SUPPORTING APPENDICES

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.

Appendix S1: Search strategy.

Database: Medline & Embase (Multifile) via OVID

Last searched on Embase Classic+Embase 1974 to 2018 June 01, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date of last search: 4th June 2018.

#	Searches
1	exp Pelvic Organ Prolapse/ use ppez
2	exp pelvic organ prolapse/ use emczd
3	(pelvic$ adj3 organ$ adj3 prolaps$).tw.
4	(urinary adj3 bladder adj3 prolaps$).tw.
5	((vagin$ or urogenital$ or genit$ or uter$ or viscer$ or anterior$ or posterior$ or apical or pelvi$ or vault$ or urethr$ or bladder$) adj3 prolaps$).tw.
6	(splanchnoptos$ or visceroptos$).tw.
7	Rectocele/ use ppez
8	rectocele/ use emczd
9	(hernia$ adj3 (pelvi$ or vagin$ or urogenital$ or uter$ or bladder$ or urethr$ or viscer$)).tw.
10	(urethroc?ele$ or enteroc?ele$ or sigmoidoc?ele$ or proctoc?ele$ or rectoc?ele$ or cystoc?ele$ or rectoenteroc?ele$ or cystourethroc?ele$).tw.
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12	Surgical Mesh/ use ppez
13	exp surgical mesh/ use emczd
14	(mesh$ or non-mesh$ or nonmesh$).tw.
15	Hysterectomy, Vaginal/ use ppez
16	vaginal hysterectomy/ use emczd
17	abdominal hysterectomy/ use emczd
18	((vagin$ or abdom$) adj3 hysterectom$).tw.
19	(total adj laparoscopic$ adj hysterectom$).tw.
20	(hysteropex$ or sacro-hysteropex$ or sacrohysteropex$ or colpopex$ or sacro-colpopex$ or sacrocolpopex$ or sacropex$ or cervicopex$ or sacro-cervicopex$ or sacrocervicopex$).tw.
21	(colporrhaph$ or perineorrhaph$ or perineoplast$ or culd?plast$).tw.
22	(manchester$ adj3 (repair$ or operation$ or procedure$ or method$ or surger$)).tw.
23	colpocl$.tw.
24	IVS.tw.
25	((intravagin$ or intra-vagin$) adj3 slingplast$).tw.
26	(TSST or STST or TSTS).tw.
27	(transfix$ adj3 (stitch$ or sutur$)).tw.
28	polypropylene/ use emczd
29	Polypropylenes/ use ppez
30	polypropylen$.tw.
31	scaffold$.tw.
32	((urethroc?ele$ or enteroc?ele$ or sigmoidoc?ele$ or proctoc?ele$ or rectoc?ele$ or cystoc?ele$ or rectoenteroc?ele$ or cystourethroc?ele$ or vault$ or anter$ or poster$ or apical$ or vagin$ or para-vagin$ or paravagin$ or utero-vagin$ or uterovagin$ or recto-vagin$ or rectovagin$ or utero-sacral$ or uterosacral$ or sacrospin$ or sacro-spin$ or prolaps$ or POP) adj3 (repair$ or suspen$ or fix$ or plicat$)).tw.
33	((POP or prolaps$) adj (surg$ or operat$)).tw.

34	((vagin$ or pelvi$) adj3 reconstruct$).tw.
35	or/12-34
36	11 and 35
37	*Pelvic Organ Prolapse/su use ppez
38	*pelvic organ prolapse/su use emczd
39	36 or 37 or 38
40	remove duplicates from 39
41	limit 40 to english language
42	limit 41 to RCTs and SRs, and general exclusions filter applied

Database: Cochrane Library via Wiley Online

Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL) and Health Technology Assessment Database (TA) and NHS Economic Evaluation Database (NHS-EED)

Date of last search: 4th June 2018.

