Mesh inlay, mesh kit or native tissue repair for women having repeat anterior or posterior prolapse surgery: randomised controlled trial (PROSPECT)

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Objective To compare standard (native tissue) repair with synthetic mesh inlays or mesh kits.

Design Randomised controlled trial.

Setting Thirty-three UK hospitals.

Population Women having surgery for recurrent prolapse.

Methods Women recruited using remote randomisation.

Main outcome measures Prolapse symptoms, condition-specific quality-of-life and serious adverse effects.

Results A Mean Pelvic Organ Prolapse Symptom Score at 1 year was similar for each comparison (standard 6.6 versus mesh inlay 6.1, mean difference [MD] −0.41, 95% CI −2.92 to 2.11: standard 6.6 versus mesh kit 5.9, MD −1.21 , 95% CI −4.13 to 1.72) but the confidence intervals did not exclude a minimally important clinical difference. There was no evidence of difference in any other outcome measure at 1 or 2 years. Serious adverse events, excluding mesh exposure, were similar at 1 year (standard 7/55 [13%] versus mesh inlay 5/52 [10%], risk ratio [RR] 1.05 [0.66–

1.68]: standard 3/25 [12%] versus mesh kit 3/46 [7%], RR 0.49 [0.11–2.16]). Cumulative mesh exposure rates over 2 years were 7/52 (13%) in the mesh inlay arm, of whom four women required surgical revision; and 4/46 in the mesh kit arm (9%), of whom two required surgical revision.

Conclusions We did not find evidence of a difference in terms of prolapse symptoms from the use of mesh inlays or mesh kits in women undergoing repeat prolapse surgery. Although the sample size was too small to be conclusive, the results provide a substantive contribution to future meta-analysis.

Keywords Pelvic organ prolapse, randomised controlled trial, repeat surgery, synthetic mesh.

Tweetable abstract There is not enough evidence to support use of synthetic mesh inlay or mesh kits for repeat prolapse surgery.

Linked article This article is commented on by K Propst, p. 1014 in this issue. To view this mini commentary visit https://doi.org/10.1111/1471-0528.16241.

Introduction

Mesh use for prolapse surgery is controversial. Government policy is changing in the light of increased evidence of adverse effects.[1] In women having a first prolapse repair,

our own multicentre randomised controlled trial (RCT) PROSPECT, set in the UK,[2] demonstrated in the short term, at 2 years, that more than 30% of women still reported either 'something coming down' or had anatomical prolapse extending beyond the hymen, irrespective of the use of mesh inlay or biological graft to reinforce the surgery. As a result of the findings from this trial, augmentation is no longer recommended for a first repair.[1]

However, Olsen et al.[3] showed that 30% of women who have had one prolapse or incontinence operation required at least one more procedure, and the time intervals between repeat procedures decreased with each successive repair. This study failed to differentiate between repeat surgery for a recurrence in the same compartment and primary surgery for a *de novo* prolapse in another compartment, or new continence procedures.[4] Nevertheless, Olsen et al.'s study suggests that a third of women would eventually undergo at least one more procedure and some would require a third or fourth one.[3]

Our study was preceded by priority assessment based on the relevant Cochrane review[5] and an Interventional Procedures review which investigated the use of mesh for women having anterior and/or posterior vaginal wall prolapse surgery.[6] These and other findings were presented to the Interventional Procedures Advisory Committee (IPAC) in January 2008 and their guidance published.[7] The committee recommended that mesh should be used only under special arrangements for clinical governance, consent and audit or research: hence, the PROSPECT Study was funded to fill the evidence gap.

We therefore compared, in an RCT, the effect of mesh inlay or mesh kit with native tissue repairs in women who had already experienced at least one failed previous prolapse repair in the same compartment.

We focused on those high-risk women whose specific compartment prolapse surgery had already failed, to try to reduce the chance that they would require further prolapse surgery. After consultation with gynaecologists and experts from specialist societies, we chose to compare mesh kits as well as mesh inlays with standard (native tissue) repairs, based on the scarcity of data about the safety and efficacy of mesh kits but their perceived potential to provide better support due to their method of insertion.

Methods

Participants

Women listed for transvaginal repair of an anterior and/or posterior prolapse were eligible if at least one of the compartments requiring surgery had been repaired previously. Women could have concomitant uterine, vault or continence surgery. Women under the care of 59 gynaecologists from 33 UK centres were enrolled into the trial between January 2010 and August 2013. All women provided written informed consent. The study was funded by the National Institute for Health Research Health Technology Assessment Programme (Project Number 07/60/18). The funder (through their peer review and funding board review process) approved the study proposal but had no role in the collection, analysis or interpretation of data, or writing of the report.

Randomisation

A remote web-based computer-generated randomisation system at the Centre for Healthcare Randomised Trials (CHaRT, University of Aberdeen, UK) was used for group allocation. We report two trials: the Mesh Inlay Trial compared standard (native tissue) repair with mesh inlay; and the Mesh Kit Trial compared standard repair with mesh kit. Not all gynaecologists offered all treatment options due to preferences or locally available resources. Therefore, women were randomised in three strata: Stratum A included women randomised to one of all three treatment options, standard repair, mesh inlay and mesh kit (in a 1:1:2 ratio); Stratum B compared standard repair with mesh inlay (in a 1:1 ratio); Stratum C compared standard repair with mesh kit (in a 1:2 ratio). Randomisation was unbalanced in the Mesh Kit Trial in favour of mesh kits to account for the number of surgeons who were trained in their use, in order to ensure adequate numbers in the groups. Because the analyses were carried out separately for each trial, data from some women in the standard repair group from Stratum A were included in both trials.

The minimisation algorithm included: age (<60 years or ≥60); planned prolapse repair (anterior, posterior or both); planned concomitant urinary continence procedure or not; planned concomitant upper vaginal prolapse procedure or not; and operating surgeon.

Further details of participants, masking and interventions are provided as online Supporting Information.

