Mesh, graft, or standard repair for women having primary transvaginal anterior or posterior compartment prolapse surgery: two parallel-group, multicentre, randomised, controlled trials (PROSPECT)

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Summary

Background The use of transvaginal mesh and biological graft material in prolapse surgery is controversial and has led to a number of enquiries into their safety and efficacy. Existing trials of these augmentations are individually too small to be conclusive. We aimed to compare the outcomes of prolapse repair involving either synthetic mesh inlays or biological grafts against standard repair in women.

Methods We did two pragmatic, parallel-group, multicentre, randomised controlled trials for our study (PROSPECT [PROlapse Surgery: Pragmatic Evaluation and randomised Controlled Trials]) in 35 centres (a mix of secondary and tertiary referral hospitals) in the UK. We recruited women undergoing primary transvaginal anterior or posterior compartment prolapse surgery by 65 gynaecological surgeons in these centres. We randomly assigned participants by a remote web-based randomisation system to one of the two trials: comparing standard (native tissue) repair alone with standard repair augmented with either synthetic mesh (the mesh trial) or biological graft (the graft trial). We assigned women (1:1:1 or 1:1) within three strata: assigned to one of the three treatment options, comparison of standard repair with mesh, and comparison of standard repair with graft. Participants, ward staff, and outcome assessors were masked to randomisation where possible; masking was obviously not possible for the surgeon. Follow-up was for 2 years after the surgery; the primary outcomes, measured at 1 year and 2 years, were participant-reported prolapse symptoms (i.e. the Pelvic Organ Prolapse Symptom Score [POP-SS]) and condition-specific (ie, prolapse-related) quality-of-life scores, analysed in the modified intention-to-treat population. This trial is registered as an International Standard Randomised Controlled Trial, number ISRCTN60695184.

Findings Between Jan 8, 2010, and Aug 30, 2013, we randomly allocated 1352 women to treatment, of whom 1348 were included in the analysis. 865 women were included in the mesh trial (430 to standard repair alone, 435 to mesh augmentation) and 735 were included in the graft trial (367 to standard repair alone, 368 to graft augmentation). Because the analyses were carried out separately for each trial (mesh trial and graft trial) some women in the standard repair arm assigned to all treatment options were included in the standard repair group of both trials. 23 of these women did not receive any surgery (15 in the mesh trial, 13 in the graft trial; five were included in both trials) and were included in the baseline analyses only. Mean POP-SS at 1 year did not differ substantially between comparisons (standard 5·4 [SD 5·5] *vs* mesh 5·5 [5·1], mean difference 0·00, 95% CI –0·70 to 0·71; p=0·99; standard 5·5 [SD 5·6] *vs* graft 5·6 [5·6]; mean difference –0·15, –0·93 to 0·63; p=0·71). Mean prolapse-related quality-of-life scores also did not differ between groups at 1 year (standard 2·0 [SD 2·7] *vs* mesh 2·2 [2·7], mean difference 0·13, 95% CI –0·25 to 0·51; p=0·50; standard 2·2 [SD 2·8] *vs* graft 2·4 [2·9]; mean difference 0·13, –0·30 to 0·56; p=0·54). Mean POP-SS at 2 years were: standard 4·9 (SD 5·1) versus mesh 5·3 (5·1), mean difference 0·32, 95% CI –0·39 to 1·03; p=0·37; standard 4·9 (SD 5·1) versus graft 5·5 (5·7); mean difference 0·32, –0·48 to 1·12; p=0·43. Prolapse-related quality-of-life scores at 2 years were: standard 1·9 (SD 2·5) versus mesh 2·2 (2·6), mean difference 0·15, 95% CI –0·23 to 0·54; p=0·44; standard 2·0 (2·5) versus graft 2·2 (2·8); mean difference 0·10, –0·33 to 0·52; p=0·66. Serious adverse events such as infection, urinary retention, or dyspareunia or other pain, excluding mesh complications, occurred with similar frequency in the groups over 1 year (mesh trial: 31/430 [7%] with standard repair *vs* 34/435 [8%] with mesh, risk ratio [RR] 1·08, 95% CI 0·68 to 1·72; p=0·73; graft trial: 23/367 [6%] with standard repair *vs* 36/368 [10%] with graft, RR 1·57, 0·95 to 2·59; p=0·08). The cumulative number of women with a mesh complication over 2 years in women actually exposed to synthetic mesh was 51 (12%) of 434.

Interpretation Augmentation of a vaginal repair with mesh or graft material did not improve women's outcomes in terms of effectiveness, quality of life, adverse effects, or any other outcome in the short term, but more than one in ten women had a mesh complication. Therefore, follow-up is vital to identify any longer-term potential benefits and serious adverse effects of mesh or graft reinforcement in vaginal prolapse surgery.

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Introduction

The use of transvaginal synthetic mesh and biological graft material in women having prolapse repair surgery has caused much controversy.[1] The known high rate of further surgery after traditional prolapse surgery (30%),[2] and evidence that mesh insertion is an effective treatment for abdominal hernia surgery,[3,4] led to the introduction of mesh for pelvic organ prolapse repair. When our study PROSPECT (PROlapse Surgery: Pragmatic Evaluation and randomised Controlled Trials) began (in 2009), evidence from 17 randomised controlled trials (appendix) supported the use of mesh and grafts in terms of better anatomical cure of prolapse, but evidence for other outcomes was absent.[5,6] Concerns have since been raised about the safety and morbidity of mesh and graft use in prolapse surgery, including pain, dyspareunia, and mesh-specific complications such as exposure within the vagina, extrusion and perforation.[7] These concerns led to increased litigation internationally, and in Scotland, UK (in June, 2014), a ban on the use of mesh until sufficient reliable evidence becomes available to inform practice.[8]

See Online for appendix

A Cochrane review[9] (published in 2016) of results from 37 trials in 4023 women reported that women are less likely to have prolapse symptoms or measureable prolapse, and fewer require repeat prolapse surgery, after repairs with synthetic non-absorbable mesh than after a standard (native tissue) repair, but not enough reliable evidence was available to suggest whether women had better quality of life. However, the comparison of biological grafts with standard repairs remained inconclusive, and with the exception of mesh exposure and bladder injury, information about other adverse effects was insufficient. Furthermore, few trials reported results separately for women undergoing their first or a repeat procedure.

Therefore we designed the PROSPECT study to compare the outcomes of prolapse repairs involving either non-absorbable synthetic mesh inlays (the mesh trial) or

Research in context

Evidence before this study

The use of synthetic mesh and biological graft material in women having prolapse repair surgery has caused much controversy, and raised enquiries about the safety and efficacy of these techniques. We undertook two secondary systematic reviews (Cochrane and IP) to identify all relevant evidence relating to the value of augmentation of prolapse surgery with synthetic absorbable or non-absorbable mesh or biological grafts. A Cochrane review of trials published in 2007 identified seven that used mesh or grafts, of which only one included non-absorbable mesh in one arm (search date May 3, 2006). An Interventional Procedures review updated the Cochrane review by including a further ten trials (search date July 5, 2007).

Findings from only two small trials using grafts reported persistent prolapse symptoms; the data were too few to be reliable. However, women in four trials of biological graft versus standard (native tissue) repair were significantly less likely to have residual objective prolapse (12% versus 22% of 553 women: risk ratio [RR] 0·55, 95% CI 0·37–0·81; and similarly for non-absorbable mesh versus standard (6% versus 28% of 369 women: RR 0·24, 0·13–0·43). Limitations of the trials, and hence the reviews, included an absence of distinction between women having a first or a repeat procedure; additionally, very few included patient-reported outcomes such as prolapse, urinary, bowel, or sexual symptoms; quality of life; or adverse effects; or health-economic outcomes. And although a more recent Cochrane review has been published, containing 37 trials, the quality of current evidence remains very low to moderate, due to poor reporting of study methods, inconsistency, and imprecision.

