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Primary surgical management of anterior pelvic organ prolapse: a systematic review, network meta-analysis and cost-effectiveness analysis

Running title: Cost-effectiveness of surgical treatments for POP

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Abstract

Background. Anterior compartment prolapse is the most common pelvic organ prolapse (POP) with a range of surgical treatment options available.

Objectives. To compare the clinical and cost effectiveness of surgical treatments for the repair of anterior POP.

Methods. We conducted a systematic review of randomised controlled trials (RCTs) comparing surgical treatments for women with POP. Network meta-analysis (NMA) was possible for anterior POP, same site recurrence outcome. A Markov model was used to compare the cost–utility of surgical treatments for the primary repair of anterior POP from a UK National Health Service perspective.

Main results. We identified 27 eligible trials for the NMA involving eight surgical treatments tested on 3,194 women. Synthetic mesh was the most effective in preventing recurrence at the same site. There was no evidence to suggest a difference between synthetic non-absorbable mesh, synthetic partially absorbable mesh, and biological mesh. The cost-utility analysis which incorporated effectiveness, complications, and cost data found non-mesh repair to have the highest probability of being cost-effective. The conclusions were robust to model inputs including effectiveness, costs, and utility values.

Conclusions. Anterior colporrhaphy augmented with mesh appeared to be cost-ineffective in women requiring primary repair of anterior POP. There is a need for further research on long-term effectiveness and the safety of mesh products to establish their relative cost-effectiveness with a greater certainty.

Keywords: pelvic organ prolapse, anterior prolapse, mesh, network meta-analysis, cost-effectiveness, outcome research, National Institute of Health and Care Excellence.

Tweetable abstract: New study finds mesh cost-ineffective in women with anterior pelvic organ prolapse

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Introduction

Anterior compartment prolapse is the most common pelvic organ prolapse (POP) with a lifetime risk of surgery estimated between 11-19%.[1] Anterior POP is defined as the descent of the anterior vaginal wall.[2] Treatments include conservative or surgical options, and depend on symptoms, POP degree, and patient preferences.[3]

Anterior colporrhaphy (AC) is considered the standard surgical treatment but is associated with a significant rate of failure.[4] Surgery with mesh augmentation was introduced to improve outcomes but there are safety concerns about its use and no data on long-term outcomes.[1] Synthetic meshes may lead to chronic complications needing long-term management. To address these concerns NHS England set up the Mesh Working Group and an independent review of transvaginal mesh implants was undertaken in Scotland.[5, 6] Mesh products have also been scrutinised by the European Commission (SCENIHR) and US Food and Drug Administration (FDA).[7, 8]

The aim of this work was to evaluate which surgical procedures are the most clinically and cost-effective in women undergoing repair of anterior POP. This analysis was used to inform a national guideline on the management of urinary incontinence and POP in women, released by the National Institute for Health and Care Excellence (NICE) in England.[9]

Methods

Methods of the systematic review and network meta-analysis

We carried out a systematic review to identify relevant randomised controlled trials (RCTs) using a predefined search strategy (see Appendix S1). The final search date was June 2018. A 10% random sample of the literature search results was screened by a second reviewer against inclusion criteria specified in the review protocol.[9]

One reviewer extracted data from the eligible studies, including study characteristics, aspects of methodological quality, outcome data, and risk of bias, which were checked by a second reviewer.[10]

RCTs on surgical procedures in women with predominantly anterior, primary or secondary repair were included. The critical outcomes in the systematic review were health-related quality of life (HRQoL), adverse events, and complications including recurrence of POP. The recurrence of anterior POP was the only dichotomous outcome that could be synthesised using network meta-analysis (NMA). Data was poorly reported for other outcomes and were insufficient to inform NMA.

