anterior and posterior vaginal wall prolapse in women undergoing transvaginal apical suspension remains unclear. The objective of this trial is to compare surgical outcomes of pelvic organ prolapse quantification (POPQ)-based surgery with outcomes of simulated apical support-based surgery for anterior or posterior vaginal wall prolapse at the time of transvaginal apical suspension.

Methods and analysis This is a randomised, multicentre, non-inferiority trial. While women who are assigned to the POPQ-based surgery group will undergo anterior or posterior colporrhaphy for all stage 2 or greater anterior or posterior vaginal prolapse, those assigned to simulated apical support-based surgery will receive anterior or posterior colporrhaphy only for the prolapse unresolved under simulated apical support. The primary outcome measure is the composite surgical success, defined as the absence of anatomical (anterior or posterior vaginal descent beyond the hymen or descent of the vaginal apex beyond the half-way point of vagina) or symptomatic (the presence of vaginal bulge symptoms) recurrence or retreatment for prolapse by either surgery or pessary, at 2 years after surgery. Secondary outcomes include the rates of anterior or posterior colporrhaphy, the changes in anatomical outcomes, condition-specific quality of life and sexual function, perioperative outcomes and adverse events.

Ethics and dissemination This study was approved by the institutional review board of each participating centre (Seoul National University College of Medicine/Seoul National University Hospital, Chonnam National University Hospital, Seoul St. Mary's Hospital, International St. Mary's Hospital). The results of the study will be published in peer-reviewed journals, and the findings will be presented at scientific meetings.

Trial registration number NCT03187054

Strengths and limitations of this study

- The findings will be strengthened by the multicentre, randomised design, the masking of both participants and outcome assessors to randomisation assignment, and the use of validated measures to assess anatomic and symptomatic outcomes.
- The support provided by the posterior half of the Graves speculum may not accurately simulate the apical support provided by contemporary surgical techniques.
- While the analysis of time-to-event outcomes minimises the selection bias due to loss of follow-up, it may overestimate surgical failure rates.
- The findings may not be extrapolated to women undergoing uterus-saving procedures or mesh augmented prolapse repairs.
- The questionnaires used do not include questions about pain, which will prevent comparing postoperative pain.

INTRODUCTION

Reconstructive surgery is the mainstay of treatment for symptomatic pelvic organ prolapse,¹ and most surgery is performed transvaginally.² Prolapse can arise from an isolated segment of the vagina but typically involves several vaginal segments. Therefore, a coordinated approach to repair is usually required. Nonetheless, there is no established guideline for how to best perform combined reconstruction.

Growing evidence supports that loss of apical support is almost always present when there is anterior or posterior vaginal prolapse that extends beyond the hymen and a concomitant apical suspension procedure at the time of prolapse surgery

can significantly reduce reoperation for recurrent prolapse.^{3–8} As a result, adequate support for the vaginal apex is now considered to be an essential component of pelvic reconstructive surgery. However, the optimal management of anterior and posterior vaginal wall prolapse in women undergoing transvaginal apical suspension remains unclear. Many surgeons perform a concomitant anterior or posterior colporrhaphy when stage 2–4 anterior or posterior vaginal prolapse is present during the preoperative pelvic organ prolapse quantification (POPQ) examination. However, others believe that this approach may expose a number of women to an unnecessary surgery with its attendant risk, and simulated apical support may help identify women who truly need a separate anterior or posterior procedure at the time of apical suspension. Indeed, a recent investigation demonstrated that a significant proportion of stage 2 or greater anterior or posterior vaginal wall prolapse is resolved when simulated apical support is provided during the POPQ examination.⁷

However, no comparative data exist about the relative efficacy and safety of these two approaches. The objective of the Preoperative POPQ versus Simulated Apical Support as a Guideline for Anterior or Posterior Repair at the Time of Transvaginal Apical Suspension (PREPARE) trial is to compare surgical outcomes of POPQ-based surgery with simulated apical support-based surgery for anterior or posterior vaginal wall prolapse at the time of transvaginal apical suspension.