Added value of this study

Our study, PROSPECT (PROlapse Surgery: Pragmatic Evaluation and randomised Controlled Trials), was large with a low risk of bias that distinguished between women having a first and a repeat procedure and used validated outcomes relevant to, and reported by, the participants. In the first 2 years after surgery, we showed that women do not benefit from having their first prolapse repair (either standard anterior or posterior repair) reinforced with synthetic mesh or biological graft, either in terms of prolapse symptoms or anatomical cure.

Implications of all the available evidence

Results of previous studies showed a benefit from the use of synthetic mesh and biological graft on objective prolapse stage. However, there are important methodological limitations in aggregating the evidence from these studies using meta-analysis, including the quality of the evidence, the failure to differentiate between primary and secondary repairs, and paucity of patient-centred, validated prolapse-specific outcomes, or quality of life. Our large, rigorous study offers strong, clinically relevant evidence for the alternative view: that mesh or graft are unlikely to be useful in terms of improving any symptoms of pelvic-floor dysfunction or women's quality of life up to 2 years after surgery. Some women had treatment for mesh complications, although most mesh exposures were small and asymptomatic. Further long-term follow-up will ultimately determine whether the use of mesh or graft in vaginal prolapse repair provides any long-term benefits.

biological grafts (the graft trial) against standard repairs (native tissue without mesh or graft) in women having a primary anterior or posterior transvaginal repair. The primary focus was patient reported outcomes (women's symptoms of prolapse) and their experience of adverse effects, in keeping with international recommendations.[10,11]

Methods

Study design and participants

For PROSPECT, we did two pragmatic, parallel-group randomised controlled trials in women undergoing primary transvaginal anterior or posterior compartment prolapse surgery in 35 centres (a mix of secondary and tertiary referral hospitals) in the UK. PROSPECT was approved by the North of Scotland Research Ethics Committee (09/SO802/56). The full protocol is available on the funders' website.[12] The planned surgery could include concomitant uterine, vault, or continence surgery. All women under the care of a collaborating surgeon were potentially eligible for inclusion if a decision had been made to have primary pelvic organ prolapse surgery for anterior or posterior vaginal wall prolapse. Only women who were unable or unwilling to give informed consent, or who were unable to complete study questionnaires, were deemed ineligible. All women who required pelvic organ prolapse surgery were identified by their surgeon or a dedicated recruitment officer in each centre. They were given a study flyer and a brief summary of the study at their initial clinic appointment, followed by the patient information leaflet with their admission documents or by separate mail if the woman agreed. Eligible surgeons had to be proficient in transvaginal anterior and posterior prolapse repair (subspecialist urogynaecologists and special interest general gynaecologists). Women who were having a repeat repair (in the same compartment) and those who were not eligible for randomisation are not reported in this Article. All women provided written informed consent.

Randomisation

We randomly assigned participants by a remote web-based randomisation system to one of the two trials: comparing standard (native tissue) repair alone with standard repair augmented with either synthetic mesh inlay (the mesh trial) or a biological graft inlay (the graft trial). A remote web-based randomisation application at the Centre for Healthcare Randomised Trials (CHaRT, University of Aberdeen, UK) was used for group allocation. Because not all surgeons could offer all three interventions (standard repair alone, standard repair with synthetic mesh, or standard repair with biological graft), women were randomly assigned (1:1:1 or 1:1) within three strata: A) women assigned to one of all three treatment options; B) comparison of standard repair with mesh; and C) comparison of standard repair with graft. We used a minimisation algorithm that included: age (<60 years or ≥60 years); type of prolapse repair planned (anterior, posterior, or both); need for a concomitant urinary continence procedure (eg, mid-urethral tape) or not; need for a concomitant upper vaginal prolapse procedure (eg, hysterectomy, cervical amputation, or vault repair) or not; and the operating surgeon.

Masking for the surgeon with respect to treatment allocated by randomisation was not feasible, but the participants and ward staff were not informed about the randomised allocation or the actual treatment received unless there was a clinical need or requested by the woman. The clinical examination at 1 year was done by an observer unaware of the allocated treatment where possible.

Procedures

The participating surgeons (subspecialist urogynaecologists and special interest general gynaecologists) used their usual surgical techniques for transvaginal mesh, graft, and standard (native tissue) repairs. They provided details of their surgical protocols, which could include midline or fascial plication if indicated, and could use any mesh or graft available to them. All surgeons doing mesh surgeries used non-absorbable type 1 monofilament macroporous polypropylene mesh for inlays. The weights of mesh ranged from 19 g/m² to 44 g/m², and hybrid (coated) mesh was allowed. The biological graft materials were porcine acellular collagen matrix, porcine small intestinal submucosa, or bovine dermal grafts. The mesh or graft was inserted below the fascial layer if possible and secured with peripheral sutures.

We measured outcomes by participant-completed postal questionnaire at baseline (before surgery), and 6 months, 1 year, and 2 years after surgery, and in a clinic review appointment at 1 year (with the Pelvic Organ Prolapse Quantification system [POP-Q]).