NMA combines direct and indirect evidence to estimate relative effects between all pairs of interventions in a network, even if some pairs of interventions have not been directly compared in head-to-head trials.[11-14] Fixed and random effects NMA models (binomial likelihood and cloglog link) were fitted in a Bayesian framework, using WinBUGS 1.4.3.[12, 15] The goodness-of-fit of each model was assessed and the model with best fit was selected as the base-case NMA model. (See Appendix S2)

Relative effects between surgical procedures were expressed as posterior median hazard ratios (HRs) with 95% credible intervals (CrIs). Surgical procedures were also ranked based on their effectiveness, with a rank of 1 representing the best procedure. Median ranks and 95% CrI are presented for each surgical procedure.

The suitability of the consistency assumption was assessed by comparing the selected base-case NMA model to an 'inconsistency', or unrelated mean effects, model and by node-splitting.[16-18] (See Appendix S2).

Methods for the cost-effectiveness analysis

We developed a de novo Markov model to estimate the cost-effectiveness of effective surgical procedures over 15 years in adult women who required surgical repair for primary anterior POP using the data obtained from the NMA (see Appendix S3). The model was run in yearly cycles and included the following health states: 'well' (i.e.

successfully managed POP), 'failure/recurrence', and 'complications'. The model considered only one recurrence following the primary repair given that few women have more than two repairs.[19]

Clinical inputs

The baseline risk of anatomical recurrence was estimated by combining the probability of surgically managed recurrence derived from a long-term naturalistic study with the probability of anatomical recurrence adjusted for the surgically managed recurrence that was derived from the AC arm of the RCT with the longest available follow-up amongst those included in the systematic review.[19, 20]

This approach was used since the identified naturalistic studies focused only on surgically-managed recurrence and the effectiveness data estimated from the NMA were for anatomical recurrence. Identified long-term rates were used to estimate the annual probabilities of recurrence. Given the uncertainty about how the recurrence risk varies with time, a constant risk was modelled each year for the duration of the model.

We applied the HRs from the NMA to the baseline risk for the reference surgical procedure (AC), to obtain absolute probabilities for all surgical treatments. Given that the follow-up times in RCTs included in the NMA were clustered around one to three years the estimated HRs of mesh procedures (versus AC) were applied during the first three years only. After the three years, the risk of recurrence in mesh groups was modelled to be the same as for women receiving AC only.

The risk of surgically managed recurrence following a secondary repair was based on an observational cohort study.[21] This study did not report the anatomical recurrence rate and so this was taken from a UK-based RCT.[22] The annual probabilities were estimated as described above for the primary repair.

The mortality rate from POP surgery is small (37 per 100,000 cases) and would only make a very small contribution to the health state utility loss because mortality is not expected to vary between surgical procedures and very few women choose to undergo

further repairs following POP recurrence.[23] Therefore mortality was not considered in the analysis.

Complications

Surgical complications other than those associated with the mesh itself were not deemed to vary much across arms and were excluded from the analysis. Surgical treatment with mesh is associated with various complications. Given the uncertainty about the long-term incidence of complications, only those assumed to have the greatest impact on HRQoL and costs, including mesh extrusion and pain, were modelled.

Rates of mesh extrusion and pain were taken from cohort studies and were used to estimate the annual probabilities attached to the synthetic mesh repairs.[24, 25] Since women continue to develop complications during long-term follow-up, the estimated annual probabilities were applied at each year for the duration of the model.

It is not known what proportion of mesh complications, including mesh extrusion and pain, resolve over time. Based on GC expert opinion, the model assumed that most complications will resolve by year two and a small proportion of mesh complications (10%) will persist for the duration of the model. The complication data were insufficient to differentiate between different synthetic mesh types (non-absorbable and partially absorbable).

The systematic review indicated that the risk of mesh extrusion was lower for biological mesh than for synthetic mesh.[9] The risk ratio estimated from the systematic review was applied to the risk of mesh extrusion with synthetic mesh to estimate the annual risk of mesh extrusion associated with the biological mesh.[9] However, given the lack of long-term clinical data on pain complications associated with the biological mesh, the same rate as for synthetic mesh was used in the analysis.

Cost data

We adopted a UK NHS perspective and considered costs of surgical procedures, mesh products, conservative management, repeat surgery, and complication management.

