

# Surgical interventions for uterine prolapse and for vault prolapse: the two VUE RCTs

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## Scientific summary

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# Scientific summary

## Background

The treatment of women with pelvic organ prolapse is a considerable burden to the UK NHS. Prolapse is a progressive condition, often initiated by childbirth, with the symptoms appearing many years later. Conservative treatment with pelvic floor exercises, oestrogens and pessaries might help in the earlier stages, but 6–20% of affected women will require surgery by the age of 80 years, with a further surgery rate of around 13%.

Surgeons and researchers have suggested that uterine preservation for uterine descent and abdominal procedures for vault prolapse might provide a better chance of cure and reduce the need for further surgery. This is important because if the failure rate is reduced, women will be exposed to less risk and the costs may be less to the NHS. However, there is growing concern about the long-term consequences of uterine preservation and abdominal procedures, especially if they require augmentation with mesh.

## Aims and objectives

The aim of the Vault or Uterine prolapse surgery Evaluation was to compare the clinical effectiveness and cost-effectiveness of treatment modalities for apical prolapse.

The primary outcome measures were women's symptoms measured using the Pelvic Organ Prolapse Symptom Score and prolapse-specific quality-of-life using a visual analogue scale. Cost-effectiveness was assessed as cost per quality-adjusted life-year gained, based on the EuroQol-5 Dimensions, three-level version.

Secondary objectives were to compare treatments in terms of bladder, bowel and sexual function, adverse events, objective measurement of anatomical prolapse stage (using the Pelvic Organ Prolapse Quantification system), further treatment, cost to the health service and patients, and satisfaction with treatment. Longer-term implications for cost-effectiveness were explored using a Markov probabilistic decision-analytic model from the perspective of the NHS.

## Methods

Research ethics approval and fully informed consent were obtained. The study included women who were deemed to require apical (vault or uterine) surgery based on symptoms and/or anatomical findings. The study excluded women who were unable or unwilling to consent or unable to complete study questionnaires.

UK hospitals with surgeons experienced in all procedures participated in the Vault or Uterine prolapse surgery Evaluation between March 2013 and January 2017.

A total of 563 eligible women participated in the Uterine trial and 208 in the Vault trial.

## Randomisation

For both the Uterine and the Vault trials, randomisation involved a computer-generated randomisation system managed by the Centre for Healthcare Randomised Trials at the University of Aberdeen. Participants were randomly allocated in a 1 : 1 ratio. The minimisation algorithm included surgeon, age (< 60 years or ≥ 60 years), type of planned apical prolapse repair, planned concomitant continence surgery and anterior and/or posterior compartment prolapse repair.

### Study interventions

Surgeons were asked to use the surgical techniques with which they were most familiar. As this was a pragmatic trial, deviation could occur both from the randomised allocation and from their normal practice for clinical reasons. Details were recorded of concomitant surgery for anterior and/or posterior prolapse and continence surgery.

### Statistical analysis

An intention-to-treat analysis was performed in which participants with observed outcome data were analysed according to their randomised allocation. Primary and secondary outcomes were compared using generalised linear mixed models, adjusting for baseline covariates.

### Health economics

Two within-trial cost-effectiveness analyses were conducted over the 12-month follow-up. All analyses were reported on the intention-to-treat principle. NHS and participant perspectives were considered, and all costs were reported in 2015–16 Great British pounds. Quality-adjusted life-years were calculated based on responses to the EuroQoL Dimensions, three-level version questionnaire. Results were reported as incremental cost-effectiveness ratios based on multiple imputations of missing data. Cost-effectiveness acceptability curves and scatterplots of the cost-effectiveness plane were used to illustrate uncertainty in the data.