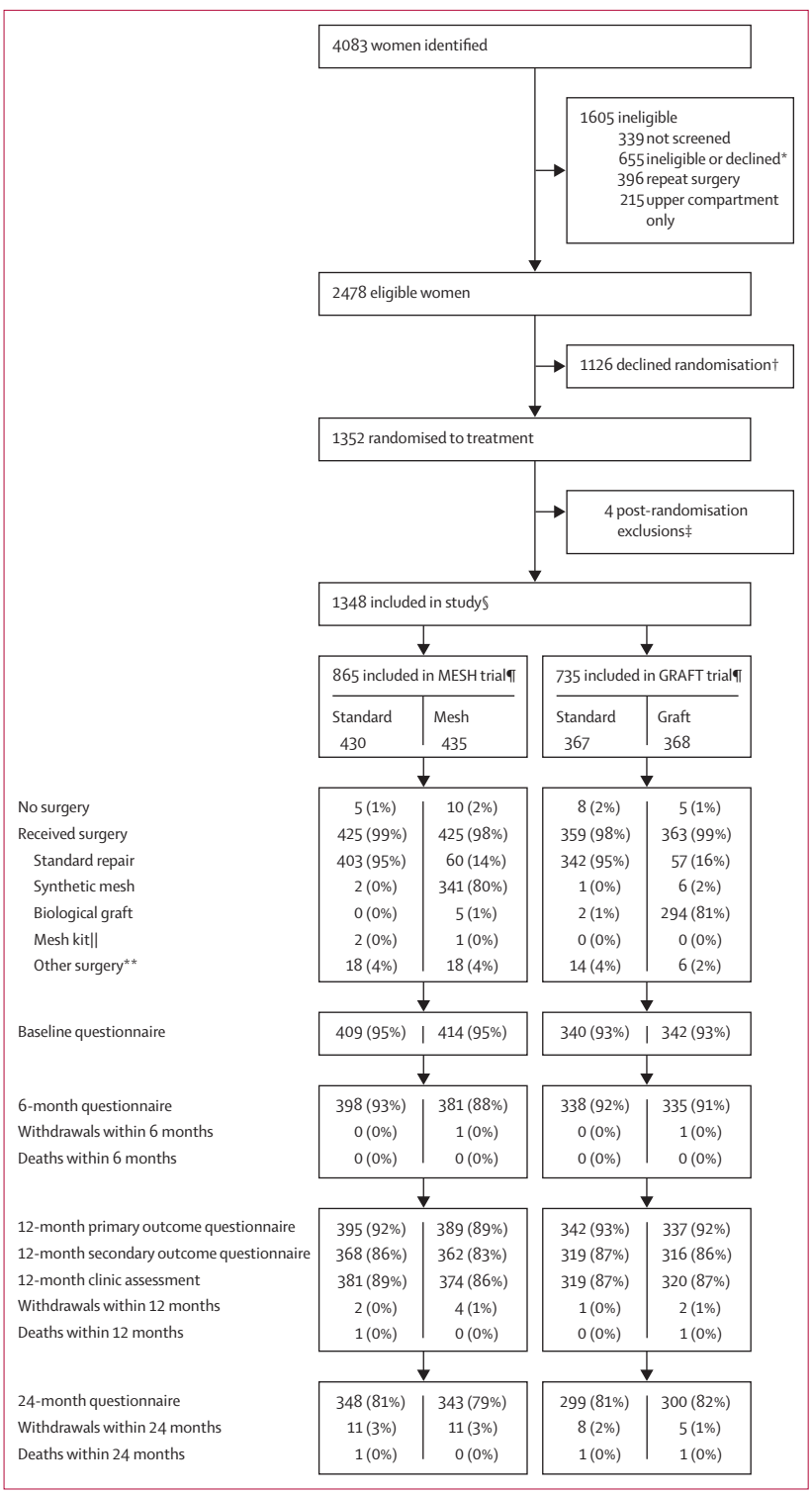
Outcomes

The primary clinical outcome was the woman's report of prolapse symptoms, in keeping with International Urogynecological Association/International Continence Society (IUGA/ICS) recommendations.[11] At 1 year after surgery to assess this primary outcome we used the Pelvic Organ Prolapse Symptom Score (POP-SS), a validated patient-completed measure that has been shown to be sensitive to change after treatment.[13,14] POP-SS contains seven items relating to frequency of prolapse symptoms in the preceding 4 weeks. Each item is scored from 0 (never) to 4 (all the time), with a possible total score ranging from 0 to 28. The minimally clinically important difference of the POP-SS is two.[15] A difference between groups in a mean score of 2 units would represent an improvement in the response to one POP-SS symptom question (for example, "a feeling of something coming down or in the vagina", improved from most of the time to occasionally). We also used the POP-SS questions to define subjective failure as POP-SS greater than 0 and any report of something coming down.

A second primary outcome was condition-specific quality of life measured using a visual analogue scale. Secondary outcomes were generic quality of life based on the EQ-5D-3L[16] and adverse effects and complications of surgery using the IUGA/ICS complications classification which includes type, severity, time of occurrence, and site.[7,17] We also measured bladder, bowel, and sexual function using validated or adapted International Consultation on Incontinence Questionnaires (ICIQ) as secondary outcomes.[18]

Objective measurement of prolapse stage using the Pelvic Organ Prolapse Quantification system (POP-Q) was undertaken by observers masked when possible to treatment allocated and received.[19] We recorded if the person undertaking the POP-Q knew the treatment that they were randomly assigned to or the treatment actually received so we could monitor the situation, but accepted that masking was not always possible. Objective failure was defined as the leading edge of the prolapse beyond the hymen (>0 cm), in line with other research.[20]

Adverse effects, need for readmission or further treatment for adverse effects, or prolapse recurrence, were reported by surgeons or participants and verified by study office staff from a second source when possible. Serious adverse events were defined using standard classifications.[21] All definitions are in keeping with the recommendations of IUGA, ICS, and the International Consultation on Incontinence.[7,11,17,18,22]



Statistical analysis

We planned to follow up 400 women in each of three arms (a total of 1200 participants) to detect a difference in the primary clinical outcome, POP-SS, of 0·25 SD (based on a SD of 8 and a minimally clinically important difference of two) with 90% power and α=0·025 (to maintain the nominal p value at 0·05 with tests for two comparisons).[15] The sample size was increased to 1450 women to allow for potentially 17·5% of them to drop out.

***Figure*: Trial profile**

*117 no prolapse or changed mind about needing surgery; 45 removed from waiting list or unfit for surgery; 32 unable to give informed consent; 16 unable to complete questionnaires; 413 not interested in participation in study or unknown; 32 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). †379 clinical decisions including wanted to use mesh, did not want to use mesh, and other; 613 participant decisions including wanted mesh, did not want mesh, wanted surgeon to decide, and did not want to be randomised; 134 other reasons including mesh unavailable, operating surgeon not trained in mesh inlays or kits, operating theatre time issues, and reasons not recorded. ‡1 had baseline comorbidities that made her ineligible for PROSPECT; 1 had prolapse surgery privately after agreeing to participate but before randomisation; 2 were having a secondary repair. §545 randomly assigned women were included in the standard repair arm, 435 in the mesh arm and 368 in the graft arm (total of 1348). 252 women were in stratum A who were included in both the mesh and graft trials, such that 430 women were in the standard repair arm of the mesh trial and 367 women in the standard repair arm of the graft trial. The numbers of participating women by individual strata are in the appendix. ¶Percentages shown represent the number of women as a proportion of those included in the analysis. ||Mesh kit defined as synthetic mesh inserted using trochars (therefore not classed as synthetic mesh inlay). **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, or vault repair.

	Mesh trial: standard repair *vs* synthetic mesh augmented repair		Graft trial: standard repair *vs* biological graft augmented repair	
	Standard repair (n=430)	Synthetic mesh (n=435)	Standard repair (n=367)	Biological graft (n=368)
Age (years)	59·8 (10·1); 430	59·5 (10·4); 435	59·7 (10·4); 367	58·9 (10·5); 368
Parity (median)	2 (0–8); 429	2 (0–9); 433	2 (0–8); 367	2 (1–7); 367
Prolapse symptoms				
POP-SS	13·7 (6·1); 409	13·7 (5·6); 414	13·8 (6·0); 340	13·7 (5·9); 342
Symptomatic prolapse*	100% (409/409)	>99% (412/414)	100% (340/340)	99% (339/342)
Prolapse-related QoL score†	6·5 (2·8); 408	6·6 (2·7); 406	6·7 (2·7); 338	6·6 (2·8); 338
EQ-5D-3L score	0·72 (0·24); 398	0·71 (0·23); 406	0·72 (0·24); 330	0·71 (0·25); 329
Urinary incontinence (severe)‡	19% (78/403)	21% (86/408)	19% (65/337)	22% (74/339)
Faecal incontinence (any)§	34% (140/408)	34% (138/406)	33% (113/338)	36% (121/338)
ICI Vaginal Symptoms Score	22·1 (9·0); 367	22·2 (9·4); 365	21·7 (8·7); 302	22·8 (9·1); 307
Severe dyspareunia¶	8% (18/217)	7% (13/197)	11% (20/175)	11% (21/186)
Previous surgery				
Previous prolapse repair	11% (49/430)	13% (56/435)	10% (37/367)	8% (30/368)
Vault repair	2% (9/430)	2% (7/435)	2% (7/367)	1% (4/368)
Hysterectomy	23% (100/430)	29% (125/435)	25% (92/367)	29% (106/368)
Continence surgery	7% (31/429)	6% (27/431)	6% (21/365)	5% (20/367)
Overall POP-Q stage				
Leading edge >0cm‖	66% (259/395)	69% (273/397)	63% (210/335)	69% (235/339)

Data are mean (SD); N or % (n/N). POP-SS=Pelvic Organ Prolapse Symptom Score. QoL=quality of life. EQ-5D-3L=European Quality of Life-5 Dimensions 3-level. ICI= International Consultation on Incontinence. POP-Q=Pelvic Organ Prolapse Quantification system. *Symptomatic defined as the number of women with POP-SS >0. †Quality of life due to prolapse symptoms measured as the overall interference of prolapse symptoms with everyday life using a visual analogue scale; scores range from 0 (not at all) to 10 (a great deal). ‡Severe urinary incontinence defined as a score of 13–21 on the International Consultation on Incontinence Questionnaire-Urinary Incontinence-Short Form questionnaire. §Faecal incontinence of solid or liquid stool (any) defined as occasionally or more. ¶Severe dyspareunia defined as answering "a lot" to the question: "Do you have pain when you have sexual intercourse?" ‖Overall POP-Q stage defined as leading edge beyond the hymen (>0 cm).