Outcomes

Women were followed up at 6 months, and 1 and 2 years after surgery by postal questionnaire and were clinically examined at 1 year.[8]

We used a wide and comprehensive panel of validated core outcomes relevant to women, focusing primarily on women's symptoms. These were based on internationally agreed terminology and recommended core outcomes.[4]

The primary outcome was women's report of prolapse symptoms at 1 year after surgery using the Pelvic Organ Prolapse Symptom Score (POP-SS), a validated measure which has been shown to be sensitive to change after treatment.[9] The POP-SS contains items relating to frequency of seven prolapse symptoms in the previous 4 weeks: each item is scored from 0 (never) to 4 (all of the time): the total score thus ranges from 0 to 28.

Secondary outcomes included prolapse-specific quality-of-life measured using a visual analogue scale (VAS) and generic quality of life based on the EQ-5D-3L,[10] and an assessment of overall global improvement in symptoms (PGI-I).[11] Bladder, bowel and sexual function were measured using validated or adapted International Consultation on Incontinence Questionnaires (ICIQ).[12] Objective measurement of prolapse stage utilised the POP-Q system.[8]

Adverse events, need for readmission/further treatment for adverse effects or prolapse recurrence were reported by surgeons or women and verified by Study Office staff from a second source when possible. Adverse events and complications of surgery were recorded using the IUGA/ICS complications classification which includes type, severity, time of occurrence and site.[13,14] Serious adverse events were defined using standard classification.[15]

All definitions are in keeping with the recommendations of IUGA, ICS and ICI.[4,12-14,16] The full Protocol is available on the funder's website.[17]

Statistical analysis

The main analysis was conducted on an intention-to-treat basis (whereby women with observed outcome data remained in their allocated group). We did not follow up randomised women who did not receive any surgery. We made two comparisons: standard repair versus mesh inlay (Mesh Inlay Trial, data from women in Strata A and B) and standard repair versus mesh kit (Mesh Kit Trial, from Strata A and C) (Figure S1). Study analyses were conducted according to a prespecified statistical analysis plan, using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

All outcome measures were presented as summaries using descriptive statistics (mean and standard deviation for continuous measures, and proportion for ordinal and dichotomous measures) and comparisons between randomised groups were analysed separately at 6 months and 1 and 2 years using generalised linear models. Models were adjusted for minimisation covariates, baseline measures where appropriate, and randomisation stratum. Continuous outcomes were analysed using linear mixed models, with surgeon fitted as a random effect. POP-Q stage and PGI-I were analysed using ordinal logistic regression (proportional odds models with cumulative logits). Dichotomous outcomes were analysed using log-binomial regression. Estimates of treatment effect size were mean differences in the linear mixed models (including the analysis of the POP-SS), odds ratios in the ordinal models and risk ratios in the binary models. For all estimates, 95% confidence intervals were calculated.

Sample size

Women were recruited opportunistically alongside those having a primary repair.[2] Based on the assumption that 30% of women requiring an anterior and/or posterior repair would receive a secondary or subsequent operation,[3] we expected that approximately 1240 women having secondary surgery would be available during the recruitment period for the primary trial.[2] Of those available, it was estimated that 50% (620 women) would agree to be randomised.

Pilot data indicated that women having secondary repairs had worse symptoms at baseline than women having their first repair (A. Elders & C. Glazener, unpubl data).[18] We considered it biologically plausible that these women might show a larger benefit from surgical treatment than would women having their first repair. We therefore calculated that, with an expected sample size of 620, it would be possible to detect, with 90% power and alpha equal to 0.025, a standardised effect size of 0.38, which equates to three points on the POP-SS scale (assuming a standard deviation of 8 units).

Results

Between January 2009 and August 2013, 396 women were found to have recurrent prolapse of the same compartment and were therefore potentially eligible for this trial. However, only 155 (39%) agreed to be randomised, of whom 154 were included in the analyses.[19]

Baseline characteristics and intervention received

The flow of women through the study is shown in the CONSORT diagram (Figure 1), in line with recommendations of the Consolidated Standards of Reporting Trials.[20] Women in the randomised groups were comparable at baseline and all were symptomatic based on at least one symptom on the POP-SS (Table S1). Two women did not receive surgery (Figure 1). Most women received their planned surgery (Figure 1).

In the standard repair group, more women (27% in the Mesh Inlay Trial and 20% in the Mesh Kit Trial) had a combined anterior/posterior repair than in the other two groups (synthetic mesh inlay 14% and mesh kit 13%; Table S2). Concomitant surgery included vaginal hysterectomy, which occurred in 7%/12% (respectively) of the standard repair groups, 8% with synthetic mesh inlay and 9% with mesh kit. A concomitant vault repair was more common in the native tissue group (25%/28%) compared with 10% in mesh inlay group and 13% in the mesh kit group. Finally, vaginal concomitant continence procedures were performed in 7%/8% of the native tissue repairs and in 4% of the mesh inlays; no continence procedures were performed with mesh kits.

Clinical symptoms and quality of life at follow up

Women's reports of prolapse symptoms (POP-SS) were less than half of the preoperative level (mean score before surgery 14.4 [SD 5.4], at 6 months 5.9 [5.7], at 1 year 6.3 [6.0], at 2 years 5.3 [5.3]) (Tables 1, S3 and S4). The improvement

	Women identified 4083

Ineligible 3687
Not screened 339
Ineligible/declined 655 [a]
Primary surgery 2478
Upper compartment only 215

	Eligible women 396

Declined randomisation 241 [b]

	RANDOMISED 155

Post randomisation exclusions 1[c]

	INCLUDED IN ANALYSIS 154 [d]