METHODS AND ANALYSIS

Study design

We hypothesise that there is no difference in surgical success rates (primary outcome) between the two treatment groups 2 years after surgery. The PREPARE trial is a multicentre, prospective, randomised trial conducted with the aim of determining the non-inferiority of the primary outcome between POPQ-based surgery and simulated apical support-based surgery for anterior or posterior vaginal wall prolapse. The study will be a single-blind study, as it is impossible to blind the study surgeon for the surgical procedure to which the subject is assigned. However, it is our intent that when feasible and ethical, all outcome assessors and the subjects will be blinded to the treatment assignment. Postoperative follow-up will take place after 4–6 weeks and 6, 12 and 24 months. Patients will undergo a standard gynaecological examination including POPQ and complete questionnaires. The design is presented in [figure 1](#). This study protocol was approved on 9 June 2017 and this manuscript details the protocol on the latest version (V.1.3) approved on 13 December 2017, which adheres to the Standard Protocol Items: Recommendations for Interventional Trials guidelines (online supplementary file 1).

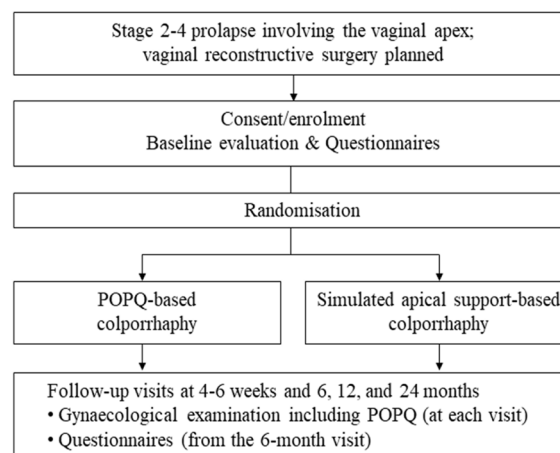


Figure 1 Study flow chart. POPQ, pelvic organ prolapse quantification.

Study setting

This study will be conducted in five tertiary hospitals in South Korea. A standardised protocol for enrolment, treatment and data collection will be employed by all sites.

Participants and recruitment

The study population will consist of women who have symptomatic stage 2–4 pelvic organ prolapse involving the vaginal apex and have opted for vaginal reconstructive surgery for prolapse repair. Participants must have prolapse of either the anterior or posterior vaginal wall resolved under simulated apical support. After screening for eligibility, information regarding the study will be provided and written informed consent will be obtained by research staff (online supplementary file 2). Inclusion and exclusion criteria are presented in [box 1](#).

Randomisation

Randomisation will be performed centrally through a website using a computer-generated randomisation table in the operating room to minimise surgeon and subject bias. The subjects will be assigned in a 1:1 ratio to receive either POPQ-based surgery or simulated apical support-based surgery. The randomisation will be stratified according to the surgeon and concomitant hysterectomy, and all subjects will receive a unique study number.

To minimise unmaking the actual procedures, the medical record will indicate the surgery by stating ‘transvaginal procedure per PREPARE protocol’. Intraoperative data collection will be conducted by the study surgeon rather than other research staff.

Intervention

Participants will undergo transvaginal surgery for prolapse, including the assigned procedure for anterior or posterior vaginal prolapse under general or spinal anaesthesia. Women who are assigned to the POPQ-based surgery group will undergo anterior or posterior colporrhaphy for all stage 2 or greater anterior or posterior

Box 1 Inclusion and exclusion criteria
Inclusion criteria

- ▶ Age >30 years.
- ▶ Stage 2, 3 or 4 prolapse.
- ▶ Descent of vaginal apex at least half-way into the vaginal canal (pelvic organ prolapse quantification point C \geq -total vaginal length/2).
- ▶ Anterior or posterior vaginal prolapse resolved under simulated apical support (from stage 2–4 to stage 0–1).
- ▶ Vaginal bulge symptoms as indicated by an affirmative response to the following questions from the Pelvic Floor Distress Inventory-20: do you usually have a bulge or something falling out that you can see or feel in your vaginal area?
- ▶ Vaginal reconstructive surgery is planned.

Exclusion criteria

- ▶ Large pelvic mass which may make vaginal surgery difficult (eg, uterus >12 weeks' size).
- ▶ History of prolapse surgery.
- ▶ Known malignancy.
- ▶ History of \geq 2 inpatient hospitalisations for medical comorbidities in the previous year.
- ▶ Subject wishes to retain her uterus.
- ▶ Subject is unable and unwilling to participate.

vaginal prolapse (ie, point Ba or Bp \geq -1); those assigned to simulated apical support-based surgery will receive anterior or posterior colporrhaphy only for the prolapse unresolved under simulated apical support (ie, remeasurement of Ba or Bp \geq -1) (table 1).