***Table 1*: Baseline characteristics of the intention-to-treat population**

We did not follow up randomly assigned participants who did not receive any surgery. Data from all women who had surgery and provided outcome data were analysed by modified intention-to-treat, remaining in the group to which they were randomised. Although crossover was not part of the study design, some women received a different surgical intervention from the one to which they were allocated. We made two comparisons: standard repair versus synthetic mesh (mesh trial, data from women in strata A and B) and standard repair versus biological graft (graft trial, data from women in strata A and C; appendix). Some women from stratum A who were assigned to standard repair were included in both trial analyses. The main analysis was a complete-case analysis, with no imputation for missing data.

All outcome measures were presented as summaries of descriptive statistics (mean [SD] for continuous measures, and proportions for ordinal and dichotomous measures) and comparisons between randomised groups were analysed separately at 6, 12, and 24 months using generalised linear models. We adjusted models for minimisation covariates, baseline measures where appropriate, and randomisation stratum. We analysed continuous outcomes using linear mixed models with the surgeon fitted as a random effect. Assumptions of linearity and normality of error distributions were examined by inspection of residual plots. POP-Q stage was analysed using ordinal logistic regression (proportional odds models with cumulative logits with score tests performed to examine the proportional odds assumption). We analysed dichotomous outcomes using log-binomial regression.[23] Estimates of treatment effect size were mean differences in the mixed models, odds ratios in the ordinal models, and risk ratios in the binary models. Although the study adjusted for the two primary comparisons when calculating the sample size (α=0·025), we present 95% CIs that have not adjusted for the multiple comparisons. We did the study analyses according to a prespecified statistical analysis plan, using SAS version 9.4 (SAS Institute, Cary, NC, USA).

PROSPECT was overseen by an independent trial steering committee and an independent data monitoring committee. This trial is registered as an International Standard Randomised Controlled Trial, number ISRCTN60695184.

Role of the funding source

The funder of the study approved the study proposal but had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

	Mesh trial: standard repair *vs* synthetic mesh augmented repair				Graft trial: standard repair *vs* biological graft augmented repair			
	Standard repair	Synthetic mesh	Estimate of treatment effect size	p value	Standard repair	Biological graft	Estimate of treatment effect size	p value
6-month outcomes	N=398	N=381	..	..	N=338	N=335	..	..
POP-SS	4·7 (5·4); 398	5·3 (5·1); 380	0·57 (–0·12 to 1·26)	0·10	5·0 (5·5); 338	4·9 (5·5); 335	–0·44 (–1·23 to 0·35)	0·28
Prolapse-related QoL score†	2·0 (2·8); 390	2·2 (2·7); 374	0·22 (–0·16 to 0·60)	0·26	2·0 (2·9); 332	2·0 (2·7); 330	–0·17 (–0·58 to 0·25)	0·43
Symptomatic prolapse*	79% (314/398)	86% (325/380)	1·07 (1 to 1·14)	0·04	81% (274/338)	81% (271/335)	1·00 (0·93 to 1·08)	0·96
Women with any report of SCD	31% (123/398)	33% (125/380)	1·09 (0·90 to 1·34)	0·38	30% (101/338)	34% (113/335)	1·11 (0·88 to 1·39)	0·38
EQ-5D-3L score	0·82 (0·26); 383	0·83 (0·22); 372	0·01 (–0·02 to 0·04)	0·40	0·82 (0·27); 326	0·82 (0·25); 318	0·01 (–0·02 to 0·05)	0·50
1-year outcomes	N=395	N=389	..	..	N=342	N=337	..	..
POP-SS	5·4 (5·5); 395	5·5 (5·1); 389	0·00 (–0·70 to 0·71)	0·99	5·5 (5·6); 342	5·6 (5·6); 337	–0·15 (–0·93 to 0·63)	0·71
Prolapse-related QoL score†	2·0 (2·7); 389	2·2 (2·7); 380	0·13 (–0·25 to 0·51)	0·50	2·2 (2·8); 335	2·4 (2·9); 330	0·13 (–0·30 to 0·56)	0·54
Symptomatic prolapse*	83% (328/395)	85% (329/389)	1·01 (0·95 to 1·08)	0·64	83% (283/342)	82% (276/337)	0·99 (0·93 to 1·06)	0·85
Women with any report of SCD	36% (143/395)	35% (138/389)	0·98 (0·82 to 1·18)	0·85	34% (117/342)	42% (140/337)	1·18 (0·97 to 1·43)	0·10
Severe urinary incontinence‡	6% (21/361)	8% (29/354)	1·34 (0·79 to 2·26)	0·27	8% (26/315)	5% (17/313)	0·61 (0·33 to 1·12)	0·11
Faecal incontinence (any)§	28% (102/365)	25% (91/358)	0·92 (0·74 to 1·13)	0·41	27% (84/316)	25% (77/314)	0·92 (0·72 to 1·17)	0·50
ICI Vaginal Symptoms Score	7·2 (7·2); 338	7·5 (8·1); 327	0·52 (–0·64 to 1·68)	0·38	7·1 (6·9); 294	9·0 (9·1); 294	1·31 (0·04 to 2·59)	0·04
Severe dyspareunia¶	4% (8/186)	5% (9/173)	1·73 (0·52 to 5·78)	0·37	6% (9/149)	5% (8/165)	1·17 (0·43 to 3·23)	0·76
EQ-5D-3L score	0·83 (0·25); 385	0·83 (0·22); 384	0·01 (–0·02 to 0·04)	0·65	0·81 (0·27); 335	0·82 (0·25); 333	0·02 (–0·01 to 0·06)	0·21
2-year outcomes	N=348	N=343	..	..	N=299	N=300	..	..
POP-SS	4·9 (5·1); 347	5·3 (5·1); 342	0·32 (–0·39 to 1·03)	0·37	4·9 (5·1); 298	5·5 (5·7); 299	0·32 (–0·48 to 1·12)	0·43
Prolapse-related QoL score†	1·9 (2·5); 335	2·2 (2·6); 329	0·15 (–0·23 to 0·54)	0·44	2·0 (2·5); 290	2·2 (2·8); 291	0·10 (–0·33 to 0·52)	0·66
Symptomatic prolapse*	82% (283/347)	85% (291/342)	1·04 (0·97 to 1·11)	0·30	81% (242/298)	82% (245/299)	0·99 (0·92 to 1·07)	0·85
Women with any report of SCD	31% (106/347)	34% (116/342)	1·06 (0·85 to 1·32)	0·59	31% (91/298)	40% (120/299)	1·26 (1·01 to 1·58)	0·04
Severe urinary incontinence‡	6% (19/343)	6% (21/334)	1·01 (0·51 to 1·99)	0·97	7% (21/294)	7% (20/297)	0·80 (0·44 to 1·46)	0·47
Faecal incontinence (any)§	26% (89/343)	27% (92/338)	1·13 (0·92 to 1·41)	0·25	27% (81/295)	26% (77/298)	0·95 (0·75 to 1·21)	0·69
ICI Vaginal Symptoms Score	7·0 (7·3); 313	7·3 (7·8); 311	–0·18 (–1·34 to 0·98)	0·76	6·8 (6·8); 271	8·1 (8·8); 278	0·36 (–0·95 to 1·67)	0·59
Severe dyspareunia¶	5% (9/166)	3% (4/145)	0·49 (0·15 to 1·55)	0·22	4% (5/125)	4% (6/154)	0·93 (0·29 to 2·99)	0·90
EQ-5D-3L score	0·81 (0·28); 340	0·83 (0·22); 334	0·02 (–0·02 to 0·06)	0·26	0·81 (0·28); 291	0·82 (0·27); 294	0·03 (–0·01 to 0·07)	0·17