#	Searches
#1	MeSH descriptor: [Pelvic Organ Prolapse] explode all trees
#2	(pelvic* near/3 organ* near/3 prolaps*):ti,ab,kw (Word variations have been searched)
#3	(urinary near/3 bladder near/3 prolaps*):ti,ab,kw (Word variations have been searched)
#4	((vagin* or urogenital* or genit* or uter* or viscer* or anterior* or posterior* or apical or pelvi* or vault* or urethr* or bladder*) near/3 prolaps*):ti,ab,kw (Word variations have been searched)
#5	(splanchnoptos* or visceroptos*):ti,ab,kw (Word variations have been searched)
#6	MeSH descriptor: [Rectocele] explode all trees
#7	(hernia* near/3 (pelvi* or vagin* or urogenital* or uter* or bladder* or urethr* or viscer*)):ti,ab,kw (Word variations have been searched)
#8	(urethrocele* or urethrocoele* or enterocele* or enterocoele* or sigmoidocoele* or sigmoidocele* or proctocele* or proctocoele* or rectocele* or rectocoele* or cystocele* or cystocoele* or rectoenterocele* or rectoenterocoele* or cystourethrocele* or cystourethrocoele*):ti,ab,kw (Word variations have been searched)
#9	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10	MeSH descriptor: [Surgical Mesh] explode all trees
#11	(mesh* or non-mesh* or nonmesh*):ti,ab,kw (Word variations have been searched)
#12	MeSH descriptor: [Hysterectomy, Vaginal] explode all trees
#13	((vagin* or abdom*) near/3 hysterectom*):ti,ab,kw (Word variations have been searched)
#14	(total next laparoscopic* next hysterectom*):ti,ab,kw (Word variations have been searched)
#15	(hysteropex* or sacro-hysteropex* or sacrohysteropex* or colpopex* or sacro-colpopex* or sacrocolpopex* or sacropex* or cervicopex* or sacro-cervicopex* or sacrocervicopex*):ti,ab,kw (Word variations have been searched)
#16	(colporrhaph* or perineorrhaph* or perineoplast* or culdoplast* or culdeplast$):ti,ab,kw (Word variations have been searched)
#17	(manchester* near/3 (repair* or operation* or procedure* or method* or surger*)):ti,ab,kw (Word variations have been searched)
#18	colpocl*:ti,ab,kw (Word variations have been searched)
#19	IVS:ti,ab,kw (Word variations have been searched)
#20	((intravagin* or intra-vagin*) near/3 slingplast*):ti,ab,kw (Word variations have been searched)
#21	(TSST or STST or TSTS):ti,ab,kw (Word variations have been searched)
#22	(transfix* near/3 (stitch* or sutur*)):ti,ab,kw (Word variations have been searched)
#23	MeSH descriptor: [Polypropylenes] explode all trees
#24	polypropylen*:ti,ab,kw (Word variations have been searched)
#25	scaffold*:ti,ab,kw (Word variations have been searched)
#26	((urethrocele* or urethrocoele* or enterocele* or enterocoele* or sigmoidocoele* or sigmoidocele* or proctocele* or proctocoele* or rectocele* or rectocoele* or cystocele* or cystocoele* or rectoenterocele* or rectoenterocoele* or cystourethrocele* or cystourethrocoele* or vault* or anter* or poster* or apical* or vagin* or para-vagin* or paravagin* or utero-vagin* or uterovagin* or recto-vagin* or rectovagin* or utero-

	sacral* or uterosacral* or sacrospin* or prolaps* or POP) near/3 (repair* or suspen* or fix* or plicat*)):ti,ab,kw (Word variations have been searched)
#27	((POP or prolaps*) next (surg* or operat*)):ti,ab,kw (Word variations have been searched)
#28	((vagin* or pelvi*) near/3 reconstruct*):ti,ab,kw (Word variations have been searched)
#29	#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28
#30	#9 and #29
#31	MeSH descriptor: [Pelvic Organ Prolapse] explode all trees and with qualifier(s): [Surgery - SU]
#32	#30 or #31

Appendix S2: NMA model fit, selection, and inconsistency checks

Both fixed effect and random effects network meta-analysis (NMA) models (binomial likelihood and cloglog link) were fitted in a Bayesian framework.[1]

In random effects model, the between-study standard deviations (SDs) were given a vague Uniform (0,5) prior, while the mean baseline and treatment effects were given vague Normal (0,10000) priors.

Each model was run until convergence was satisfactory and then the results were based on a further sample of iterations on three separate chains (Table A1). Convergence was assessed by inspecting history plots and plots of the Gelman-Rubin statistic.[2,3]

Model fit and selection

The goodness-of-fit of each model was assessed and compared by examining the posterior mean of the total residual deviance contributions. Smaller values are preferred and in a well-fitting model, this should be approximately equal to the number of data points (each study arm contributes 1 data point).[4] The fixed and random effects models were also compared using the Deviance Information Criterion (DIC), which is equal to the sum of the posterior mean of the residual deviance and the effective number of parameters. Lower values are preferred and differences of 5 points were considered meaningful.[5] Finally, the posterior distribution of the between-study standard deviation (SD) was also considered when determining if heterogeneity should be captured by a random effects model. The model with lowest DIC was selected as the base-case NMA model. Model fit statistics for the fixed and random-effects models are summarised in Table A1.

The random effects model had more favourable fit to the data, therefore all analyses are based on that model.

Table A1. NMA model fit statistics.