The repeat surgery cost was modelled as the average of surgical mesh and non-mesh procedure costs, and also an apical procedure cost as recurrent anterior vaginal wall POP could be associated with apical descent.

The cost associated with conservative management was obtained from a UK-based RCT which included treatment with pelvic floor exercises, oestrogens and pessaries.[26] It was assumed that only half of women experiencing recurrence would require treatment; symptoms in other women were not severe enough to require treatment for their POP.[27]

The economic analysis also included complementary tests (blood tests and urea and electrolytes) and consultations that would typically be carried out before and after surgery.

It was assumed that just over half of women with a mesh extrusion would require surgical revision, while for the rest treatment included topical oestrogens and close surveillance.[24] Pain management included pharmacological treatments, vaginal oestrogen, dilators, psychosexual counselling, physiotherapy, or mesh removal. Costs associated with persistent mesh complications were modelled to be equivalent to the initial management cost. Therefore, the initial cost associated with a complication was apportioned over the time horizon of the model to approximate the annual cost associated with managing persistent mesh complications.

Unit costs were derived from national sources expressed in 2016/17 prices.[28-31]

Utility values

In order to express outcomes in the form of quality-adjusted life years (QALYs), the health states of the economic model needed to be linked to appropriate utility scores. Utility values were required for active POP, resolved POP, recurrent POP, and complications. Utility estimates were derived from the published UK RCT that reported the EuroQol (EQ-5D-3L) utility scores, estimated using the UK Time Trade-Off Tariff.[26]

Handling uncertainty

To account for the uncertainty around the input parameter point estimates, a probabilistic analysis was undertaken, in which input parameters were assigned probabilistic distributions.[32] Subsequently, 10,000 iterations were performed, each drawing random values out of the specified distributions. Mean costs, QALYs and the Net Monetary Benefit (NMB) for each surgical treatment were calculated by averaging across 10,000 iterations. We conducted a full incremental analysis, reporting incremental cost-effectiveness ratios (ICERs), interpreted as the additional expected cost per additional unit gain in utility for a surgical procedure compared with the previous non-dominated surgical procedure. We represented uncertainty in the optimal surgical procedure by estimating the probability of each surgical procedure being cost-effective at £20,000-30,000 threshold values. A range of deterministic sensitivity analyses were undertaken.

Table S1 (see Supplementary material) summarises all model inputs including clinical data inputs, cost data and utility estimates and evidence sources; and provides details on the types of distributions assigned to each.

Results

Results of the systematic review and NMA

A total of 2,378 studies were identified in the literature searches with 27 trials (3,194 participants) contributing data to the NMA outcome of same site recurrence (Figure 1).

Insert Figure 1.

Eight surgical procedures were included. One study was excluded from the NMA because treatments were not connected to the rest of the network.[33, 34] A further study was excluded because the definition of recurrence was unclear.[34] The resulting network of trials contributing data to the NMA is presented in Figure 2. (The details of the included studies in the NMA and the final data file used are presented in Table S2 and Table S3, respectively).

Insert Figure 2.

Approximately 30% of the included trials were assessed as being unclear or at high risk of selection bias, namely for allocation concealment and sequence generation. Not unexpectedly, the majority of trials (96%) were unclear or at high risk of performance bias for blinding, since blinding is more difficult to incorporate in trials of surgical procedures. Approximately 40% of the included trials were unclear or at high risk of attrition bias, reporting bias, and other biases.

Each NMA model (fixed or random effects) was run until convergence was satisfactory; results were then based on a further sample of iterations on three separate chains. The random effects model had more favourable fit to the data, and so all further analyses are based on that model (τ=0.63, 95% CrI 0.38 to 0.97). (See Appendix S2).

Table 1 reports the posterior median HRs and 95% CrIs for each surgical procedure relative to AC for recurrence outcome. Paravaginal repair & synthetic non-absorbable mesh had the lowest HRs (best) of recurrence when compared with AC (HR 0.25, 95% CrI 0.04-1.26). However, this procedure was tested on small numbers of women across studies and the result was characterised by considerable uncertainty, as indicated by wide 95% CrI.

Insert Table 1.