Data are mean (SD); n or % (n/N). Estimates of treatment effect size are mean (95% CI). For all negative continuous outcomes eg, POP-SS (Pelvic Organ Prolapse Symptom Score): a positive effect size favours standard. For all positive continuous outcomes eg, EQ-5D-3L (European Quality of Life-5 Dimensions 3-level): a positive effect size favours synthetic or biological. For all negative dichotomous outcomes: an effect size more than 1 favours standard. For all positive dichotomous outcomes: an effect size more than 1 favours synthetic or biological. SCD=something coming down. QoL=quality of life. ICI= International Consultation on Incontinence. *Symptomatic defined as the number of women with POP-SS >0. †Quality of life due to prolapse symptoms measured as the overall interference of prolapse symptoms with everyday life using a visual analogue scale; scores range from 0 (not at all) to 10 (a great deal). ‡Severe urinary incontinence defined as a score of 13–21 on the International Consultation on Incontinence Questionnaire-Urinary Incontinence-Short Form questionnaire. §Faecal incontinence of solid or liquid stool (any) defined as occasionally or more. ¶Severe dyspareunia defined as answering "a lot" to the question: "Do you have pain when you have sexual intercourse?"

***Table 2*: Clinical symptoms and quality of life outcomes**

Results

Between Jan 8, 2010, and Aug 30, 2013, we randomly assigned 1352 (55%) of 2478 eligible women (figure), of whom four were excluded post-randomisation and were not included in the analyses. Thus, 1348 women were included in the analysis, but 23 women who did not receive any surgical intervention (15 women in the mesh trial and 13 women in the graft trial; five of whom were included in both trials) were included in the baseline analyses only. The remaining 1126 women either declined randomisation or were deemed ineligible for randomisation due to clinical reasons. 865 women were assigned to the mesh trial (430 assigned to standard repair alone, 435 to mesh augmentation) and 735 were assigned to the graft trial (367 assigned to standard repair alone, 368 to graft augmentation). Because the analyses were carried out separately for each trial (mesh and graft trial), some women in the standard repair group randomly assigned to three treatment options were included in the standard repair group of both trials.

Baseline demographic and clinical characteristics of the women having a primary repair were similar between groups (table 1); some women received a different surgical intervention from the one to which they were allocated. The proportion of women who had surgery and received their allocated treatment was 95% for the standard arms in both trials (mesh trial 403/425, graft trial 342/359), versus 80% for mesh (341/425) and 81% for graft (294/363). The reasons for non-compliance with randomised allocation are in the appendix. Consultants or doctors who had completed their specialty training did 78% and 81% of procedures in the mesh trial arms, and 69% and 75% in the graft trial arms, respectively. The remainder were undertaken by experienced registrars or junior doctors. Primary outcome data at 1 year were

	Mesh trial: standard repair *vs* synthetic mesh augmented repair				Graft trial: standard repair *vs* biological graft augmented repair			
	Standard repair (n=381)	Synthetic mesh (n=374)	Estimate of treatment effect size	p value	Standard repair (n=319)	Biological graft (n=319)	Estimate of treatment effect size	p value
POP-Q (cm from hymen)								
Ba (anterior edge)	–1·3 (1·6); 323	–1·3 (1·6); 327	0·06 (–0·17 to 0·29)	0·62	–1·3 (1·7); 299	–1·2 (1·7); 293	0·12 (–0·1 to 0·4)	0·34
C (cervix/vault)	–6·0 (2·1); 318	–6·0 (2·3); 321	–0·03 (–0·36 to 0·31)	0·88	–5·8 (1·9); 292	–5·7 (2·1); 292	0·15 (–0·2 to 0·5)	0·37
Bp (posterior edge)	–2·0 (1·2); 322	–2·1 (1·1); 326	–0·03 (–0·21 to 0·15)	0·74	–2·1 (1·2); 299	–2·0 (1·2); 290	0·13 (–0·1 to 0·3)	0·20
Total vaginal length	8·1 (1·2); 320	8·2 (1·3); 318	0·12 (–0·07 to 0·30)	0·21	7·8 (1·2); 291	7·8 (1·2); 286	0·07 (–0·1 to 0·3)	0·50
Overall POP-Q stage*								
0	16% (56/341)	14% (48/339)	1·11 (0·83 to 1·47)	0·49	17% (51/305)	14% (42/299)	1·26 (0·93 to 1·71)	0·13
1	32% (108/341)	33% (113/339)	..	..	31% (96/305)	28% (85/299)	..	..
2	45% (153/341)	47% (158/339)	..	..	44% (135/305)	48% (144/299)	..	..
3	6% (22/341)	6% (19/339)	..	..	7% (21/305)	8% (25/299)	..	..
4	<1% (2/341)	<1% (1/339)	..	..	<1% (2/305)	1% (3/299)	..	..
2b, 3, or 4†	14% (47/338)	16% (54/336)	1·12 (0·79 to 1·60)	0·52	16% (47/303)	18% (54/298)	1·14 (0·80 to 1·62)	0·47

Data are mean (SD); n or % (n/N). Estimates of treatment effect size are mean (95% CI). POP-Q=Pelvic Organ Prolapse Quantification system. Ba=the most dependent part of the anterior vaginal wall. C=the most dependent part of the cervix or the vaginal cuff if patient has no cervix. Bp=the most dependent part of the posterior vaginal wall.. ..=no available data here. *Calculated from POP-Q, or stage as reported by clinicians when POP-Q not done. †Objective prolapse: stage 2b, 3, or 4, defined as leading edge beyond the hymen (>0 cm) when POP-Q data available.

***Table 3*: Objective measures of prolapse at 1-year clinical review**

available for 91% (784/865) of the women in the mesh trial and 92% (679/735) of the women in the graft trial (table 2). Details of surgery and concomitant procedures received are in the appendix.

Mean POP-SS at 1 year did not differ for each comparison (standard 5·4 [SD 5·5] *vs* mesh 5·5 [5·1], mean difference 0·00, 95% CI –0·70 to 0·71; p=0·99; standard 5·5 [SD 5·6] *vs* graft 5·6 [5·6]; mean difference –0·15, –0·93 to 0·63; p=0·71; table 2). Mean prolapse-related quality-of-life scores also did not differ between groups at 1 year (standard 2·0 [SD 2·7] *vs* mesh 2·2 [2·7], mean difference 0·13, 95% CI –0·25 to 0·51; p=0·50; standard 2·2 [SD 2·8] *vs* graft 2·4 [2·9]; mean difference 0·13, –0·30 to 0·56; p=0·54; table 2).

The EQ-5D-3L scores also did not differ between groups (table 2). There were no significant subgroup interaction effects by treatment from any of the planned subgroup analyses, including surgeon effect. A per-protocol analysis excluding those who did not receive their randomised intervention also did not affect the overall result: standard mean 5·5 (SD 5·6) versus mesh 5·3 (5·2), mean difference –0·19, 95% CI –0·95 to 0·57; standard mean 5·5 (SD 5·6) versus graft 5·5 (5·6); mean difference –0·31, –1·14 to 0·52.

