**Study Protocol**

A prospective cohort study for success of vaginal hysterectomy with vault suspension compared to Manchester-Fothergill Procedure for utero-vaginal prolapse

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**Definitions**

|  |  |
| --- | --- |
| POP | Pelvic organ prolapse |
| RCT | Randomised Controlled Trial |
| MP | Manchester-Fothergill Procedure |
| VH | Vaginal Hysterectomy |

**Study synopsis**

**Protocol number version 1**

**Protocol title**

A prospective cohort study for success of vaginal hysterectomy with vault suspension compared to Manchester-Fothergill Procedure for utero-vaginal prolapse

**Public Title**

Comparing Vaginal Hysterectomy and Manchester Procedure for uterine prolapse

**Short Title**

The VaMP Study

**Type of study**

Multi-centre prospective cohort study

Study Locations

* Mercy Hospital for Women, 163 Studley Rd, Heidelberg VIC 3084
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**Resources**

As this study will compare operations already performed at the Monash Urogynaecology unit, there will not be additional resources required beyond the efforts required to consent, assess and follow-up participants, as well as analyze data and report findings.

**Study Objectives**

To evaluate MP versus VH for the treatment of Utero-vaginal prolapse

**Study population**

Female patients between the ages of 18-80 years with symptoms of POP who request surgical treatment

**Study duration**

Primary outcome efficacy at 24 months follow up. Ongoing follow up to 5 years

**Number of participants**

TBA

1. **Background & Rationale of study**

The Manchester Procedure (MP) and vaginal hysterectomy with vault suspension (VH) are two surgical options for the treatment of pelvic organ prolapse (POP)[1]. The evidence of benefit is currently limited to one prospective trial and several retrospective reviews[2]. This data was collated recently in a meta-analysis reviewing options for uterine preservation vs hysterectomy in pelvic organ prolapse surgery[2]. This study was able to pool data to show that blood loss, risk of transfusion and operating time favoured MP but there was no difference in hospital stay. The only prospective trial was performed in Turkey [3], involved 94 patients with a follow up time of 5 years and demonstrated no difference in the c-point post-operatively, but a longer total vaginal length (TVL) in the MP group. There was no record in this paper for the indication for surgery. Recurrent prolapse requiring reoperation was not significantly different (3 in VH vs 1 in MP) between the groups although the study was not setup to detect this difference. Presumably, based on this statistic, they determined that the recurrence rate for prolapse was 2.04% and 6.6% for MP and VH respectively. In fact, there is no explanation of how a sample size was reached. There is no explanation of how the vault was suspended for the VH group.

Recent Danish registry data in a matched cohort study (n=590)[4] showed recurrent or de novo POP in any compartment was higher after VH (18.3%) compared with the MP (7.8%) (Hazard ratio, HR= 2.5, 95% confidence interval (CI): 1.3–4.8). Recurrence in the apical compartment occurred in 5.1% after VH vs. 0.3% after the MP (hazard ratio (HR) = 10.0, 95% confidence interval (CI) 1.3–78.1). This study defined Recurrent POP as one or more of the following:

* POP treated with pessary or surgery
* POP-Q stage II with POP symptoms
* POP-Q stage ≥ III independent of POP symptoms

Additionally, Danish registry data shows that the hazard ratio for a repeat operation in the apical compartment was higher in the VH group versus the MP group with a 5 year reoperation rate of 11% and 7% respectively[5].

The two procedures have been studied in isolation though much more data exists for VH. For MP, a prospective cohort of MP procedures took place[6], and demonstrated 99% (c < -1) success for the apical compartment but only 49% in the anterior compartment (Ba < -1) at 12 months in 148 women. 96% of this group report cure or significant improvement.

In a RCT comparing VH with uterosacral suspension versus sacrospinous hysterectomy, The Pelvic Floor Disorders Network demonstrated surgical success rates of 64.5% and 63.1% using a stricter criteria [7]:

* No apical descent greater than 1/3 of TVL of posterior/anterior vaginal wall beyond hymen
* No bothersome vaginal bulge
* No re-treatment for prolapse at 2 year

5 year follow-up of the same patients showed poorer outcomes of 61% and 70% failure[8].

In addition to the question of effectiveness of the procedure, the economic benefits of MP versus VH have been studied in the international literature. Costs for the first 20 months after the operation were higher in the VH group when analyzing the primary operation only, and higher still when including subsequent activities within 20 months[9].