Treatment arm	MESH INLAY TRIAL [e] 107		MESH KIT TRIAL [e] 71	
	Standard 55	Mesh inlay 52	Standard 25	Mesh kit 46
No surgery	0 (0%)	1 (2%)	0 (0%)	1 (2%)
Received surgery	55 (100%)	51 (98%)	25 (100%)	45 (98%)
Standard repair	49 (89%)	9 (18%)	20 (80%)	4 (9%)
Synthetic mesh	2 (4%)	37 (73%)	1 (4%)	17 (16%)
Mesh kit	0 (0%)	2 (4%)	0 (0%)	31 (69%)
Biological graft	1 (2%)	0 (0%)	1 (4%)	1 (2%)
Other surgery [f]	3 (5%)	3 (6%)	3 (12%)	2 (4%)
Baseline questionnaire	54 (98%)	50 (96%)	24 (96%)	43 (93%)
6 month questionnaire	50 (91%)	47 (90%)	22 (88%)	43 (93%)
Withdrawals within 6 months	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Deaths within 6 months	0 (0%)	0 (0%)	0 (0%)	0 (0%)
12 month 1º outcome	49 (89%)	44 (85%)	21 (84%)	44 (96%)
12 month 2º outcome	46 (84%)	39 (75%)	21 (84%)	41 (89%)
12 month clinic assessment	46 (84%)	44 (85%)	21 (84%)	38 (83%)
Withdrawals within 12 months	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Deaths within 12 months	1 (2%)	0 (0%)	1 (4%)	1 (0%)
24 month questionnaire	43 (78%)	39 (75%)	20 (80%)	39 (85%)
Withdrawals within 24 months	1 (2%)	3 (6%)	0 (0%)	2 (4%)
Deaths within 24 months	1 (2%)	0 (0%)	1 (4%)	0 (0%)

Footnotes

a   655 women were ineligible or declined recruitment to PROSPECT after screening: No prolapse/changed mind about needing surgery (117); Removed from waiting list/unfit for surgery (45); Unable to give informed consent (32); Unable to complete questionnaires (16); Not interested in participation in study/unknown (413); Other reasons for non-recruitment (including 'psychological or family problems', 'not clinically or medically suitable to take part in a research study' and 'consultant wished to decide procedure')(32).

b   241 women declined randomisation:
'Clinical decision' includes 'wanted to use mesh', 'did not want to use mesh' and 'other clinical reason' (133);
'Participant decision' includes 'wanted mesh', 'did not want mesh' 'wanted surgeon to decide' and 'did not want to be randomised' (96)
'Other' reasons include 'mesh unavailable', 'operating surgeon not trained in mesh inlays/kits', 'theatre time issues' and 'not recorded' (12)

c   Post randomisation exclusion: 1 woman had secondary prolapse surgery after consenting but prior to randomisation. She was followed up the cohort study (CC2).

d   56 randomised women were included in the standard repair arm, 52 in the synthetic mesh inlay arm and 46 in the synthetic mesh kit arm (total 154). 24 women in Stratum A were included in both the Mesh Inlay and Mesh Kit Trials, such that there were a total of 55 women in the standard repair arm of the Mesh Inlay Trial and 25 women in the standard repair arm of the Mesh Kit Trial. The numbers of participating women by individual strata are set out in Supplementary Figure 1.

e   Percentages shown represent the number of women as a proportion of those included in the analysis.

f   Other surgery includes women who did not have either an anterior or posterior repair, but did receive one or more of: tape for urinary incontinence, vaginal hysterectomy or suspension, cervical amputation, vault repair

Figure 1. CONSORT diagram

Table 1. Clinical symptoms and quality of life outcomes at 1 and 2 years: (a) Mesh Inlay Trial, (b) Mesh Kit Trial

	(a) Mesh Inlay Trial: Standard versus Synthetic Mesh Inlay				
	Standard	**Mesh Inlay**	**Est.**	**95% CI**	**P-value**
1-year outcomes	N = 49	N = 44			
POP-SS at 1 year	6.6 (6.0) 49	6.1 (6.4) 44	−0.41	−2.92 to 2.11	0.747
Prolapse-related QoL score[a]	2.5 (2.9) 47	3.0 (3.4) 44	0.43	−0.90 to 1.75	0.522
Symptomatic prolapse[b]	81.6% 40/49	88.6% 39/44	1.05	0.82–1.33	0.714
Women with any report of SCD[c]	44.9% 22/49	40.9% 18/44	0.91	0.58–1.43	0.680
Urinary incontinence (severe)[d]	2.2% 1/46	12.8% 5/39	5.52	0.68–44.77	0.110
Fecal incontinence (any)[e]	26.1% 12/46	43.6% 17/39	1.41	0.84–2.35	0.190
ICI Vaginal Symptoms Score	8.3 (7.4) 44	7.9 (8.6) 37	−1.29	−4.99 to 2.42	0.487
Dyspareunia (severe)[f]	0.0% 0/18	13.0% 3/23	n/a	n/a	n/a
EQ-5D-3L score at 1 year	0.74 (0.30) 50	0.83 (0.22) 43	0.03	−0.07 to 0.14	0.519
PGI-I at 1 year[g]	76.7% 33/43	81.6% 31/38	1.18	0.47–2.95	0.731
2-year outcomes	N = 43	N = 39			
POP-SS at 2 years	4.8 (5.0) 43	5.4 (5.5) 39	0.58	−1.68 to 2.84	0.607
Prolapse-related QoL score[a]	1.7 (2.4) 41	2.4 (2.7) 36	0.38	−0.84 to 1.60	0.529
Symptomatic prolapse[b]	83.7% 36/43	82.1% 32/39	1.00	0.80–1.24	0.981
Women with any report of SCD[c]	30.2% 13/43	25.6% 10/39	0.78	0.38–1.60	0.497
Urinary incontinence (severe)[d]	7.1% 3/42	10.3% 4/39	1.64	0.38–7.07	0.507
Faecal incontinence (any)[e]	27.9% 12/43	44.7% 17/38	1.35	0.74–2.47	0.326
ICI Vaginal Symptoms Score	7.3 (7.6) 39	7.9 (7.8) 37	−0.64	−4.56 to 3.28	0.742
Dyspareunia (severe)[f]	0.0% 0/15	4.5% 1/22	n/a	n/a	n/a
EQ-5D-3L score at 2 years	0.76 (0.29) 42	0.82 (0.19) 38	0.00	−0.11 to 0.11	0.975
PGI-I at 2 years[g]	81.0% 34/42	74.4% 29/39	1.01	0.41–2.49	0.974