Model	Between-study standard deviation (median, 95% CrI)	Residual deviance[1]	DIC	Iterations
Fixed effect – consistency model	---	112.5	357.487	50,000 on 3 chains after a burn-in of 50,000
Random effects – consistency model	0.63 (0.38, 0.97)	51.91	309.925	50,000 on 3 chains after a burn-in of 50,000
Random effects - inconsistency	0.66 (0.42, 1.06)	51.81	310.837	60,000 on 3 chains after a burn-in of 30,000

Note: CrI: credible interval; DIC: deviance information criterion

[1]*Compare to 55 data points*

Inconsistency checks

A basic assumption of NMA is that direct and indirect evidence estimate the same parameter i.e. the evidence is consistent.[6] That is, the relative effect between A and B measured directly from an A versus B trial is the same as the relative effect between A and B estimated indirectly from A versus C and B versus C trials. Inconsistency arises when there is a conflict between direct evidence (from an A versus B trial) and indirect evidence (inferred from A versus C and B versus C trials).[7]

The purpose of this analysis was to assess the consistency assumption in the NMA model. To determine if there is evidence of inconsistency, the selected base-case consistency model (fixed or random effects) was compared to an "inconsistency", or unrelated mean effects, model.[7] The latter is equivalent to having separate, unrelated, meta-analyses for every pairwise contrast, with a common between-study variance parameter in the case of random effects models.
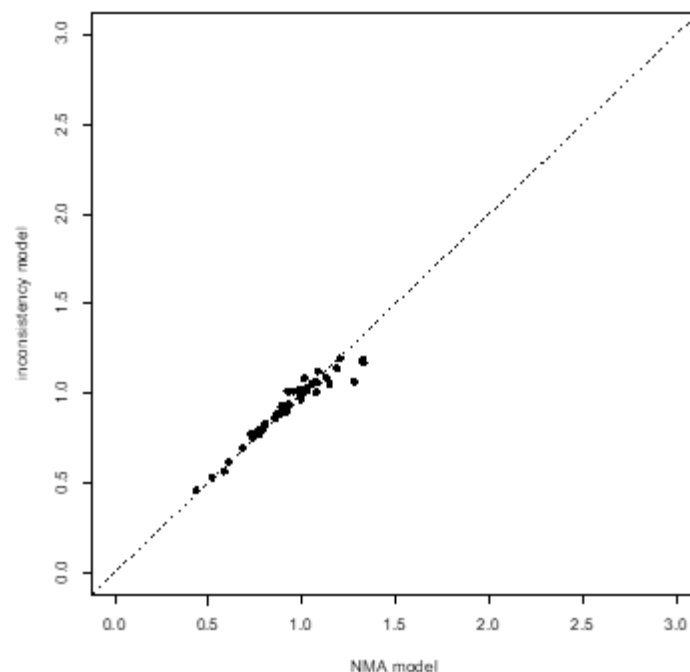
We performed further checks for evidence of inconsistency through node-splitting.[1,8,9] This method permits the direct and indirect evidence contributing to an estimate of a relative effect to be split and compared.

Since there were closed loops of direct evidence within the network that were informed by at least 3 distinct sets of trials, inconsistency checks were possible for recurrence (at the same site) outcome. For details on convergence see Table A1.

No evidence of inconsistency was found through comparison of the consistency and inconsistency random effects models, as little difference was observed between the fit of the models (Table A1). The area below the line of equality in Figure A1 highlights where the inconsistency model better predicted data points and the improvements were minimal. The additional parameters in the inconsistency model, which reduces variation between treatment contrasts, did not result in a decrease in the between-study heterogeneity (Table A1).

Figure A1: Deviance contributions for the random effects consistency and inconsistency models.

Further checks for inconsistency using the node-splitting method (random effects model) did not find any evidence of inconsistency between the direct and indirect estimates (Table A2, Figure A2). In addition to the relative effects estimated through NMA, we present direct (when available) and indirect estimates in Table A3. Where direct evidence is available on treatment comparisons, the direct and indirect estimates are reported based on results given by the node-splitting models. Otherwise, the indirect estimates are taken from the NMA

model. All NMA estimates are reported based on the results from the random effects model that assumes consistency.[1]

In summary, the inconsistency checks did not identify any evidence of inconsistency between the direct and indirect evidence included in the NMA.

Sensitivity analysis

During the peer-review process, it was discovered that Delroy 2013 and Dias 2016 are based on the same RCT. The two studies have different recruitment dates and include a different number of women. However, the study authors confirmed that there was some variation in numbers due to the lost follow-up and additional patients were included in Dias 2016.

A sensitivity analysis was undertaken where Delroy 2013 was removed. However, due to its small sample and weight in the NMA, the effect estimates were unchanged (Table A4). As a result, the original dataset and analysis was retained.

Table A2: Summary of node-splitting results.