The anterior or posterior colporrhaphy will be performed in a traditional manner with midline plication of the fibromuscular layer using 2–0 delayed absorbable sutures (Vicryl or Polydioxanone II; Ethicon, Somerville, New Jersey, USA).^{9 10} Levator ani plication can be included in the posterior colporrhaphy in cases of sexually inactive patients. Perineorrhaphy can also be performed, if indicated (ie, when a perineal defect, separation of the perineal muscles, is noted at the time of surgery). The use of biological or synthetic graft materials will not be allowed in either anterior or posterior colporrhaphy.

Concomitant procedures will be performed as intended prior to surgery. Women with a uterus in situ will undergo hysterectomy, and all women will receive transvaginal vault suspension, including uterosacral ligament suspension,

sacrospinous ligament fixation and iliooccygeal suspension with both delayed absorbable and permanent sutures (Polydioxanone II and Prolene 0; Ethicon), according to the preference of the surgeon. A reassessment of pelvic support will be performed at the completion of all the above procedures under anaesthesia without Valsalva. In the event that the anterior or posterior vaginal walls are not located at least 1 cm above the hymen (ie, POPQ point Ba or Bp \geq -1), a corrective anterior or posterior colporrhaphy will be performed and recorded within the text of the operative report. Incontinence surgery will also be performed for women with urodynamic stress incontinence (ie, involuntary leakage of urine during filling cystometry, associated with increased intra-abdominal pressure, in the absence of a detrusor contraction).

Participating surgeons are required to have performed a minimum of 20 of each procedure prior to beginning subject enrolment to eliminate a learning curve effect. All women will receive perioperative antibiotics. Postoperatively a vaginal pack will be placed and removed within 24 hours. A voiding trial will take place on postoperative day 2. A postvoid residual 150 mL or greater is considered abnormal. Patients with elevated postvoid residuals will continue mechanical bladder drainage either via continuous transurethral Foley catheter or intermittent self-catheterisation until postvoid residuals are consistently less than 150 mL. Patients will receive analgesics in accordance with the local hospital protocol. All patients are advised to abstain from heavy physical work for a minimal period of 6 weeks.

Data collection

At baseline, the following data will be collected: demographics, a medical history, a standardised POPQ examination in a 45° upright sitting position with an empty bladder and remeasurement of anterior or posterior vaginal points (point Ba or Bp) during maximal Valsalva with simulated apical support (ie, while holding the apex at approximately the depth of total vaginal length using the posterior blade of a standard Graves speculum).^{7 11} The Graves blade will be positioned with its tip at the apex over the posterior vagina while remeasuring the anterior vaginal points, and over the anterior vagina while remeasuring the posterior points.⁷ Patients will be asked to

Table 1 Intervention assignments according to the results of the POPQ examination with or without apical support

POPQ value		POPQ-based surgery group	SAS-based surgery group
Without apical support	With apical support		
Ba \geq -1, Bp \geq -1	Ba $<$ -1, Bp \geq -1	AR+PR	PR
Ba \geq -1, Bp \geq -1	Ba \geq -1, Bp $<$ -1	AR+PR	AR
Ba \geq -1, Bp \geq -1	Ba $<$ -1, Bp $<$ -1	AR+PR	–
Ba \geq -1, Bp $<$ -1	Ba $<$ -1, Bp $<$ -1	AR	–
Ba $<$ -1, Bp \geq -1	Ba $<$ -1, Bp $<$ -1	PR	–

AR, anterior repair; POPQ, pelvic organ prolapse quantification; PR, posterior repair; SAS, simulated apical support.

complete validated questionnaires regarding condition-specific quality of life (Pelvic Floor Distress Inventory-20 and Pelvic Floor Impact Questionnaire-7) and sexual function (Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire-12).^{12 13}

Scheduled in-person follow-up will occur at 4–6 weeks and 6, 12 and 24 months. Each follow-up visit will include a clinical examination including POPQ and written questionnaires identical to those at baseline (starting with the 6-month visit). In addition, an update of current medications, an assessment of new or continuing pelvic floor disorders and adverse events that occurred since the previous evaluation will be obtained at each visit. All data will be anonymised and collected using cases report forms by examiners or trained research coordinators at each participating centre who are blinded to the treatment assignment. Quality checks will be performed by all centres and reviewed every 3 months by an independent data monitoring committee.

Primary and secondary outcome measures

The primary outcome measure will be surgical success assessed 2 years after surgery. Success will be defined as the absence of all of the following: (1) anterior or posterior vaginal descent beyond the hymen (ie, point Ba or Bp >0); (2) descent of the vaginal apex beyond the half-way point of vagina (ie, point C >−1/2×total vaginal length); (3) vaginal bulge symptoms; (4) retreatment for prolapse by either surgery or pessary. Secondary outcomes will include the rates of anterior or posterior colporrhaphy, the changes in anatomical outcomes, condition-specific quality of life and sexual function, perioperative outcomes and adverse events.