	(b) Mesh Kit Trial: Standard versus Mesh Kit				
	Standard	**Mesh Kit**	**Est.**	**95% CI**	**P-value**
1-year outcomes	N = 21	N = 44			
POP-SS at 1 year	6.6 (5.5) 21	5.9 (5.3) 44	−1.21	−4.13 to 1.72	0.408
Prolapse-related QoL score[c]	2.0 (2.6) 21	2.3 (2.8) 43	−0.31	−1.99 to 1.36	0.706
Symptomatic prolapse[a]	90.5% 19/21	86.4% 38/44	0.93	0.67–1.28	0.638
Women with any report of SCD[b]	57.1% 12/21	36.4% 16/44	0.57	0.29–1.10	0.094
Urinary incontinence (severe)[d]	0.0% 0/21	10.0% 4/40	n/a	n/a	n/a
Faecal incontinence (any)[e]	28.6% 6/21	39.0% 16/41	1.59	0.57–4.49	0.378
ICI Vaginal Symptoms Score	6.7 (6.0) 18	5.8 (4.8) 35	−2.82	−6.67 to 1.02	0.143
Dyspareunia (severe)[f]	0.0% 0/6	5.6% 1/18	n/a	n/a	n/a
EQ-5D-3L score at 1 year	0.79 (0.27) 22	0.83 (0.19) 41	0.05	−0.07 to 0.17	0.411
PGI-I at 1 year[g]	77.8% 14/18	87.2% 34/39	0.58	0.18–1.90	0.372
2-year outcomes	N = 20	N = 39			
POP-SS at 2 years	3.9 (4.4) 20	5.4 (5.3) 39	0.65	−2.20 to 3.50	0.642
Prolapse-related QoL score[c]	1.5 (2.6) 18	2.5 (2.7) 37	0.32	−1.45 to 2.09	0.712
Symptomatic prolapse[a]	85.0% 17/20	76.9% 30/39	0.92	0.63–1.33	0.655
Women with any report of SCD[b]	25.0% 5/20	35.9% 14/39	1.17	0.47–2.87	0.739
Urinary incontinence (severe)[d]	5.0% 1/20	10.3% 4/39	1.58	0.20–12.48	0.663
Faecal incontinence (any)[e]	30.0% 6/20	38.5% 15/39	1.04	0.47–2.31	0.918
ICI Vaginal Symptoms Score	6.1 (6.2) 17	7.9 (7.4) 36	0.08	−4.91 to 5.08	0.973
Dyspareunia (severe)[f]	0.0% 0/6	0.0% 0/16	n/a	n/a	n/a

Table 1. (Continued)

	(b) Mesh Kit Trial: Standard versus Mesh Kit				
	Standard	**Mesh Kit**	**Est.**	**95% CI**	***P*-value**
EQ-5D-3L score at 2 years	0.76 (0.29) 20	0.87 (0.14) 38	0.13	0.02–0.25	0.025
PGI-I at 2 years[g]	85.0% 17/20	89.5% 34/38	1.53	0.47–4.96	0.478

Continuous variables presented as mean (SD). *n/N*, dichotomous variables presented as % *n/N*.

Effect size: For all negative continuous outcomes, e.g. POP-SS, a positive effect size favours standard repair. For all positive continuous outcomes, e.g. EQ5D, a positive effect size favours the synthetic/mesh kit. For all negative dichotomous outcomes, e.g. urinary incontinence, an effect size more than 1 favours standard repair. For all positive dichotomous outcomes e.g. prolapse better, an effect size more than 1 favours the synthetic/mesh kit.

[a]Quality of life due to prolapse symptoms measured as 'overall interference of prolapse symptoms with everyday life' using a visual analogue scale (VAS); score range from 0 (not at all) to 10 (a great deal).

[b]Symptomatic defined as POP-SS >0.

[c]Women with any report of something slipping down.

[d]Severe urinary incontinence defined as ICIQ-SF score 13–21.

[e]Fecal incontinence of solid or liquid stool: any = occasionally or more.

[f]Severe dyspareunia defined as 'Do you have pain when you have sexual intercourse: 'a lot''. Denominators confined to sexually active women.

[g]PGI-I Patient-Global impression of Improvement = very much or much better (versus a little better, no change, a little worse, much worse, very much worse). Effect sizes are odds ratios estimated from ordinal logistic regression.

at 1 year was maintained at 2 years, with respect to all the prolapse and quality of life outcomes measured.

In the Mesh Inlay Trial, the mean difference (MD) in the POP-SS score at 1 year for standard repair (mean 6.6, SD 6.0) versus synthetic mesh inlay (mean 6.1, SD 6.4), based on combined data from women in Stratum A (three-way randomisation) and Stratum B (two-way randomisation), was −0.41 (95% CI −2.92 to 2.11).

In the Mesh Kit Trial, the MD in the POP-SS score at 1 year for standard repair (mean 6.6, SD 5.5) versus mesh kit (mean 5.9, SD 5.3), based on combined data from women in Stratum A (three-way randomisation) and Stratum C (two-way randomisation), was −1.21 (95% CI −4.13 to 1.72).

At 2 years, the study found that women having a mesh kit had a better generic QoL score, measured with EQ-5D-3L, than did those who had a standard repair (MD 0.13 [95% CI 0.02–0.25]: *P* = 0.025; Table 1).

The other key symptoms of pelvic floor dysfunction – urinary, faecal, vaginal and sexual symptoms – are presented in Tables 1 and S4. Although there was a decrease in the proportion of women with severe urinary incontinence after surgery, there was no difference between the randomised groups in either the Mesh Inlay Trial or the Mesh Kit Trial in respect of any of the urinary outcomes measured. Frequency of bowel movement and constipation were largely unchanged after prolapse surgery. There were no differences between the randomised groups in respect of any of the bowel outcomes measured.

Many women reported improvements in their vaginal and sexual function outcomes after surgery: this was evident from a reduction of the ICI-Q Vaginal Symptoms score

(Table 1). After surgery, fewer women cited prolapse symptoms as a reason for not having a sex life (around 35% before surgery, versus around 10% after). Four women had severe dyspareunia at 1 year (Mesh Inlay group = 3, Mesh Kit group = 1), but only one at 2 years (Mesh Inlay group). However, there were no statistically significant differences between the randomised groups in respect of any of the vaginal or sexual symptom outcomes measured.[19]

Satisfaction with treatment

Most women reported that their prolapse symptoms were very much or much better than before surgery, with no statistically significant differences between the groups in either trial (Table S4).