Given the MP is performed far less frequently in Australia, presumably due to patient selection and surgeon preference, there is a benefit for the local and international community to learn more about the differences in outcome between the procedures. Local data that shows equivalent outcomes may encourage increased uptake of the procedure which may lead to health gains for the patient and improved economic outcomes for hospitals.

1. **Hypothesis**

MP is non-inferior to VH for prolapse recurrence

1. **Aims**

Primary outcome

To assess the success of MP versus VH at 6 months, 2 years, 5 years defined as

* Objective: No recurrent prolapse requiring repeat prolapse surgery or pessary
* Subjective: Absence of bulge sensation

Secondary outcomes

1. Anatomical:
	1. All POPQ points
2. Subjective success
	1. Absence of vaginal bulge
3. Reoperation
	1. Repeat surgery
		1. Surgery for complications
		2. Surgery for stress urinary incontinence
4. PT satisfaction-
	1. PGII
	2. Quality of life- IIQ7
	3. POP symptoms- POPDI
	4. Lower urinary tract symptoms- UDI-6
	5. Bowel dysfunction -CRADI
	6. Sexual function- PISQ-12
5. Complications-Clavien-Dindo
	1. Ureteric kinking
6. Post-operative pain
7. Peri-operative outcomes
	1. Bloods loss
	2. Hospital stay
	3. Analgaesia requirements

Outcomes will be reported in line with recommendations and terminology from The International Urogynecological Association (IUGA) and The International Continence Society (ICS)[10].

1. **Methodology**

Study Design

Multi-centre prospective Cohort study.

Participants

Recruitment: All participants with symptomatic POP requesting surgical management for their symptoms. Patients will be recruited from public and private clinics. Screening will take place if patients request surgery for POP. Initial approach will be by investigators in person at pelvic floor clinics. Potential participants will receive the patient information and consent form. Patients will have weeks-months to consider if they would like to be part of the study.

Intervention

As is usual practice participants would be offered uterine preserving surgery such as MP as well as hysterectomy. Operations would be performed by accredited members of the urogynaecology unit for either operation.

Operative standardisation will be conducted to ensure similar operating methods.

Surgical approach in the MP group will conform to the following approach:

* Cervical incision with dissection of bladder and vaginal epithelium from cervix
* Identification of uterosacral ligaments and subsequent development of uterosacral pedicles
* Amputation of cervix
* Anterior repair as required
* Attachment of uterosacral ligaments to cervical stump with 0 PDS
* Sturndorf sutures to re-epithelialise cervix
* Posterior Repair as required

Surgical approach in the VH group will conform to the following approach:

* Vaginal hysterectomy as per surgeon preference
* Use of O PDS for bilateral uterosacral suspension x2, or Modified McCall suspension sutured to vaginal vault
* Anterior wall repair if required as determined by surgeon
* Posterior repair if required
* Cystoscopy

Sample Size Calculation

Based on 2-year follow up of composite Success in a previous trial (SAVE-U), if there is truly no difference between the standard and experimental treatment (assuming 76% in both groups), an RCT would require 202 patients are required to be 80% sure that the upper limit of a one-sided 95% confidence interval (or equivalently a 90% two-sided confidence interval) will exclude a difference in favour of the standard group of more than 15%. This will be the first prospective cohort study performed comparing these procedures and so sample size will be 200 participants. At Monash Hospital, VH is more common than MP and so we anticipate to recruit 150 VH and 50 MP.

Study Duration

Patients are recruited from 2021-2025 unless sample size is reached earlier.

* Follow up will be performed for 5 years

Inclusion Criteria

All participants between the ages of 18-80 with symptomatic stage I-III POP requesting surgery including hysterectomy

Capable of providing informed consent and able to return for follow up.

Exclusion Criteria

Any previous prolapse surgery

Previous surgery in the treatment area in the last year.

Systemic steroids use within the last 3 months

Pelvic organ prolapse (POP) > stage 3 according to pelvic organ prolapse quantification system

Past history of prolapse surgery with transvaginal mesh

Serious systemic disease or any chronic condition that could interfere with study compliance

Uterine pathology that would make uterine preservation inappropriate

Co-morbidities or surgical history that would make a particular approach inappropriate

Any other reason that, in the opinion of the investigator, prevents the subject from participating in the study or compromise the subject safety

Consent

Informed consent will obtained by providing verbal and written information about the interventions being offered. The information sheets will be presented to patients by an investigator and patients will be able to ask the investigator any questions. Patients will be allowed as much time as required to consider their participation in the research.