A de novo probabilistic Markov cohort model was developed to reflect the treatment pathway for women requiring prolapse surgery and extrapolated the Uterine trial results over the longer term. The model assigned a cohort of 1000 women, with an average age of 63 years, to mutually exclusive health states (failure, complications and well) in monthly cycles over a 30-year time horizon. All-cause mortality was included in the model as a competing risk. Transition probabilities between health states were based on time to failure (requiring re-operation) and complications (requiring hospitalisation) observed in the trial and extrapolated over the longer term using Weibull survival regression models. Utilities and costs of each modelled health state were obtained from generalised linear regression models to determine the effect of state membership on costs and quality-adjusted life-years using the trial data. All data were incorporated into the model probabilistically, sampling from statistical distributions for each model parameter. The model's results are reported as discounted (3.5% per annum) incremental costs per quality-adjusted life-year from a UK NHS perspective.

## Results

In total, 2088 women were screened for eligibility. In the Uterine trial, 563 (41%) women were randomised from 1365 eligible women, and 208 (49%) women were randomised to the Vault trial from 428 eligible women. The main reason for declining randomisation was the woman's or the surgeon's preference for a specific treatment. The majority of women, 469 (83%) in the Uterine trial and 175 (84%) in the Vault trial, received their allocated treatment.

In the Uterine trial, 29 (10%) women randomised to uterine preservation underwent a vaginal hysterectomy, 31 (11%) did not receive any apical surgery and five (2%) underwent another apical intervention. Among those women randomised to vaginal hysterectomy, five (2%) had a uterine preservation, 22 (8%) had no apical surgery and two (< 1%) had other apical surgery.

In the Vault trial, seven (6.7%) women randomised to an abdominal procedure underwent a vaginal procedure and 11 (10.6%) had no apical surgery. Among those women randomised to a vaginal procedure, four (3.8%) had an abdominal procedure and 10 (9.6%) had no apical surgery.

The 12-month follow-up appointment was well attended [i.e. 466 (83%) of those women randomised in the Uterine trial, and 178 (86%) of those women randomised in the Vault trial] and 478 (85%) of Uterine trial participants and 177 (85%) of Vault trial participants completed the 12-month questionnaire (primary outcome).

### **Prolapse symptoms reported by women**

The primary outcome was women's report of prolapse symptoms on the Pelvic Organ Prolapse Symptom Score. The score ranged from 0 to 28 at 12 months after randomisation. After adjusting for baseline scores and minimisation covariates, the mean Pelvic Organ Prolapse Symptom Score was similar for each comparison:

- Uterine trial: a mean Pelvic Organ Prolapse Symptom Score for the uterine preservation group of 4.2 (standard deviation 4.9) versus a mean Pelvic Organ Prolapse Symptom Score for the vaginal hysterectomy group of 4.2 (standard deviation 5.3) (mean difference  $-0.05$ , 95% confidence interval  $-0.91$  to  $0.81$ ).
- Vault trial: a mean Pelvic Organ Prolapse Symptom Score for the abdominal procedure group of 5.6 (standard deviation 5.4) versus a mean Pelvic Organ Prolapse Symptom Score for the vaginal procedure group of 5.9 (standard deviation 5.4) (mean difference  $-0.61$ , 95% confidence interval  $-2.08$  to  $0.86$ ).

There was also no statistically significant difference in the prolapse-related quality-of-life score (range 0–10), measured as the interference of prolapse symptoms with everyday life:

- Uterine trial: a mean prolapse-related quality-of-life score for the uterine preservation group of 1.7 (standard deviation 2.5) versus a mean prolapse-related quality-of-life score for the vaginal hysterectomy group of 1.5 (standard deviation 2.5) (mean difference  $0.12$ , 95% confidence interval  $-0.26$  to  $0.49$ ).
- Vault trial: a mean prolapse-related quality-of-life score for the abdominal procedure group of 2.3 (standard deviation 3.0) versus a mean prolapse-related quality-of-life score for the vaginal procedure group of 2.6 (standard deviation 2.8) (mean difference  $-0.25$ , 95% confidence interval  $-1.10$  to  $0.59$ ).