Objective outcomes

At 1 year, 83% of women attended for clinical review. Objective measurement showed improvement in each of the three prolapse compartments. The proportion of women with the leading prolapse edge beyond the hymen (POPQ >0 cm) reduced substantially. In the Mesh Inlay Trial, the difference between groups based on clinician's estimates of stage was RR 0.75, 95% CI 0.33–1.68, *P* = 0.479, and the proportion with more severe objective prolapse defined as 'leading edge of the prolapse at >0 cm beyond the hymen on POP-Q' was 14% in each group (RR 0.59, 95% CI 0.18–1.92, *P* = 0.380 (Table 2).

In the Mesh Kit Trial, women who had a standard repair were more likely to have prolapse compared with those who were randomised to mesh kit based on clinician's estimates of all stages (RR 0.24, 95% CI 0.07–0.83, *P* = 0.024;

Table 2. Objective measures of prolapse at 1 year

One-year review	Mesh Inlay Trial					Mesh Kit Trial				
	Standard *n* = 46	Mesh Inlay *n* = 44	Est.	95% CI	*P*-value	Standard *n* = 21	Mesh kit *n* = 38	Est.	95% CI	*P*-value
POP-Q										
Ba	−1.4 (1.5) 42	−1.4 (1.4) 41	−0.22	−0.80 to 0.36	0.445	−1.2 (1.9) 19	−1.8 (1.0) 35	−0.74	−1.4 to −0.10	0.026
C	−5.6 (2.4) 41	−6.2 (1.5) 41	−0.61	−1.38 to 0.16	0.119	−5.1 (2.7) 18	−6.0 (1.8) 33	−0.65	−1.6 to 0.3	0.173
Bp	−1.8 (1.6) 41	−2.2 (1.1) 41	−0.49	−1.08 to 0.10	0.099	−1.9 (1.7) 18	−2.2 (0.8) 34	−0.38	−1.2 to 0.4	0.317
Tvl	7.7 (1.2) 43	7.9 (1.4) 42	0.09	−0.47 to 0.65	0.746	7.7 (1.0) 19	8.1 (1.2) 33	0.64	0.1 to 1.20	0.028
Overall POP-Q stage										
Stage 0	13.6% 6/44	7.0% 3/43	0.75	0.33–1.68	0.479	10.5% 2/19	14.3% 5/35	0.24	0.07–0.83	0.024
Stage 1	36.4% 16/44	44.2% 19/43				31.6% 6/19	45.7% 16/35			
Stage 2	40.9% 18/44	46.5% 20/43				42.1% 8/19	40.0% 14/35			
Stage 3	9.1% 4/44	2.3% 1/43				15.8% 3/19	0.0% 0/35			
Stage 4	0.0% 0/44	0.0% 0/43				0.0% 0/19	0.0% 0/35			
Stage 2b, 3 or 4[a]	14.0% 6/43	14.0% 6/43	0.59	0.18–1.92	0.380	16.7% 3/18	0.0% 0/35	n/a	n/a	n/a

% *n/N* or mean (SD).
[a]Objective prolapse: stage 2b, 3, or 4, defined as leading edge beyond the hymen (>0 cm) when POP-Q data available.

Table 2). However, for more severe objective prolapse (defined as above), 3/18 (17%) of standard repair women had residual prolapse compared with none of 35 women after a mesh kit procedure.

Readmission, adverse effects and further treatment
Five women were readmitted in the first 6 months after surgery (Standard group = 2, Mesh Inlay group = 3; Table 3). Two subsequent readmissions were for revision of prolapse surgery (Fenton's operation)—one in the Mesh Kit group and one in the Mesh Inlay group.

Individual serious adverse events were rare, the most common being infection, pain and urinary retention (Table S5). In the first year, the number of women with serious non-mesh adverse events were as follows: Mesh Inlay Trial: standard 7/55, 12.7% versus mesh inlay 5/52, 9.6%, RR 1.05, 95% CI 0.66–1.68, *P* = 0.831; Mesh Kit Trial: standard 3/25, 12.0% versus mesh kit 3/46, 6.5%, RR 0.49, 95% CI 0.11–2.16, *P* = 0.345. No women experienced cystotomies or bladder perforations during either mesh insertion or native tissue repair. One woman, in the mesh kit arm, required a blood transfusion. Non-serious adverse events were also rare (Table S6).

In the first 2 years, 7/52 women had vaginal mesh exposure in the mesh inlay arm (13%), of whom four required surgical revision; and 4/46 women had vaginal mesh exposure in the mesh kit arm (8%), of whom two needed surgical revision. Hence in total, six women needed further surgery to address an area of mesh exposure (all but one <1 cm^2) 2 years after surgery. There were no reports of mesh perforation of the bladder or bowel at insertion but

one woman in the Mesh Inlay Trial experienced a bowel perforation during mesh removal. The other mesh exposures were managed conservatively by observation, topical estrogens or cautery.

At 2 years after surgery, around 20% of women who had a standard repair required further treatment for prolapse compared with 11% who had a mesh inlay and 5% who had a mesh kit (Table 3): however, there was no statistical difference between the randomised groups.

Discussion

Main findings
There were no statistically significant differences at 1 year in the primary clinical outcomes after prolapse surgery using native tissue, polypropylene non-absorbable mesh or a mesh kit to reinforce the repair in either trial. The uncertainty around this finding is reflected in the wide confidence intervals around the primary outcome (POP-SS) at 1 year (RR −0.41, 95% CI −2.92 to 2.11 in the Mesh Inlay Trial and RR −1.21, 95% CI −4.13 to 1.72 in the Mesh Kit Trial). Women in the Mesh Kit Trial were less likely to have prolapse beyond Stage 2 at 1 year and had a higher (better) EQ-5D-3L score at 2 years. However, these may have been chance findings and their clinical significance is uncertain as there were no differences in any other subjective outcomes between the randomised groups at any time point.