In both trials, a few differences occurred in other prolapse outcomes between the randomised groups at 6 months, 1 year, or 2 years; the number of women with at least one symptom (symptomatic prolapse [POP-SS>0]) was significantly greater in the mesh group compared with the standard group at 6 months, ICI Vaginal Symptoms Scores were significantly higher in the graft group compared with the standard group at 1 year, and the number of women with a feeling of something coming down was significantly greater in the graft group compared with the standard group at 2 years (table 2).

No differences were noted in urinary outcomes between the groups in either trial at 1 or 2 years (table 2). Additionally, the groups did not differ in terms of faecal incontinence or severe dyspareunia, and there were no differences in quality of life related to urinary, bowel, vaginal, or sexual symptoms, or satisfaction rates after surgery (appendix).

Objective outcome assessment was carried out by observers masked to randomisation in 581 (88%) of 657 women in the mesh trial, and 539 (94%) of 573 in the graft trial. Consultants carried out 59% of the examinations; the rest were undertaken by recruitment officers (24%), junior registrars (15%) and unknown (2%). Although a higher proportion of women had objective failure (leading edge >0 cm beyond hymen) in the synthetic mesh and biological graft arms compared with standard repair, this did not reach statistical significance in either case for POP-Q stage 2b, 3, or 4 (table 3).

Within the first 2 years, 6% of women underwent new prolapse surgery in the same or in another compartment for symptomatic and objective failure, with no differences between either of the randomised groups. There were no differences between the groups in either trial for women requiring new surgery for urinary incontinence in the first or second years of follow-up (table 4).

Overall, the number of women with serious adverse effects (complications) during and after prolapse surgery was less than 10% in the first year, with no significant differences between the groups in either trial, except for mesh exposure and subsequent treatment for mesh complications (table 4). This was reflected in the low

	Mesh trial: standard repair *vs* synthetic mesh augmented repair				Graft trial: standard repair *vs* biological graft augmented repair			
	Standard repair	Synthetic mesh	Estimate of treatment effect size	p value	Standard repair	Biological graft	Estimate of treatment effect size	p value
6-month outcomes	N=398	N=381	..	..	N=338	N=335	..	..
Number readmitted (0–6 months)*	3% (11/398)	3% (12/381)	1·15 (0·51 to 2·57)	0·74	3% (9/338)	4% (14/335)	1·54 (0·68 to 3·51)	0·30
1-year outcomes	N=395	N=389			N=342	N=337		
Number readmitted (6–12 months)*	1% (4/395)	1% (5/389)	1·32 (0·36 to 4·81)	0·68	1% (4/342)	2% (6/337)	1·67 (0·48 to 5·79)	0·42
New prolapse operation	2% (6/395)	3% (12/389)	1·99 (0·76 to 5·24)	0·16	2% (7/342)	3% (10/337)	1·44 (0·56 to 3·73)	0·45
Same compartment	<1% (3/395)	2% (8/389)	2·55 (0·68 to 9·53)	0·16	1% (5/342)	1% (5/337)	0·98 (0·29 to 3·34)	0·98
Different compartment	<1% (3/395)	1% (4/389)	1·35 (0·31 to 5·96)	0·69	<1% (2/342)	1% (5/337)	2·50 (0·49 to 12·74)	0·27
New continence operation	1% (5/395)	<1% (2/389)	0·40 (0·08 to 2·04)	0·27	<1% (2/342)	2% (7/337)	3·49 (0·73 to 16·66)	0·12
Adverse effects in the first year								
Any serious adverse effects† (excluding mesh complications)	7% (31/430)	8% (34/435)	1·08 (0·68 to 1·72)	0·73	6% (23/367)	10% (36/368)	1·57 (0·95 to 2·59)	0·08
Any mesh complications‡	<1% (2/430)	7% (32/435)	..	..	<1% (2/367)	<1% (2/368)	..	..
Surgical removal§	<1% (2/430)	5% (23/435)	..	..	<1% (2/367)	<1% (1/368)	..	..
Conservative treatment	(0/430)	2% (8/435)	..	..	(0/367)	(0/368)	..	..
No treatment	(0/430)	<1% (1/435)	..	..	(0/367)	<1% (1/368)	..	..
De novo mesh procedure¶	<1% (1/430)	6·2% (27/435)	..	..	(0/367)	(0/368)	..	..
Concomitant mesh procedure‖	<1% (1/430)	1% (5/435)	..	..	<1% (2/367)	<1% (2/368)	..	..
2-year outcomes	N=348	N=343	..	..	N=299	N=300	..	..
Number readmitted (12–24 months)*	<1% (3/348)	(0/343)	..	..	<1% (2/299)	1% (4/300)	1·95 (0·36 to 10·56)	0·44
New prolapse operation	5% (16/348)	4% (15/343)	0·94 (0·47 to 1·88)	0·87	5% (15/299)	5% (15/300)	0·99 (0·49 to 1·98)	0·98
Same compartment	3% (9/348)	2% (7/343)	0·79 (0·30 to 2·11)	0·64	2% (7/299)	3% (8/300)	1·13 (0·41 to 3·06)	0·82
Different compartment	2% (7/348)	2% (8/343)	1·14 (0·42 to 3·10)	0·80	3% (8/299)	2% (7/300)	0·86 (0·32 to 2·33)	0·76
New continence operation	1% (4/348)	1% (5/343)	1·28 (0·35 to 4·73)	0·71	2% (7/299)	1% (4/300)	0·56 (0·17 to 1·90)	0·35
Adverse effects in second year								
Any serious adverse effects† (excluding mesh complications)	1% (6/430)	<1% (4/435)	0·66 (0·19 to 2·30)	0·51	1% (4/367)	1 % (5/368)	1·25 (0·34 to 4·60)	0·74
Any mesh complications	<1% (1/430)	6% (25/435)	..	..	<1% (1/367)	<1% (1/368)	..	..
Surgical removal**	(0/430)	4% (17/435)	..	..	(0/367)	(0/368)	..	..
Conservative	<1% (1/430)	<1% (4/435)	..	..	<1% (1/367)	(0/368)	..	..
No treatment	(0/430)	<1% (4/435)	..	..	(0/367)	<1% (1/368)	..	..
De novo mesh procedure¶	(0/430)	5·3% (23/435)	..	..	(0/367)	(0/368)	..	..
Concomitant mesh procedure‖	<1% (1/430)	<1% (2/435)	..	..	(0/367)	<1% (1/368)	..	..

Data are mean (SD); n or % (n/N). Estimates of treatment effect size are risk ratio (95% CI). =analyses of mesh complications were not applicable as the comparisons were between surgery with mesh and surgery without. *Readmissions defined as related to prolapse surgery (excluding for new prolapse surgery, continence surgery, or mesh removal). †Serious adverse effects defined as causing death, requiring admission to hospital or prolongation of existing hospital admission, threatening life, resulting in significant incapacity or disability, or otherwise considered important by the investigator. ‡Treatment for mesh complications: surgical removal=admission to hospital for removal or oversewing of exposed mesh in theatre. Conservative=local oestrogen, cautery with silver nitrate, or trimming of exposed mesh in outpatient setting. No treatment=none required. §Surgical removal of mesh in first year N=27: asymptomatic 20, symptomatic 7 (of which pain 5, infection 1); Mesh exposure >1cm²: 9; Number of women having surgery in first 2 months: 3 (remainder between 2 and 12 months). ¶De novo defined as mesh inserted for the first time at the index PROSPECT surgery as part of the vaginal anterior or posterior prolapse repair. ‖Concomitant mesh procedure defined as mesh that was used for a surgical procedure carried out at the same time as the index vaginal anterior or posterior prolapse repair. That would include mesh (tape) inserted as a continence procedure or for vaginal vault or uterine suspension. **Surgical removal of mesh in second year N=17: asymptomatic 13, symptomatic 4 (of which pain 1); mesh exposure >1cm²: 7.