### **Objective clinical outcomes**

There were no clinical differences in the number of women with an overall or residual apical objective prolapse beyond the hymen at 12 months after their operation:

- Uterine trial: 31.8% of women had an overall objective prolapse in the uterine preservation group versus 34.1% of women in the vaginal hysterectomy group (odds ratio 0.85, 95% confidence interval 0.55 to 1.32).  
Apical objective prolapses occurred in 5.7% of women in the uterine preservation group versus 5.3% of women in the vaginal hysterectomy group (odds ratio 1.18, 95% confidence interval 0.48 to 2.94).
- Vault trial: 32.6% of women had an overall objective prolapse in the abdominal procedure group versus 46.9% of women in the vaginal procedure group (odds ratio 0.50, 95% confidence interval 0.25 to 1.02).  
Apical objective prolapses occurred in 6.0% of women in the abdominal group versus 9.0% of women in the vaginal group (odds ratio 0.61, 95% confidence interval 0.18 to 2.08). Objective anterior prolapse stage 2b or more was higher in women in the vaginal group (odds ratio 0.38, 95% confidence interval 0.18 to 0.79).

### **Adverse events**

The number of women with serious adverse events was similar between the groups in the first 12 months, with blood loss ( $n = 5$ ) and haematoma ( $n = 7$ ) being the most common types of adverse event in the Uterine trial and injury to bladder ( $n = 3$ ) being the most common in the Vault trial. There were no statistically significant differences between the randomised groups for any adverse event measure at any time period.

- Uterine trial: 5.4% of women in the uterine preservation group had an adverse event versus 5.9% of women in the vaginal hysterectomy group (risk ratio 0.82, 95% confidence interval 0.38 to 1.75).  
Of the 129 procedures (apical and concomitant) using a mesh implant, one mesh exposure/extrusion was identified and required surgical treatment in the first 12 months after surgery.
- Vault trial: 5.9% of women in the abdominal procedure group had an adverse event versus 6.0% in the vaginal procedure group (risk ratio 0.97, 95% confidence interval 0.27 to 3.44).  
Of the 106 procedures (apical and concomitant) using a mesh implant, one concomitant continence mesh exposure/extrusion was identified and required surgical treatment in the first 12 months after surgery.

## Economic outcomes

- Uterine trial: the base-case analysis shows that, on average, uterine preservation is £235 (95% confidence interval £6 to £464) more expensive than vaginal hysterectomy and generates non-significantly fewer quality-adjusted life-years (adjusted mean difference  $-0.004$ , 95% confidence interval  $-0.026$  to  $0.019$ ). Uterine preservation was associated with a 15% chance of cost-effectiveness if society is willing to pay £30,000 for a quality-adjusted life-year. The findings are driven slightly by the use of mesh for the initial intervention procedure and a greater number of failure procedures over follow-up in the uterine preservation group.
- Vault trial: abdominal vault repair was £570 (95% confidence interval £459 to £682) more expensive than vaginal vault repair and generated more quality-adjusted life-years (mean difference  $0.004$ , 95% confidence interval  $-0.031$  to  $0.041$ ), this generation of more quality-adjusted life-years was statistically not significant. Abdominal repair had a 17% probability of being cost-effectiveness at a threshold of £30,000 per quality-adjusted life-year.

The base-case model results echo the trial findings over a lifetime horizon. Future analysis will update the model with longer-term follow-up data to validate the modelling assumptions regarding the trade-offs between failures and complications following both surgeries.

## Conclusions

There was evidence of no benefit from uterine preservation compared with vaginal hysterectomy in terms of efficacy, quality of life, adverse events or any other outcome in women for uterine prolapse in the short term. These findings were replicated when a comparison was made between abdominal and vaginal procedures for vault prolapse. One woman in the Uterine trial required surgery for mesh exposure for the apical procedure and one woman in the Vault trial required surgery for mesh exposure because of a concomitant continence procedure using mesh.

## Recommendations for future research

Long-term follow-up to at least 6 years after randomisation is ongoing to identify the recurrence rates, need for further prolapse surgery and adverse events.

## Trial registration

This trial is registered as ISRCTN86784244.

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