The overall incidence of non-mesh-related serious adverse events was around 10% and comprised primarily pain, infection and urinary retention. As women could only have a mesh-related complication if they received mesh,

Table 3. Readmission, adverse effects and further treatment

| | Mesh Inlay Trial: Standard versus Synthetic Mesh Inlay | | | | | Mesh Kit Trial: Standard versus Mesh Kit | | | | |
	Standard N = 43	Mesh Inlay N = 38	Est.	95% CI	P-value	Standard N = 20	Mesh Kit N = 39	Est.	95% CI	P-value
Readmissions 0–6 months	4.0% 2/50*	6.4% 3/47**	1.76	0.30–10.37	0.532	0% 0/22	0% 0/43	n/a	n/a	n/a
Readmissions 6–12 months	0% 0/49	0% 0/44	n/a	n/a	n/a	0% 0/21	2.3% 1/44***	n/a	n/a	n/a
Readmissions 12–24 months	0% 0/43	2.6% 1/39****	n/a	n/a	n/a	0% 0/20	0% 0/39	n/a	n/a	n/a
Any serious adverse effects in 1st year (excluding mesh exposures)	12.7% 7/55	11.5% 6/52	0.87	0.32–2.35	0.777	12.0% 3/25	6.5% 3/46	0.49	0.11–2.16	0.345
Any serious adverse effects in 2nd year (excluding mesh exposures)	0% 0/55	0% 0/52	n/a	n/a	n/a	0% 0/25	4.3% 2/46	n/a	n/a	n/a
Any mesh exposure (cumulative by 2 years)	0% 0/55	13.5% 7/52	n/a	n/a	n/a	0.0% 0/25	8.7% 4/46	n/a	n/a	n/a
Surgical removal of mesh exposure (cumulative by 2 years)	0.0% 0/43	10.5% 4/38	n/a	n/a	n/a	0.0% 0/20	5.1% 2/39	n/a	n/a	n/a
New prolapse operation (any by 2 years)	14.0% 6/43	7.9% 3/38	0.49	0.14–1.82	0.290	20.0% 4/20	2.6% 1/39	0.13	0.02–1.12	0.063
Same compartment	11.6% 5/43	2.6% 1/38	0.22	0.03–1.83	0.162	15.0% 3/20	2.6% 1/39	0.28	0.03–2.92	0.285
Different compartment	2.3% 1/43	5.3% 2/38	1.74	0.16–18.79	0.647	5.0% 1/20	0.0% 0/39	n/a	n/a	n/a
Pessary (by 2 years)	7.0% 3/43	2.6% 1/38	0.43	0.05–3.85	0.450	5.0% 1/20	2.6% 1/39	0.56	0.04–8.28	0.673
Pessary or prolapse surgery combined (by 2 years)	18.6% 8/43	10.5% 4/38	0.45	0.15–1.40	0.170	20.0% 4/20	5.1% 2/39	0.27	0.05–1.33	0.107

*Reasons for readmission (Standard; 0–6 months): infection (2).
**Reasons for readmission (Synthetic; 0–6 months): retention (1), adhesions (1), constipation (1).
***Reasons for readmission (Kit; 6–12 months): Revision prolapse surgery (Fenton's) (1).
****Reasons for readmission (Synthetic; 12–24 months): Revision prolapse surgery (Fenton's) (1).

the total numbers for this outcome are small, with six women needing further surgery to address mesh exposure.

Strengths and limitations

PROSPECT is rare in being one of the few RCTs in the field to distinguish rigorously between primary and secondary surgery. Unfortunately, our secondary trials on their own did not attain sufficient power to detect a difference. In future, studies should report prolapse surgery trials using the subgroups of Primary and Secondary (the latter defined as 'repeat surgery in the same compartment').

Another strength was the pragmatic reflection of actual practice in the UK. We included surgeons from a large number of hospital settings. It was not possible for all surgeons to randomise women between all three options, but the analysis by strata accommodated this.

Our secure and effective randomisation programme ensured that women were comparable at baseline and that concomitant surgery and other confounding variables were accounted for. We used validated outcome measures to measure women's symptoms of pelvic floor dysfunction. We captured a wide range of adverse effects and made efforts to verify these from alternative sources when possible. Essential missing data were actively sought from the women. Participants, outcome assessors and data entry clerks were blinded to randomisation as far as possible.

Limitations of our study should be acknowledged. The complex design of the study (with three interventions across three strata) generated multiple comparisons, particularly across the secondary outcomes, so care must be taken not to over-interpret the results, as it is likely that some differences may have occurred by chance.

Furthermore, we identified fewer women than expected (396 rather than 1240) because of our more rigorous definition of repeat surgery (same compartment rather than any compartment, 30%).[1] In addition, fewer women than expected were randomised (39% rather than 50%): this was more often due to a clinical decision rather than the women's choice (54% versus 39%). This resulted in fewer women than estimated (155 rather than 620) being randomised. Thus, we were not able to recruit to the sample size that would have given us enough power to identify a difference of three points on the POP-SS.

We and other researchers have suggested that prolapse beyond the hymen (>0 cm on POP-Q) is a sign of severe objective failure.[21] However, we recognise that women with worse anatomical findings may not have symptoms and, vice versa, women with an objective 'cure' may still have prolapse symptoms.

Longer follow up is required: the average time to a repeat operation (in any compartment) is around 12 years.[1] While we did not identify differences in the repeat surgery rate between the groups, it is likely that 2 years is too short a time scale to provide a definitive answer. Both the natural history of prolapse and the long-term ongoing tissue interactions with polypropylene indicate that it is important that trials pursue longer term follow up of outcomes and complications, ideally over 12 years.[3] We have commenced follow up of the PRO-SPECT women for at least 6 years after surgery and also plan electronic data linkage to capture outcomes from non-responders about further admission for prolapse surgery.

Interpretation (in light of other evidence)

The most recent Cochrane review[22] identified 37 trials of mesh or graft in women having anterior, posterior or apical prolapse surgery. Only two of those RCTs published separate data from women having repeat surgery for recurrent anterior or posterior prolapse,[23,24] although most trials included some such women. Both relevant RCTs compared native tissue repair with a mesh kit (Prolift® Gynaecare, inserted with trochars, which is no longer available). Altman reported only a composite failure rate at 1 year in 53 women (20/25 versus 14/28).[23] Withagen reported long-term prolapse symptoms at 7 years in up to 142 women (sensation of bulge at 7 years: 17/76 with native tissue versus 14/66 with mesh kit).[24] Although anatomical failure rates were less in the mesh group (47/67 versus 28/53 at

7 years), there was little difference in the further prolapse surgery rate (11/69 versus 14/56). The mesh exposure rate in the mesh kit group (42% at 7 years) was high and 54% were symptomatic, while a third of the women required surgical revision. Neither trial was conclusive.