There was evidence to suggest that AC with synthetic non-absorbable mesh (HR 0.38, 95% CrI 0.24-0.59), AC with synthetic partially absorbable mesh (HR 0.27, 95% CrI 0.11-0.62), and AC with biological mesh (HR 0.44, 95% CrI 0.26-0.73) were more effective when compared with AC alone. However, there was no difference between various mesh types.

The treatment with the best posterior median rank were AC with synthetic partially absorbable mesh (1st, 95% CrI 1st to 5th) followed by paravaginal repair with synthetic non-absorbable mesh (2nd, 95% CrI 1st to 7th), AC with synthetic non-absorbable mesh (3rd, 95% CrI 1st to 6th), AC with biological mesh (4th, 95% CrI 1st to 6th), AC with synthetic

absorbable mesh, paravaginal repair with biological mesh (6th, 95% CrI 2nd to 8th), and AC only (7th, 95% CrI 5th to 8th).

No evidence of inconsistency between direct and indirect estimates was identified. (See Appendix S3)

Results of the cost-effectiveness analysis

Table 2 shows the expected total costs and QALYs for each surgical procedure. It also provides the results of the incremental analysis, the mean NMB of each procedure at the £20,000 per QALY threshold, the ranking of procedures by NMB, and also the probability of each surgical procedure being cost effective at threshold values. Surgical procedures are ordered by increasing expected total cost. All treatments were dominated by AC, which was more effective in terms of increased QALYs and less expensive than all other surgical procedures (Table 2). AC with synthetic non-absorbable mesh had the highest expected cost and the lowest expected QALYs.

Insert Table 2.

The expected NMB at a £20,000 threshold is highest for AC (£189,156), followed by AC with biological mesh (£187,869), AC with synthetic partially absorbable mesh (£186,337), and lowest for AC with synthetic non-absorbable mesh (£186,306). Also, AC has the highest probability of being cost-effective (Table 2). As the threshold increases, the probability of AC with biological mesh increases but this probability never exceeds 26%.

Sensitivity analyses

Results were robust to model inputs including effectiveness, costs, and utilities. Under all scenarios examined AC remained the preferred surgical procedure. For example, in the base-case analysis, it was assumed that treatment effectiveness at four years onwards for mesh procedures will be the same as for AC. Assuming that treatment effectiveness is sustained for the duration of the model did not change the conclusions.

Most mesh extrusion cases happened in the first year with the risk decreasing over time.[24] This was derived from a small study and there were little data on the frequency of mesh complications occurring in the long-term; however, the GC were aware of women who experienced mesh complications many years after mesh insertion. Nevertheless, the mesh was cost-ineffective even when we only used the available rates of mesh complications.

The results of all deterministic sensitivity analyses are presented in Table S4 (see Supplementary Information).

Discussion

Main findings

Overall, the results from the NMA indicate that the use of mesh is more successful than non-mesh surgical procedures in preventing anterior POP recurrence. The cost-effectiveness analysis attempted to bring together the information on clinical effectiveness, complications, and costs, and suggested that, although mesh is more effective, it causes more complications and is cost-ineffective for women who require primary repair of anterior POP. It should be noted that the long term safety of mesh is unclear and there is considerable uncertainty in this model input. Nevertheless, overall the conclusions were robust to changes in this and other model inputs.

Strengths and limitations

To our knowledge this is the first urogynecologic NMA to compare multiple competing treatments for POP in a cost-utility analysis. We conducted a detailed search, and took considerable effort to include all available RCT data. We synthesised the effectiveness data from multiple RCTs using NMA methodology, and, where possible, the long-term baseline risks and the incidence rates of complications were obtained from cohort studies with the longest available follow-up.

Despite robust methodology, not all trials provided data on key outcomes and this is a limitation of the study. Although it could be argued that surgically managed recurrence is a more important efficacy measure, there were insufficient data to allow synthesis of trial data on this outcome using NMA methodology.

