Clinical effectiveness and cost-effectiveness of surgical options for the management of anterior and/or posterior vaginal wall prolapse: two randomised controlled trials within a comprehensive cohort study – results from the PROSPECT Study

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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 caused by childbirth, but symptoms appear many years later. Conservative treatment with pelvic floor exercises, oestrogens and pessaries might help in the earlier stages but 10% of women will require surgery, which has a high failure rate: 3 out of 10 women require further surgery. Surgeons and researchers have suggested that mesh or graft reinforcement of the repair might provide a better chance of cure and prevent the need for more 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 augmentation with foreign material.

Aims and objectives

The PROlapse Surgery: Pragmatic Evaluation and randomised Controlled Trials (PROSPECT) study comprises a panel of pragmatic, parallel-group randomised controlled trials (RCTs) set within a comprehensive cohort (CC) design. The aim was designed primarily to compare the clinical effectiveness and cost-effectiveness of three treatment modalities [(1) synthetic non-absorbable mesh inlay; (2) biological graft; and (3) mesh kit using similar material] compared with a standard repair in women with pelvic organ prolapse of the anterior or posterior vaginal walls.

Primary outcome measures were women's symptoms measured using the Pelvic Organ Prolapse Symptom Score (POP-SS) and prolapse-specific quality-of-life (QoL) visual analogue scale. Cost-effectiveness was assessed as cost per quality-adjusted life-year (QALY) gained, based on the EuroQol-5 Dimensions (3-level version).

Secondary objectives were to compare the three treatments in terms of bladder, bowel and sexual function, adverse effects, objective measurement of anatomical prolapse stage [using the Pelvic Organ Prolapse Quantification (POP-Q) 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

A total of 3087 women who were having prolapse surgery in 35 UK centres were consented between January 2010 and August 2013. Women who had anterior and/or posterior prolapse, and who were willing to be randomised, were eligible for one of two trials: the Primary trial (RCT1) for women who had de novo prolapse in one or both compartments, and the Secondary trial (RCT2) for those who had had at least one previous repair in the prolapsed compartment. Women who did not wish to be randomised, or who were advised by their surgeons to avoid randomisation, were followed up in matching observational CCs: primary women in CC1, secondary in CC2 and those with a uterine or vault prolapse alone in CC3.

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

Study set-up

Women in RCT1 were randomised within three strata: stratum 1A included women who were randomised to one of all of the three treatment options – standard repair, mesh inlay and biological graft; stratum 1B compared standard repair with mesh inlay; and stratum 1C standard repair with biological graft inlay. In RCT2, women were randomised to one of three treatment options: stratum 2A (standard repair, mesh inlay and mesh kit); stratum 2B, comparing standard repair with mesh inlay; and stratum 2D, comparing standard repair with mesh kit.

Randomisation

Randomisation involved a computer-generated randomisation system managed by the Centre for Healthcare Randomised Trials (CHaRT) at the University of Aberdeen. Participants were randomly allocated 1 : 1 : 1 to one of the arms in the stratum for which they were eligible in the Primary trial, and 1 : 1 : 2 in the Secondary trial. The minimisation algorithm included surgeon, age (< 60 years or ≥ 60 years), type of planned prolapse repair (anterior, posterior or both), planned concomitant continence surgery and planned concomitant upper compartment prolapse repair. Women in the CCs received the surgery that they and their gynaecologist thought was most acceptable and suitable.

Study interventions

Surgeons were asked to use the surgical techniques with which they were most familiar. They informed us of their normal use of mesh and graft materials and details of their surgical techniques, but, as this was a pragmatic trial, deviation could occur both from the randomised allocation and their normal practice for clinical reasons. We recorded details of concomitant surgery for uterine or vault prolapse, continence surgery and the use of mesh.

Statistical analysis

An intention-to-treat analysis was performed. Primary and secondary outcomes were compared using generalised linear mixed models, adjusting for baseline covariates. Trial-based cost-effectiveness analysis assessed mean differences (MDs) in costs and QALYs at 1 year and 2 years. Estimates of cost-effectiveness were extrapolated to 5 years using a probabilistic Markov decision-analytic model. Estimates of cost-effectiveness were expressed as incremental costs per QALY gained, and the net monetary benefit approach was used to identify the optimal treatment modality on grounds of cost-effectiveness, based on a ceiling willingness to pay of £30,000 per QALY gained.