Meta-analysis of the PROSPECT data with the two trials examining mesh kits showed that more women had prolapse symptoms with native tissue (68%) than with mesh kits (42%) in the first year (RR 1.56, 95% CI 1.11–2.18) but this difference did not persist in the longer term (23 versus 27%: RR 0.92, 95% CI 0.55–1.52). More women had persistent objective prolapse at 1 year (40 versus 7%, RR 4.97, 95% CI 2.52–9.81) but this was not reflected in repeat prolapse surgery rates (17 versus 18%, RR 0.85, 95% CI 0.46–1.54) at up to 7 years' follow up. Four of 52 women required surgery for mesh exposure after a mesh inlay, and 9/99 women after a mesh kit, although many mesh exposures were small and asymptomatic.

PROSPECT was the only trial to compare native tissue repairs with synthetic mesh inlays.

In any case, in the light of increased evidence of adverse effects, it is unlikely that further trials of mesh will be conducted.[1]

Conclusions

Based on the evidence available in this trial, we are unable to say whether a mesh inlay or a mesh kit confers more benefit to women having a repeat prolapse repair than native tissue surgery in the first 2 years after surgery. Some women required an additional surgical procedure to remove exposed mesh, which may be considered to be an unnecessary risk. However, long-term follow up may reveal whether the excess risks are offset by a potential decrease in the need for repeat surgery, which in itself is associated with higher risks.

PROSPECT is rare in being one of the few RCTs to distinguish rigorously between primary and repeat surgery. We would strongly encourage future studies to use our approach. Although our trial did not have sufficient power to demonstrate a statistical difference, the information is available for meta-analysis with other trials.[19] Further long-term follow up will ultimately determine whether the use of synthetic mesh in vaginal prolapse repair confers any long-term benefits in women whose prolapse surgery has already failed at least once. Large international datasets will be required to make true progress in this field.

Disclosure of interests

conduct of the study; grants from the University of Edinburgh during the conduct of the study; and Membership of the following NIHR boards: CPR decision-making committee; HTA Commissioning Board; HTA Commissioning Sub-Board (EOI); HTA Funding Boards Policy Group; HTA General Board; HTA Post-Board funding teleconference; NIHR CTU Standing Advisory Committee; NIHR HTA & EME Editorial Board; Pre-exposure Prophylaxis Impact Review Panel. All other authors report no conflict of interest. Completed disclosure of interests forms are available to view online as supporting information.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Extended CONSORT diagram for secondary trial.

Table S1. Baseline characteristics of the intention-to-treat population.

Table S2. Surgery actually carried out, including concomitant procedures.

Table S3. Clinical symptoms and quality of life outcomes at 6 months.

Table S4. Condition-specific quality of life measures and satisfaction at 1 and 2 years.

Table S5. Serious and related adverse effects within first and second years.

Table S6. Other (non-serious) related adverse effects within first and second years. ■

References

1 NICE Guideline [IPG599]. Transvaginal mesh repair of anterior or posterior vaginal wall prolapse. 2017 [www.nice.org.uk/guidance/ipg599]. Accessed 05 February 2019.

2 Glazener C, Breeman S, Elders A, Hemming C, Cooper K, Freeman R, et al. Mesh, graft, or standard repair for women having primary transvaginal anterior or posterior compartment prolapse surgery: two parallel-group, multicentre, randomised, controlled trials (PROSPECT). *Lancet* 2017;28:381–92.

3 Olsen A, Smith V, Bergstrom J, Colling J, Clark A. Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. *Obstet Gynecol* 1997;89:501–6.

4 Toozs-Hobson P, Freeman R, Barber M, Maher C, Haylen B, Athanasiou S, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for reporting outcomes of surgical procedures for pelvic organ prolapse. *Int Urogynecol J* 2012;23:527–35.

5 Maher C, Baessler K, Glazener CMA, Adams EJ, Hagen S. Surgical management of pelvic organ prolapse in women (withdrawn paper. 2007, art. no. CD004014). *Cochrane Database Syst Rev* 2007;(3):CD004014.

6 Jia X, Glazener C, Mowatt G, MacLennan G, Bain C, Fraser C, et al. Efficacy and safety of using mesh or grafts in surgery for anterior and/or posterior vaginal wall prolapse: systematic review and meta-analysis. *BJOG* 2008;115:1350.

7 National Institute for Health and Care Excellence (NICE). Surgical repair of vaginal wall prolapse using mesh. Interventional procedures guidance IPG267. 2008 [www.nice.org.uk/guidance/ipg267]. Accessed 30 June 2008.

8 Bump R, Mattiasson A, Bo K, Brubaker L, DeLancey J, Klarskov P. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. *Obstet Gynecol* 1996;175:10–7.

9 Hagen S, Glazener C, Sinclair L, Stark D, Bugge C. Psychometric properties of the pelvic organ prolapse symptom score. *BJOG* 2009;116:25–31.

10 Dolan P. Modeling valuations for EuroQol health states. *Med Care* 1997;35:1095–108.

11 Srikrishna S, Robinson D, Cardozo L. Validation of the patient global impression of improvement (PGI-I) for urogenital prolapse. *Int Urogynecol J* 2010;21:523–8.

12 Abrams P, Avery K, Gardener N, Donovan J. The ICIQ advisory board. the international consultation on incontinence modular questionnaire: www.iciq.net. *J Urol* 2006;175:1063–6.

13 Haylen B, Freeman R, Swift S, Cosson M, Davila G, Deprest J, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint terminology and classification of the complications related directly to the insertion of prostheses (meshes, implants, tapes) & grafts in female pelvic floor surgery. *Int Urogynecol J* 2011;22:3–15.

14 Haylen B, Freeman R, Lee J, Swift S, Cosson M, Deprest J, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint terminology and classification of the complications related to native tissue female pelvic floor surgery. *Int Urogynecol J* 2012;23:515–26.

15 Health Research Authority. [www.hra.nhs.uk/]. Accessed 03 December 2015.

16 Haylen B, de Ridder D, Freeman R, Swift S, Berghmans B, Lee J, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. *Neurourol Urodyn* 2010;29:4–20.