Table 4: **Serious adverse effects related to prolapse surgery, readmissions, and treatment**

readmission rates (from 9/338 [2·7%] to 14/335 [4·2%] in the first 6 months, 4/395 [1·0%] to 6/337 [1·8%] in the next 6 months, and 0 to 4/300 [1·3%] in the second year). There were also no clinically important differences in either trial in individual serious adverse effects such as infection, urinary retention, dyspareunia or other pain (table 4, appendix), or other (non-serious) adverse effects (appendix) in the first or second years after surgery.

In the mesh trial, 25 women had surgery to remove part of the mesh in the first year, of whom two were in the standard group; 18 (72%) were asymptomatic and 16 (64%) had exposures <1 cm². One woman had total mesh removal within 2 weeks of surgery because of severe infection. In the second year, 17 women had surgery to remove part of the mesh (of whom 13 [76%] were asymptomatic and 10 [59%] had exposures <1 cm²). The remaining women who had a mesh complication received

outpatient treatment that consisted of observation only, topical treatment with oestrogen, mesh trimming, or cautery. Most mesh exposures were small or asymptomatic requiring partial removal as a day case (table 4).

Although it might seem counterintuitive that women in the standard (no-mesh) arms could have a mesh complication, this could occur if the surgeon chose to use mesh for the repair or for a concomitant procedure (figure). Restricting the data to women who actually received synthetic mesh either as part of their anterior or prolapse repair or as a concomitant vault, uterine, or continence procedure, the number of women with a mesh complication in the first two years was 51 (12%) of 434, of whom 37 required a surgical removal (9%). Restricting the data further to include women who only received synthetic mesh as part of their anterior or posterior prolapse repair, with no other concomitant mesh procedure or mesh inserted historically, the mesh complication rate in the first two years was 14% (41/284). In the graft trial, four women had a mesh complication in the first year, but all had concomitant synthetic mesh and only three required surgical intervention (none were symptomatic or had exposures >1 cm^2). Two women had a mesh complication in the second year, but neither required surgical treatment.

Discussion

There was no evidence of a significant difference at 1 year in the primary outcome after transvaginal prolapse surgery with or without synthetic non-absorbable mesh or biological graft material to reinforce the repair. The CI around the primary outcome measure of women's symptoms, the POP-SS, was smaller than the prespecified minimally clinically important difference of 2, suggesting that a clinically significant difference between the groups in either of the trials was unlikely.[15] This result was unchanged when those who did not receive the randomised intervention were excluded from the analysis. There were also no important clinical differences between groups in the secondary clinical or objective outcomes at 1 and 2 years. Apart from mesh complications, the proportion of women requiring further treatment in both the trials was similar.

The overall incidence of serious adverse effects, other than mesh-related, was similar in the groups in each trial. By definition women could only have a mesh-related complication if they received mesh (whether de novo for the anterior or posterior repair, or as a concomitant procedure for continence, or for vault or uterine prolapse); in around a third of women this was treated conservatively. Additionally, only one woman had total mesh removal because of infection during follow-up. In most women, the exposure or extrusion of mesh into the vagina was small or asymptomatic, requiring only partial removal as a day case. The overall mesh complication rate in women who actually received synthetic mesh—either in the mesh trial or concomitantly—was 12%. There was also no difference in dyspareunia rates with or without mesh or biological graft.

PROSPECT was the largest randomised study of the use of mesh or graft in transvaginal prolapse surgery to date. It was powered to detect a clinically meaningful difference in prolapse symptoms if these existed. Although we fell short of our stated recruitment target of 1450, this assumed a 17·5% dropout rate which would have given 1196 women with analysable data. We achieved a much better retention rate for the primary outcome (<10%), giving 1226 with analysable data, exceeding the 1196 target.

Our pragmatic design is a reflection of actual practice of experienced UK prolapse surgeons across many hospital settings, using validated terminology and outcome measures in women who had a mix of prolapse types. We distinguished between women having a primary or secondary repair in the compartment requiring surgery (ie, women who were classed as having a primary prolapse in a new compartment could have had surgery in a different compartment previously). This also enabled us subsequently to differentiate between repeat surgery in the operated compartment and further surgery in the opposite one: both occurred equally often. Additionally, the proportions of women having concomitant upper compartment prolapse or continence surgery were evenly distributed between the randomised groups, and therefore did not affect the findings of the two trials.

The POP-Q system defines stage 2 as a measurement from –1 cm inside the hymen to 1 cm beyond.[19] We and other researchers subdivided stage 2 and used a cutoff of more than 0 cm to indicate objective failure.[20] Use of the full stage 2 range would imply that at least 50% of women were not objectively cured after their prolapse surgery. However, our results show that the outcomes would have been the same whichever stage of prolapse was chosen as the cutoff.

We used strata to allow surgeons who could not offer all three interventions to participate, thus boosting the potential population and shortening the recruitment period to the trial. One limitation was that to calculate unbiased estimates of treatment effects, we could only use two of three strata in any analysis (A plus B for comparisons with synthetic mesh, A plus C for comparisons with biological graft). However, the power of the analysis was only reduced by a modest amount, because the three-arm stratum A was the largest stratum and was used in every analysis.

Few women (15) seemed to be classed as stage 0 or 1 on POP-Q before surgery. In some cases, there was evidence that the full descent had not been measured, or prolapse might have been documented at a previous visit. All these women had symptoms, and met the inclusion criteria that their surgeon deemed sufficient indication for prolapse surgery. However, the variation in baseline measurements suggests inconsistency between surgeons in their indications for surgery.

The surgical team could not be masked to delivery of the randomised operation, and knowledge of the surgical option might have influenced the ascertainment of the outcomes reported. However, in 1126 cases, the women or their surgeons did have firm preconceptions about the use of mesh and declined randomisation. More than 85% of the clinicians responsible for ascertaining objective outcomes were masked to randomised allocation before their clinical examination at follow-up.

Although we did not formally record the number of women who either knew which treatment they received (eg, because they needed further treatment or asked for the information) or thought they knew, we believe the proportion was low, based on discussions with the trial investigators and the participants themselves, often at the time of the clinical assessment at 1 year. Even for these women, the interval between surgery and outcome measurement—when there would have been plenty of scope for further interventions according to clinical need—makes it unlikely that any preconceptions or prejudices about their surgery created any substantial bias in treatment estimates.

PROSPECT was a pragmatic effectiveness trial, to assess the benefits and possible harms of prolapse surgery enhanced by mesh or graft against standard repair, in an unselected group of women operated on by appropriately experienced surgeons using their usual techniques and mesh or graft materials. PROSPECT was not an efficacy trial, in selected women being operated on exclusively by the most experienced surgeons in the highest volume centres using a specific brand of mesh or graft with a highly protocolised technique. Our pragmatic effectiveness design allowed PROSPECT to generate, using a well done study, high quality evidence for the real-world comparison of these surgical options. The findings are therefore directly relevant to all women facing this operation in the UK National Health Service.

A specific brand of mesh or graft could, in the hands of specialist surgeons (who are perhaps the most expert or gifted at that technique) and on selected women, produce better outcomes. However, one would still face the challenge of extending that benefit to more women by better surgical training and more frequent use of the specific techniques, assuming that the particular mesh or graft was affordable and acceptable to the women, and safe in all comers.