Results

In total, 3744 women waiting for prolapse surgery were screened for eligibility, of whom 3089 (83%) consented to participate in PROSPECT. Five of the 1507 (0.3%) who agreed to be randomised were excluded after randomisation. Of those included, 1348 were randomised in RCT1, with 1126 enrolled in CC1. Another 154 having a repeat repair were randomised in RCT2, with 244 in CC2. Finally, 215 women who were having either uterine or vault prolapse repair enrolled in CC3. The main reason for declining randomisation was the woman's or the surgeon's preference for a specific treatment. The majority (1264, 84%) of those randomised received their allocated treatment, 218 (15%) received a study treatment other than that randomised and 25 (2%) did not receive any of the study treatments. The 12-month follow-up appointment was well attended (1299, 86% of those randomised attended) and 1368 randomised participants (91%) completed the 12-month questionnaires (primary outcome).

Primary trials

Prolapse symptoms reported by women

The primary outcome was women's report of prolapse symptoms on the Pelvic Organ Prolapse Symptom Scale (score range 0–28) at 12 months after surgery. Adjusting for baseline scores and minimisation covariates, the mean POP-SS was similar for each comparison [trial 1: standard 5.4 vs. mesh 5.5; MD 0.00,

95% confidence interval (CI) –0.70 to 0.71; trial 2: standard 5.5 vs. graft 5.6; MD –0.15, 95% CI –0.93 to 0.63]. There was also no statistically significant difference in the prolapse-related QoL score (range 0–10) measured as the interference of prolapse symptoms with everyday life (trial 1: standard 2.0 vs. mesh 2.2; MD 0.13, 95% CI –0.25 to 0.51; trial 2: standard 2.2 vs. graft 2.4; MD 0.13, 95% CI –0.30 to 0.56).

Adverse effects

The number of women with serious non-mesh adverse effects, such as infection, pain, urinary retention and dyspareunia, was similar between the groups in the first year [standard 7.2% vs. mesh 7.8%; risk ratio (RR) 1.08, 95% CI 0.68 to 1.72; standard 6.3% vs. graft 9.8%; RR 1.57, 95% CI 0.95 to 2.59]. There were no statistically significant differences between the randomised groups for any adverse effect measure at any time period. The cumulative mesh complication rates over 2 years were 2 of 430 (0.5%) for standard repair (trial 1), 46 of 435 (10.6%) for mesh inlay and 2 of 368 (0.5%) for biological graft. The findings from CC1 were comparable.

Mesh complications in the Primary trials

In the first year, 2 of 430 women in the standard group and 32 of 435 in the mesh inlay group had mesh complications, with a further 2 out 368 mesh complications in the biological group. One woman in the standard group received mesh for her prolapse repair and had subsequent mesh exposure; the other had mesh exposure resulting from a concomitant procedure. Both women in the standard group, and 23 in the mesh inlay group, had surgery to remove or overlay the mesh [of whom 18 (72%) were asymptomatic and 16 (64%) had exposures of < 1 cm^2]. In the second year, 1 of 430 in the standard group and 25 of 435 in the mesh inlay group had a mesh complication (a repeat occurrence in 1 and 11 women, respectively). Of these, 17 in the mesh inlay group required surgical correction of the exposure [of whom 13 (76%) were asymptomatic and 10 (59%) had exposures of < 1 cm^2]. The remaining women received conservative treatment (such as mesh trimming in outpatients, oestrogen treatment or cautery with silver nitrate) or no treatment.

Economic outcomes

Both mesh repairs were more costly to perform, driven by the material cost of mesh. There was no evidence of differences in follow-up use of health services at 2 years. Synthetic mesh inlay was £363 more costly (95% CI –£32 to £758). Biological graft was significantly more costly (+£565) than standard repair (95% CI £180 to £950). The participant and wider societal costs added 40% to the total NHS costs across the treatment groups for all women, although there were no differences across treatment groups. Synthetic mesh had, on average, 0.071 additional QALYs (95% CI –0.004 to 0.145) relative to standard repair, whereas biological graft had, on average, 0.039 (95% CI –0.041 to 0.120). There was substantial uncertainty regarding the most cost-effective treatment strategy. None of the treatment strategies demonstrated a probability of being the most cost-effective strategy of $> 84\%$ (if society was willing to pay £30,000 for a QALY gained). Uncertainty remained across the range of sensitivity analyses undertaken.

A decision-analytic model to extrapolate results of RCT1 over a longer time shows that at 5 years there is no evidence that either mesh strategy would be a cost-effective use of NHS resources. Standard repair was, on average, the most cost-effective because of lower intervention costs, lower costs of treating mesh-related complications and similar rates of surgical failure at 2 years. However, further long-term follow-up is required to validate the extrapolation models used.