Sample size and power considerations

The aim of this study was to assess the non-inferiority of both interventions regarding the primary endpoint. Randomised trials with 2-year follow-up using similar definitions to ours have demonstrated that the surgical success rates after transvaginal apical suspension were between 67% and 80%.^{14–16} Based on this information, we assumed that the surgical success rate in each group will be 80% at 2 years and set the non-inferiority margin at 13%. We calculated that a minimum of 149 subjects per group would be required to have 80% power for a non-inferiority margin of 13% using a two-sided test with a 5% level of significance. Considering a 10% dropout rate, we will recruit and randomise 332 subjects in this protocol.

Data analysis

Baseline characteristics between the two groups will be compared using a two-sample t-test or Mann-Whitney U test for continuous variables and a χ^2 test or Fisher's exact test for categorical variables.

The analyses for all outcome measures will be performed on both an intention-to-treat and as-treated basis, but the principle analysis will be the intention-to-treat analysis for the effectiveness and the as-treated analysis for

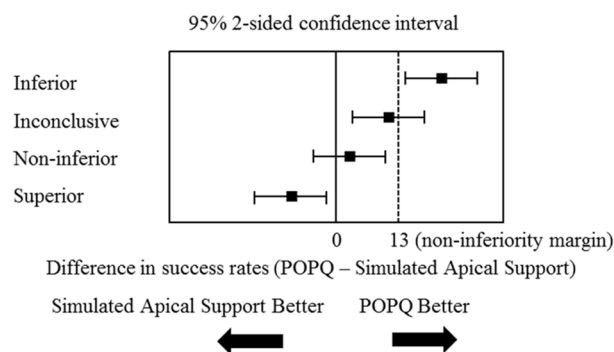


Figure 2 Examples of scenarios for non-inferiority trials with trial conclusions. POPQ, pelvic organ prolapse quantification.

the safety. Imputation of missing values will not be done for primary and secondary outcome measures. We will use the Kaplan-Meier method to estimate success rates at 2 years. Non-inferiority will be declared if the upper boundary of the 95% CI for the between-group difference in the success rate is less than 13% (figure 2). We will use Cox proportional-hazards models or time-dependent Cox regression to estimate HRs and 95% CIs, according to the result of Schoenfeld residual tests. If differences between groups are found, the baseline variable will be included as covariates. The difference in treatment effect between subgroups will also be examined by including an interaction between the treatment group and the subgroup variable.

The rates of anterior or posterior colporrhaphy between the two groups will be compared with a χ^2 test. Outcomes regarding anatomical outcomes, condition-specific quality of life and sexual function will be analysed using linear mixed models, with adjustment for baseline values. Perioperative outcomes and adverse events were compared with a two-sample t-test or Mann-Whitney U test (continuous outcomes) and a χ^2 test or Fisher's exact test (dichotomous outcomes). If differences between groups are found, the baseline variable will be included as covariates in the linear mixed models and multivariable logistic regression analyses.

Patient and public involvement

Neither patients nor the public were involved in the design, conduct, reporting or dissemination of this study.

Data monitoring

Data monitoring will be performed every 3 months by an independent data monitoring committee. The committee will monitor protocol deviations, violations, data quality and serious adverse events. No interim analysis is planned during this trial.

ETHICS APPROVAL AND DISSEMINATION

The study will be conducted in accordance with the principles of the Declaration of Helsinki and 'good clinical practice' guidelines. Prior to randomisation, informed

consent will be obtained. All participant-identifiable data, such as consent forms, screening and identification logs will be stored in the investigator site files, accessible only to delegated members of the study team. Any personal information will neither be recorded in case report forms nor shared with others. The datasets used and/or analysed after completing the study will be available from the corresponding author under reasonable requests. The results of the study will be published in peer-reviewed journals, and the findings will be presented at scientific meetings. Authorship will be determined by the guidelines set out by the International Committee of Medical Journal Editors.