Withdrawals

Participation is voluntary. Participants are free to withdraw from the project at any stage and their medical management and follow up will not be affected at any time.

In the event of withdrawal, we will request permission to include clinical data in our final analyses.

Trial Flow

All patients with symptomatic stage I-III POP requesting surgery including hysterectomy will be screened.

The treating doctor (consultant urogynaecologist / urogynaecology fellow) will review the inclusion/exclusion criteria and if eligible, provide patient information and obtain consent to be included in the study.

Pre-treatment assessment will include collection of demographic data such as age, weight, height, parity, hormone replacement therapy status, past surgical history, pertinent medical history and results of physical examination. Severity of prolapse will be evaluated following the standard terminology of POPQ recommended by the International Continence Society[11]. Questionnaires used will be validated grade A questionnaires and are summarized in the table below. Pelvic ultrasound will be performed to exclude uterine and ovarian pathology if a Manchester procedure is planned, unless recent result is available.

Peri-operative parameters will be recorded during the participant’s admission including operative time, complications (including infection and failed trial of void), ureteric obstruction, blood loss, and analgesia requirements.

Follow up will formally occur at 6weeks, 6 months, yearly to 5 years and involve similar assessments as performed in the pre-operative setting. This will include assessment of the primary and secondary outcomes as outlined above and summarized in the table below

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Baseline | Operation | 6 Weeks | 6 Months | Yearly |
| Event | T1 | T2 | T3 | T4 | T5 |
| History  | X |  |  |  |  |
| Inclusion/ Exclusion criteria  | X |  |  |  |  |
| Urogynaecological examination (POP-Q assessment)) | X |  | X | X | X |
| Pelvic US for MP group if needed | X |  |  |  |  |
| Demographic data | X |  |  |  |  |
| QOL questionnaires | X |  |  | X | X |
| CRADI | X |  |  | X | X |
| UDI-6 | X |  |  | X | X |
| PISQ | X |  |  | X | X |
| PGII |  |  |  | X | X |
| IIQ-7 | x |  |  | x | x |
| Peri-operative outcomes |  | X |  |  |  |
| Complications |  | X |  | X | X |
| Symptomatic Recurrence |  |  |  | X | X |
| POP re-treatment (surgery or pessary) |  |  |  | X | X |

1. **Adverse events**

Both operations are performed at Monash Health and participants will be counselled in the standard manner. Common potential complications include:

* Bleeding
* Infection
* Venous thromboembolism
* Trauma to viscera
* Recurrence of prolapse
* De Novo SUI
* With regard to the MP
	+ It is a shorter procedure, with reduced blood loss.
	+ Retaining the uterus and cervix retains the risk of uterine and cervical cancers
* With regards to VH
	+ A longer procedure with more blood loss.
	+ Possible removal of fallopian tubes reduces risk of ovarian cancer by 50%
1. **Statistical analysis**

Outcomes were compared with Pearson chi squared test for categorical data and Student *t* test or Wilcoxon signed rank Test for continuous data as appropriate. 2 sided 95% confidence intervals will be used. Regression analysis will be performed as appropriate.

Pre-treatment & post-treatment changes in patient reported outcomes were analysed using Analaysis of covariance (ANCOVA) to adjust for baseline data.

1. **Data Monitoring Committee**

Monash Hospital

1. **Administrative Procedures**

Amendments to protocol

All modifications to this study will be written and filed as amendments to this protocol. Such modification(s) will be made jointly by the principal investigators with approval of the Ethics Committee. Any modifications to the study will be applied for all subsequent patients after Ethics Committee approval.

Confidentiality

Participant confidentiality will be maintained at all times. All study documents will be held at the Monash Hospital Urogynaecology Department in a locked cupboard. All participant data will be de-identified and held electronically in a password protected database. Where records are recorded digitally (e.g. REDCAPS), they will be stored securely within The University Server.

Retention of records

All documents associated with this study will be kept for 15 years. Upon study completion, study records will be securely stored offsite (e.g. Iron Mountain). After 15 years, study documents will be securely disposed of.

1. **Feasibility**

We have conducted several large studies through our unit. We perform the surgeries to be studied in this trial on a regular basis. The large sample size means recruitment will take years but it would be reasonable to expect to recruit 4-6 participants/month. There is likely to be a high uptake from participant’s screened due to the fact that the operations to be performed are not a departure from standard care.

1. **Results and Outcomes**

It is intended that this research will be published in an appropriate peer-reviewed journal. Participants will be able to access results from the research once the results are published. There are no plans for secondary use of the data obtained.

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