The length of follow-up in the RCTs informing the NMA was clustered around 12 to 36 months and the cost-effectiveness analysis was confined to short-term effectiveness. Given the uncertainty surrounding the long-term effects associated with mesh procedures, it was conservatively modelled that treatment effectiveness at four years onwards for mesh procedures will be the same as for non-mesh procedure. This is in keeping with the review of observational studies which suggest that the long-term recurrence rates following mesh surgery and non-mesh surgery were nearly identical.[9]

Complication rates were poorly reported; therefore safety assessment was limited to data from single studies and at best provides only proxies for serious mesh complications. Despite this limitation, the conclusions were robust to changes in complication rates.

It was recognised that POP procedures may be associated with a number of other complications. For example, de novo stress urinary incontinence (SUI) has been recognised as an important complication. However, the rate of SUI is similar following mesh and non-mesh surgery.[9] The risk of urge incontinence (UUI) is higher following mesh surgery.[9] However, the majority of UUI cases are successfully managed with low-cost anticholinergic drugs and only a small proportion of women require treatment with higher-cost botulinum toxin. Similarly, in most cases constipation is easily managed with low-cost laxatives. Although, women who have obstructed defecation may require more intensive management, the rate of constipation is higher following mesh surgery and the exclusion of constipation only underestimated the cost-effectiveness of non-mesh surgery.[9] The management of dyspareunia is partially captured by considering pain complications and since the rate of dyspareunia is higher in the mesh surgery, its omission only underestimated the cost-effectiveness of non-mesh surgery.[9]

Another limitation of the study is that the literature search is over a year old. However, a literature search on PubMed (conducted April 2019) failed to identify any relevant new RCTs. Also, the GC were not aware of any relevant recently published RCTs.

Interpretation

Our finding that AC augmented with mesh is cost-ineffective is in line with current thinking among healthcare professionals. Even though the effectiveness data favour mesh, it is associated with an increased risk of complications. The cost-effectiveness analysis confirmed that mesh complications have a longer-term impact on women, and also on healthcare resources. It is worth pointing out that the clinical effectiveness plays a lesser role in the cost-effectiveness estimate since the probability of surgically managed recurrence is low and a large proportion of women are asymptomatic following recurrence.

Our findings are consistent with a previous UK analysis which also found mesh augmentation to be cost-ineffective.[35] The findings of a second economic evaluation were inconclusive, however the results are not directly comparable because they included women with AC and/or posterior colporrhaphy.[22]

Conclusions

Overall the analysis indicated that mesh was cost-ineffective in the primary repair of anterior POP, and, despite little long-term evidence on the efficacy and complications, our findings were robust. As a result, the NICE guideline recommended that mesh be considered only in recurrent anterior POP if apical support is adequate or an abdominal approach is contraindicated, after regional multidisciplinary team review and a detailed discussion with the woman about the risks of mesh insertion.

Given the safety concerns associated with mesh products, future research may be unethical to answer this question with more certainty. However, as recommended in the NICE guideline, a national data registry would provide a better picture of long-term mesh complications, enable a more definite assessment of the cost-effectiveness of mesh

procedures, and help identify clinically important subgroups where a mesh procedure may be an option. In the meantime, the data from this analysis should preclude the use of mesh products in women who require primary anterior POP repair.

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KW was the topic lead for Urinary Incontinence on the NICE Guideline Committee for Incontinence and Pelvic Organ prolapse.

MC None declared.

RK was the topic lead for Pelvic Organ Prolapse on the NICE Guideline Committee for Incontinence and Pelvic Organ prolapse.

Contribution of authorship

CD contributed to the NMA and conducted inconsistency checks

EH performed and CM assisted with the search strategy

ES carried out the initial NMA and the economic analysis

IM contributed to the NMA planning

SD contributed to the NMA planning and inconsistency checks

KW, RK, FM provided clinical input and interpretation of the results and their clinical implications

MH and CM provided clinical input

PC carried out the systematic reviews and analyses

VDN oversaw the development of the systematic reviews and analyses

All authors contributed to the write up of the manuscript and approved the final version for submission.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Input parameters utilised in the economic model.

Table S2. Included studies in the NMA.