17 Glazener C, Breeman S, Elders A, Hemming C, Cooper K, Freeman R, et al. PROlapse surgery: pragmatic evaluation and randomised controlled trials – clinical 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. [www.nets.nihr.ac.uk/projects/hta/076018]. Accessed 09 December 2015.

18 Allahdin S, Glazener C, Bain C. A randomised controlled trial evaluating the use of polyglactin mesh, polydioxanone and polyglactin sutures for pelvic organ prolapse surgery. *J Obstet Gynaecol* 2008;28:427–31.

19 Glazener C, Breeman S, Elders A, Hemming C, Cooper K, Freeman R, et al. 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. *Health Technol Assess* 2016;20:1–452.

20 Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:698–702.

21 Nygaard I, Brubaker L, Zyczynski H, Cundiff G, Richter H, Gantz M, et al. Long-term outcomes following abdominal sacrocolpopexy for pelvic organ prolapse. *JAMA* 2013;309:2016–24.

22 Maher C, Feiner B, Baessler K, Christmann-Schmid C, Haya N, Marjoribanks J. Transvaginal mesh or grafts compared with native tissue repair for vaginal prolapse. *Cochrane Database Syst Rev* 2016; (9):CD012079.

23 Altman D, Väyrynen T, Engh M, Axelsen S, Falconer C. Anterior colporrhaphy versus transvaginal mesh for pelvic-organ prolapse. *NEJM* 2011;364:1826–36.

24 Withagen M, Milani A, den Boon J, Vervest H, Vierhout M. Trocar-guided mesh compared with conventional vaginal repair in recurrent prolapse: a randomized controlled trial. *Obstet Gynecol* 2011;117:242–50.

Appendix 1

All members of the local recruitment teams and gynaecologists at the 33 recruiting centres are members of the PROSPECT STUDY Group:

Aberdeen: Christine Hemming/Bain*, Kevin Cooper, Peter Terry, Mohamed Abdel Fattah, Lynn Swan, Christine Dallas, Angela Allan, Christina Henderson. Ayrshire & Arran: Wael Agur*, David Rae, Margo Henry, Danielle Gilmour. Barnsley: Khalid Farag*, Meenakshi Dass, Michelle Reid. Birmingham: Philip Toozs-Hobson*, Claire Burton, Pallavi Latthe, Matthew Parsons, Paula Trinham, Anna Zhao. Bolton: Abimbola Williams*, Philip Chia, Nadia Ali-Ross, Katrina Rhead, Raksha Mistry. Bradford: Carmel Ramage*, Sue Calvert, Anne Bowyer. Bristol: Philip Smith*, Jenny Cloete, Leigh Morrison, Heather Wilcox. Brighton: Sharif Ismail*. Chester: Mofid Ibraheim*, Lorraine Dinardo, Denise Archer, Nichola Kearsley, Janet Spriggs, Hollie Devlin. Cumbria: Mohamed Matar*, Claire Hagon, Toni Wilson. Derby: Jay Dasgupta*, Victor Chilaka, Jill Smith. Harrogate: Adrian Barnett*, Tracy Jackson, Rachael Worton, Caroline Bennett. Huddersfield: Yi Ling Chan*, A Bondili, Judith Kitchingman. Hull: Jagdish Gandhi*, Helen Bexhell. Imperial: Vik Khullar*, Ruwan Fernando, Alex Digesu, Jenny Underwood, Anand Singh. Leicester: Douglas Tincello*, Victoria Fowler, Carla Christie, Katie Warwick. Luton: Abdalla Fayyad*, Victoria Bastion, Rose Ann Chin. Manchester: Anthony Smith*, Fiona Reid, Karen Ward, Karen Rose, David Iles, Lucy Dwyer, Linda Green, Rachel Biancardi, Wilfred Kumakech, Stephanie Bateman. Maidstone: Rowan Connell*, Susan Lord, Sharon Jones, Tracey Nolan, Rebecca Casey. Mid Yorkshire: Kathryn Fishwick*, Tracey Lowry, Jackie Ward, Sarah Buckley, Claire Townend. North Devon: Seumas Eckford*, Osama Eskander, Geraldine Belcher, Amanda Skinner, Lucia Stancombe, Deborah Passmore. Nottingham: Richard Parkinson*, Paul Hooper, Mausumi Das, Rosario Hannigan, Andy Jarvis, Emma Hickman, Delia Bester, Sarah Heawood. Plymouth: Robert Freeman*, Luigi Bombieri, Paula Brockman, Angela King, Beverley Cree, Heidi Hollands. Portsmouth: Patrick Hogston*, Richard Parkinson, Denise Wright, Elinor Jenkins. Preston: Sanjeev Prashar*, Pauline MacDonald, Julie Butler, Sue Flintoff. Rotherham: Daksha Patel*, Janet Field, Rachel Walker, Mishell Cunningham, Sally Anne Pearson, Meredyth Harris. Royal Devon & Exeter: Myles Taylor*, Rachel Sturley, Karen Brown, Sarah Irvine, Julia Halpin, Alison Potter, Caroline Renton. South Tees: Paul Ballard*, Aethele Khunda, Colette Anderson, Julie Potts. Sunderland: Jonathan Chamberlain*, Denise Milford, Eileen Walton. Torbay: Subramanian Narayanan*, Andrew Hall, Pauline Mercer, Barbara Finson. West Middlesex: Fabian Imoh-Ita*, Manal Reyad, Mehari Teklay, Christine Adamson. Whipps Cross: Sarah Hussain*, Shankar Visvanathan,

Bashir Dawlatly, Zandile Maseko. Wolverhampton: Ayman El Naqa*, Charles Cox, Khaled Afifi, Sharon Kempson, Nick Denyer.

*Principal Investigator.

Study oversight

The PROSPECT study was overseen by an independent Trial Steering Committee (Henry Kitchener [Chair], Ranee Thakar [Clinician], Pamela Warner [Statistician], Trish Emerson [Patient Representative, 2012—present], Catherine Rodger [Patient Representative, 2010–2012]) and an independent Data Monitoring Committee (James Neilson [Chair], Lucia Dolan [Clinician], Paula Williamson [Statistician], Gill Gyte [Patient Representative]).