The PROSPECT study has shown that, in the first 2 years after surgery, there is no benefit to women having their first prolapse repair from the use of transvaginal synthetic mesh or biological graft to reinforce a standard anterior or posterior repair, either in terms of prolapse symptoms or in short term anatomical cure. This contrasts with the conclusions of the most recent Cochrane review, updated in 2016 and including 37 trials,[9] which reported a reduction in the number of women with awareness of prolapse with synthetic mesh and fewer with anatomical recurrence;[9] our findings concur with the uncertainty of the evidence for a difference for biological grafts but with narrower CIs.[9] However, the quality of this evidence remained very low to moderate, due to poor reporting of study methods, inconsistency, and imprecision in the included trials.

When the PROSPECT data from this report were added to the Cochrane review results on July 6, 2016,[9] the summary statistics still favoured mesh both in terms of awareness of prolapse (RR 0·83, 95% CI 0·71 to 0·96) and anatomical recurrence (RR 0·42, 0·32 to 0·56). However, there was heterogeneity in the trials included in the Cochrane review, with some done in women with uterine or vault prolapse rather than the lower compartments. Few trials differentiated between women having primary and secondary repairs, and some used mesh kits rather than inlays. The trials also varied in their inclusion criteria regarding concomitant procedures and continence surgery. By contrast, PROSPECT randomly assigned a strictly defined group of women having their first repair in an anterior or posterior compartment and used non-absorbable mesh inlays only. A single large trial that is free from risk of bias might be more powerful and reliable for the specific population included than a meta-analysis of many smaller trials.

The women included in the two PROSPECT trials were representative of the whole population of women presenting with prolapse symptoms, including those with multicompartment prolapse or urinary incontinence. Our findings provide robust evidence on which to base counselling for surgical decision making. However, these findings are confined to the first 2 years after surgery and to women having their first repair only. Longer-term follow-up is required to truly assess any potential benefits of transvaginal mesh or graft on which reliable recommendations for women requiring anterior or posterior prolapse surgery can be based.

Our study showed that more than 30% of women who have prolapse surgery have a residual feeling of something coming down and more than 80% have at least one residual prolapse symptom, highlighting the poor short term outcomes of transvaginal anterior or posterior prolapse surgery with or without reinforcement. New research should be aimed at finding and testing methods that will improve those outcomes.

Given that recurrent prolapse requiring repeat repair occurs on average 12 years after a first standard repair, ongoing follow-up is essential to determine whether mesh or graft repairs might yet prove more durable in the long term, and to identify further adverse sequelae of mesh or graft insertion.

The PROSPECT study showed that augmenting a primary transvaginal anterior or posterior prolapse repair with non-absorbable synthetic mesh or biological graft confers no symptomatic or anatomical benefit to women in the short term. More than one in ten women had a mesh complication, but most were asymptomatic, and most of the mesh exposures measured less than 1 cm^2. Although no evidence was apparent of differences

between standard, mesh, or graft repair in other adverse effects up to 2 years after surgery, mesh use did result in the need for additional surgical procedures for exposures and extrusion in the first 2 years, which might be considered to be an unnecessary risk. This additional risk suggests that in the future mesh should only be used in the context of trials aimed at identifying benefit from modifying mesh type or insertion techniques, or in defined categories of high-risk women. Long-term follow-up to assess both effectiveness and adverse effects, which is ongoing,[12] is vital.

Contributors

CMAG, CH, KGC, RMF, ARBS, SH, IM, AMcD, GMcP, GMacL, FR, and JN designed the study. CMAG, SB, and AMcD managed the study with support, input, and oversight from CH, KGC, RMF, ARBS, SH, IM, MK, GMcP, GMacL and JN. AE, DB, and MK analysed the data, which were interpreted by all other authors. CMAG, SB, and AE wrote the first draft of the manuscript which was reviewed, modified, and approved by all other authors. All the authors vouch for the accuracy and completeness of the data reported and for the fidelity of the study to the protocol. All members of the local recruitment teams and gynaecologists at the 35 recruiting centres are members of the PROSPECT STUDY Group:
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Declaration of interests

RMF reports personal fees from speaker fees for Astellas and Pfizer, outside the submitted work. JN reports non-financial support from the Health Technology Assessment (HTA) Commissioning Board, personal fees from National Institute for Health Research HTA & Efficacy and Mechanism Evaluation Editorial Board, outside the submitted work. All other authors declare no competing interests.

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References

1 Haylen BT, Sand PK, Swift SE, Maher C, Moran PA, Freeman RM. Transvaginal placement of surgical mesh for pelvic organ prolapse: more FDA concerns-positive reactions are possible. *Int Urogynecol J* 2012; **23:** 11–13.
2 Olsen AL, Smith VJ, Bergstrom JO, Colling JC, Clark AL. Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. *Obstet Gynecol* 1997; **89:** 501–06.
3 McCormack K, Scott N, Go PM, Ross SJ, Grant A. Laparoscopic techniques versus open techniques for inguinal hernia repair. *Cochrane Database Syst Rev,* **1**: Chichester: John Wiley & Sons Ltd; 2006.
4 Scott NW, Go PM, Graham P, McCormack K, Ross SJ, Grant AM. Open mesh versus non-mesh for of femoral and inguinal hernia. *Cochrane Database Syst Rev* 2002; **4:** CD002197.
5 Maher C, Baessler K, Glazener CMA, Adams E, Hagen S. Surgical management of pelvic organ prolapse in women. *Cochrane Database Syst Rev*, issue 3. Chichester, UK: John Wiley & Sons Ltd; 2007.
6 Jia X, CGlazener CMA, Mowatt G, MacLennan G, Fraser C, Burr J. Systematic review of the efficacy and safety of using mesh or grafts in surgery for anterior and/or posterior vaginal wall prolapse. 2008. http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11363 (accessed June 30, 2008).
7 Haylen BT, Freeman RM, Swift SE, 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.
8 Wilkie L, O'Kelly T, Davies S, et al. The Scottish independent review of the use, safety and efficacy of transvaginal mesh implants in the treatment of stress urinary incontinence and pelvic organ prolapse in women: interim report. http://www.gov.scot/About/Review/Transvaginal-Mesh-Implants (accessed Oct 2, 2015).
9 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; **2:** CD012079.

10 Barber MD, Brubaker L, Nygaard I, et al. Defining success after surgery for pelvic organ prolapse. *Obstet Gynecol* 2009; **114:** 600–09.

11 Toozs-Hobson P, Freeman R, Barber M, 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.

12 Glazener CMA, Breeman S, Elders A, 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. http://www.nets.nihr.ac.uk/projects/hta/076018 (accessed Dec 9, 2015).

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

14 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.

15 Hagen S, Glazener C, Cook J, Herbison P, Toozs-Hobson P. Further properties of the pelvic organ prolapse symptom score: minimally important change and test-retest reliability. *Neurourol Urodyn* 2010; **29:** 1055–56.

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

17 Haylen BT, Freeman RM, Lee 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.

18 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:** 1063–66.

19 Bump RC, Mattiasson A, Bo K, Brubaker LP, DeLancey JO, Klarskov Pe. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. *Obstet Gynecol* 1996; **175:** 10–17.

20 Nygaard I, Brubaker L, Zyczynski HM, et al. Long-term Outcomes Following Abdominal Sacrocolpopexy for Pelvic Organ Prolapse. *JAMA* 2013; **309:** 2016–24.

21 Health Research Authority. http://www.hra.nhs.uk/ (accessed Dec 3, 2015).

22 Haylen BT, de Ridder D, Freeman RM, 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.

23 McNutt L-A, Wu C, Xue X, Hafner JP. Estimating the relative risk in cohort studies and clinical trials of common outcomes. *Am J Epidemiol* 2003; **157:** 940–43.