Secondary and clinical outcomes in the Primary trials

There were no statistically significant differences in any of the measures of bladder, bowel or sexual function in any of the randomised groups. There were no statistically significant differences in the number of women with residual prolapse beyond the hymen (objective measurement of anatomical cure of prolapse using the POP-Q system) (trial 1: standard 13.9% vs. mesh inlay 16.1%; RR 1.12, 95% CI 0.79 to 1.60; trial 2: standard 15.5% vs. graft 18.1%; RR 1.14, 95% CI 0.80 to 1.62).

Secondary trials

Prolapse symptoms reported by women

The primary outcome was prolapse symptoms (POP-SS, range 0–28) at 12 months after surgery. Adjusting for baseline scores and minimisation covariates, the mean POP-SS was similar for each comparison {trial 3: standard 6.6 [standard deviation (SD) 6.0] vs. mesh 6.1 (SD 6.4); MD –0.41, 95% CI –2.92 to 2.11; trial 4: standard 6.6 (SD 5.5) vs. mesh kit 5.9 (SD 5.3); MD –1.21, 95% CI –4.13 to 1.72}. There was also no statistically significant difference in the prolapse-related QoL score (range 0–10) measured as the interference of prolapse symptoms with everyday life (trial 3: standard 2.5 vs. mesh inlay 3.0; MD 0.43, 95% CI–0.90 to 1.75; trial 4: standard 2.0 vs. mesh kit 2.3; MD –0.31, 95% CI –1.99 to 1.36).

Adverse effects

The number of women with serious non-mesh adverse effects was similar between the groups in the first year (trial 3: standard 7/55, 12.7% vs. mesh inlay 5/52, 9.6%; RR 1.05, 95% CI 0.66 to 1.68; trial 4: standard 3/25, 12.0% vs. mesh kit 3/46, 6.5%; RR 0.49, 95% CI 0.11 to 2.16). The cumulative mesh complication rates over 2 years were 7 of 52 (13.5%) for mesh inlay and 4 of 46 (8.7%) for mesh kit, with no mesh exposures after standard repair. There were no statistically significant differences between the randomised groups in any other outcome measure at any time. The findings from CC2 were comparable.

Mesh complications in the Secondary trials

In the first year, none of the women in the standard group, 6 of 52 in the mesh inlay group and 3 of 46 in the mesh kit group had a mesh complication. Three women in the mesh inlay group and one in the mesh kit group had surgery to remove or overlay the mesh. In the second year, none of the women in the standard group, 2 of 52 in the mesh inlay group and 2 of 46 in the mesh kit group had a mesh complication. Of these, one woman in the mesh inlay and one in the mesh kit group required surgical correction. In total, six women required mesh surgery in the 2 years of follow-up. A further six women received conservative treatment and the rest required no treatment.

Economic outcomes

The additional cost of providing mesh inlay and mesh kits for women who were having a secondary prolapse repair were £398 (95% CI –£197 to £993) and £914 (95% CI £349 to £1478), respectively. At 2 years, synthetic mesh inlay was, on average, £238 more costly than standard repair (95% CI –£929 to £1405) and mesh kits were £873 more costly (95% CI –£27 to £1774). Incremental QALYs relative to standard repair were 0.018 (95% CI –0.149 to 0.185 QALYs) and 0.096 (95% CI –0.081 to 0.274 QALYs) for synthetic mesh and mesh kits, respectively. Owing to small sample sizes for the Secondary trial, there was not enough evidence to determine the most cost-effective treatment strategy.

Secondary and clinical outcomes in the Secondary trials

There were no statistically significant differences in the number of women with residual prolapse beyond the hymen (standard 14.0% vs. mesh inlay 14.0%; RR 0.59, 95% CI 0.18 to 1.92; standard 16.7% vs. mesh kit 0%). There were also no statistically significant differences in any of the measures of bladder, bowel or sexual function, but the sample size was too small to be conclusive.

Conclusions

There was evidence of no benefit from the use of mesh inlay or biological graft compared with standard repair in terms of efficacy, QoL, adverse effects (other than mesh complications) or any other outcome in women who were having a primary repair in the first 2 years. In those randomised to synthetic mesh in the Primary trial, the cumulative incidence of mesh complications was 10.6% over 2 years. Some women required surgery for mesh exposure but the majority were asymptomatic or had small exposures.

Unless there is a significant decrease in reoperation rates for failure in the medium or long term, it is unlikely that any type of mesh or graft would be cost-effective, given the excess cost over standard repair and the excess cost of treatments for mesh complications.

The sample size in the Secondary trial comparisons was too small to be conclusive.

Recommendations for future research

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

Trial registration

This trial is registered as ISRCTN60695184.

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