Table S3. Final data file for the NMA.

Table S4. Results of deterministic sensitivity analyses.

Appendix S1. Search strategy.

Appendix S2. NMA model fit, selection, inconsistency checks, and sensitivity analysis.

Appendix S3. Markov model for comparison of different surgical procedures for women with anterior POP.

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TABLES AND FIGURES

Table 1. Posterior median hazard ratios and 95% CrI for recurrence at the same site for every surgical procedure compared with each other in women with anterior POP.

Paravaginal repair & biological mesh	-	-	-	-	-	-	0.84 (0.17, 4.22)
0.72 (0.05, 9.90)	Paravaginal defect repair (abdominal)	-	-	-	-	-	-
3.44 (0.66, 19.17)	4.79 (0.32, 73.79)	Paravaginal repair & synthetic non-absorbable mesh	-	-	-	-	0.25 (0.04, 1.37)
0.95 (0.12, 7.42)	1.31 (0.27, 6.58)	0.28 (0.03, 2.41)	AC & synthetic absorbable mesh	-	-	-	0.88 (0.20, 3.96)
3.17 (0.56, 18.37)	4.36 (0.45, 44.13)	0.92 (0.14, 5.99)	3.31 (0.67, 17.30)	AC & synthetic partially absorbable mesh[1]	-	0.82 (0.17, 4.01)	**0.25 (0.08, 0.72)**
1.91 (0.39, 9.68)	2.66 (0.30, 24.16)	0.56 (0.09, 3.15)	2.01 (0.46, 8.98)	0.61 (0.22, 1.63)	AC & biological mesh[1]	0.85 (0.27, 2.46)	**0.48 (0.26, 0.89)**
2.19 (0.46, 10.88)	3.04 (0.35, 27.35)	0.64 (0.11, 3.58)	2.31 (0.55, 10.13)	0.70 (0.28, 1.71)	1.15 (0.63, 2.13)	AC & synthetic non-absorbable mesh[1]	**0.36 (0.20, 0.60)**
0.84 (0.18, 3.82)	1.17 (0.14, 9.80)	0.25 (0.04, 1.26)	0.89 (0.22, 3.52)	**0.27 (0.11, 0.62)**	**0.44 (0.26, 0.73)**	**0.38 (0.24, 0.59)**	AC

[1] indicates that the surgical procedure was included in the cost-effectiveness analysis

AC: anterior colporrhaphy; CrI: credible intervals; HR: Hazard ratio; NMA: network meta-analysis, POP: pelvic organ prolapse

Note: Lower diagonal: Posterior median HRs and 95% CrIs from NMA. HRs lower than 1 favour the column defining treatment, HRs higher than 1 favour the row defining treatment. Upper diagonal: HR and 95% CrIs from direct pairwise meta-analysis. HRs lower than 1 favour the row defining treatment, HRs higher than 1 favour the column defining treatment. Bolded cells indicate effects which do not cross the line of no treatment effect.

Table 2. Cost-effectiveness of surgical procedures for adult women with anterior POP; results of probabilistic analysis. Mean values for a cohort of 100 women over 15 years.

Surgical procedure	Mean QALYs[1]	Mean total costs (£)	Incremental analysis & ICERs (£/QALY)	Mean NMB (£)	Ranking by highest NMB	Probability of being cost-effective at a £20,000-30,000/QALY threshold
AC only	9.667	£4,192	Dominant	£189,156	1	0.695-0.676
AC with biological mesh	9.641	£4,959	Dominated	£187,869	2	0.177-0.211
AC with synthetic partially absorbable mesh	9.557	£4,809	Dominated	£186,337	3	0.098-0.091
AC with synthetic non-absorbable mesh	9.558	£4,859	Dominated	£186,306	4	0.030-0.022

[1] Procedures ranked from the most to the least effective according to the number of QALYs

AC: anterior colporrhaphy, ICER: incremental cost-effectiveness ratio, NMB: net monetary benefit, estimated using a willingness to pay £20,000/QALY, POP: pelvic organ prolapse, QALY: quality adjusted life years