Author affiliations

¹Obstetrics and Gynecology, Seoul National University College of Medicine, Seoul, Republic of Korea

²Obstetrics and Gynecology, Chonnam National University Medical School, Gwangju, Republic of Korea

³Obstetrics and Gynecology, The Catholic University of Korea, Eunpyeong St. Mary's Hospital, Seoul, Republic of Korea

⁴Obstetrics and Gynecology, Seoul National University Bundang Hospital, Seongnam, Republic of Korea

⁵Obstetrics and Gynecology, International St. Mary's Hospital, Catholic Kwandong University College of Medicine, Incheon, Republic of Korea

Contributors All authors contributed to the conception and design of the research protocol. MJJ is the principal investigator of the entire study. CHK, H-HC, DHS and SRK are the site principal investigators at each research centre. MJJ drafted the original manuscript, and CHK, H-HC, DHS and SRK revised it. All authors approved the final version.

Funding This work was supported by the SNUH Research Fund (grant number 05-2017-0050). The funding body has no role in the design of the study, the collection, analysis, interpretation of data and writing the manuscript.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This trial was approved by the institutional review board of each participating centre (Seoul National University College of Medicine/Seoul National University Hospital, Chonnam National University Hospital, Seoul St. Mary's Hospital, International St. Mary's Hospital).

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iD

Myung Jae Jeon <http://orcid.org/0000-0001-5582-1488>

REFERENCES

- 1 Suskind AM, Jin C, Walter LC, *et al*. Frailty and the role of obliterative versus reconstructive surgery for pelvic organ prolapse: a national study. *J Urol* 2017;197:1502–6.
- 2 Haya N, Baessler K, Christmann-Schmid C, *et al*. Prolapse and continence surgery in countries of the organization for economic cooperation and development in 2012. *Am J Obstet Gynecol* 2015;212:755.e1–27.
- 3 Rooney K, Kenton K, Mueller ER, *et al*. Advanced anterior vaginal wall prolapse is highly correlated with apical prolapse. *Am J Obstet Gynecol* 2006;195:1837–40.
- 4 Summers A, Winkel LA, Hussain HK, *et al*. The relationship between anterior and apical compartment support. *Am J Obstet Gynecol* 2006;194:1438–43.
- 5 Chen L, Ashton-Miller JA, Hsu Y, *et al*. Interaction among apical support, levator ani impairment, and anterior vaginal wall prolapse. *Obstet Gynecol* 2006;108:324–32.
- 6 Hsu Y, Chen L, Summers A, *et al*. Anterior vaginal wall length and degree of anterior compartment prolapse seen on dynamic MRI. *Int Urogynecol J* 2007;19:137–42.
- 7 Lowder JL, Park AJ, Ellison R, *et al*. The role of apical vaginal support in the appearance of anterior and posterior vaginal prolapse. *Obstet Gynecol* 2008;111:152–7.
- 8 Eilber KS, Alperin M, Khan A, *et al*. Outcomes of vaginal prolapse surgery among female Medicare beneficiaries: the role of apical support. *Obstet Gynecol* 2013;122:981–7.
- 9 Altman D, Väyrynen T, Engh ME, *et al*. Anterior colporrhaphy versus transvaginal mesh for pelvic-organ prolapse. *N Engl J Med* 2011;364:1826–36.
- 10 Kudish BI, Iglesia CB. Posterior wall prolapse and repair. *Clin Obstet Gynecol* 2010;53:59–71.
- 11 Bump RC, Mattiasson A, Bø K, *et al*. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. *Am J Obstet Gynecol* 1996;175:10–17.
- 12 Yoo E-H, Jeon MJ, Ahn K-H, *et al*. Translation and linguistic validation of Korean version of short form of pelvic floor distress inventory-20, pelvic floor impact questionnaire-7. *Obstet Gynecol Sci* 2013;56:330–2.
- 13 Yoo EH, Jeon MJ, Ahn KH, *et al*. Translation and linguistic validation of Korean version of short form of PISQ (pelvic organ prolapse and incontinence sexual questionnaire). *Kor J Urogynecol* 2012;14:42–7.
- 14 Benson JT, Lucente V, McClellan E. Vaginal versus abdominal reconstructive surgery for the treatment of pelvic support defects: a prospective randomized study with long-term outcome evaluation. *Am J Obstet Gynecol* 1996;175:1418–22.
- 15 Barber MD, Brubaker L, Burgio KL, *et al*. Comparison of 2 transvaginal surgical approaches and perioperative behavioral therapy for apical vaginal prolapse. *JAMA* 2014;311:1023–34.
- 16 Detollenaere RJ, Kreuvel IAM, Dijkstra JR, *et al*. The impact of Sacrospinous Hysteropexy and vaginal hysterectomy with suspension of the Uterosacral ligaments on sexual function in women with uterine prolapse: a secondary analysis of a randomized comparative study. *J Sex Med* 2016;13:213–9.