Node split model	Heterogeneity (SD)		Residual deviance	DIC	p-value[a]
	median	95% CrI			
AC vs. AC & synthetic non-absorbable mesh	0.65	(0.41, 1.05)	48.89	93.31	0.47
AC vs. AC & biological mesh	0.65	(0.41, 1.04)	48.59	92.85	0.34
AC vs. AC & synthetic partially absorbable mesh	0.65	(0.41, 1.06)	49.03	93.40	0.86
AC & synthetic non-absorbable mesh vs. AC & biological mesh	0.65	(0.41, 1.04)	48.66	92.97	0.34
AC & synthetic non-absorbable mesh vs. AC & synthetic partially absorbable mesh	0.65	(0.41, 1.04)	49.02	93.42	0.87
NMA (no nodes split)	**0.63**	**(0.40, 1.00)**	**48.89**	**92.73**	---

[a] *Posterior mean residual deviance compared to 55 total data points*

Figure A2: Direct, indirect and network estimates of relative treatment effects based on node-splitting results.
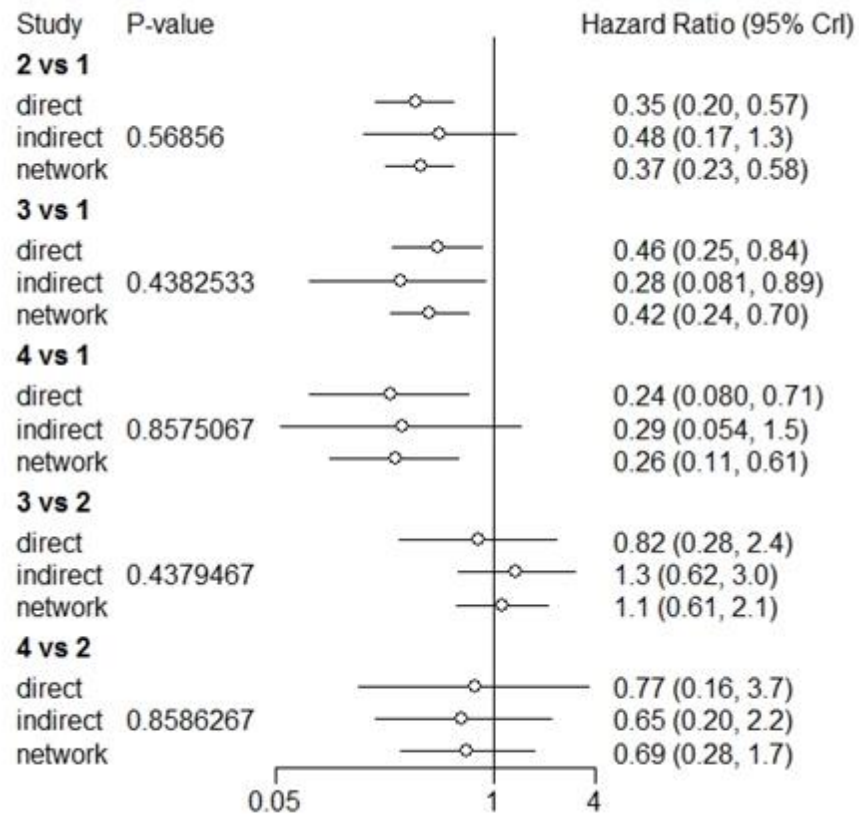
Treatments codes: 1 – AC, 2 – AC & synthetic non-absorbable mesh, 3 – AC & biological mesh, 4 – AC & synthetic partially absorbable mesh.

Table A3: Direct, indirect and NMA estimates of all relative treatment effects.

Treatment 1	Treatment 2	Direct[a] median log(HR)	2.50%	97.50%	Indirect[b] median log(HR)	2.5%	97.5%	NMA[c] median log(HR)	2.5%	97.5%
AC	AC & synthetic non-absorbable mesh	-1.06	-1.63	-0.56	-0.74	-1.78	0.30	-0.96	-1.44	-0.53
AC	AC & biological mesh	-0.77	-1.39	-0.17	-1.27	-2.52	-0.12	-0.82	-1.36	-0.31
AC	AC & synthetic partially absorbable mesh	-1.41	-2.52	-0.34	-1.24	-2.93	0.38	-1.32	-2.20	-0.47
AC	AC & synthetic absorbable mesh				-0.12	-1.52	1.28	-0.12	-1.52	1.28
AC	Paravaginal repair & synthetic non-absorbable mesh				-1.40	-3.12	0.22	-1.40	-3.12	0.22
AC	Paravaginal defect repair (abdominal)				0.16	-1.97	2.29	0.16	-1.97	2.29
AC	Paravaginal repair & biological mesh				-0.17	-1.68	1.34	-0.17	-1.68	1.34
AC & synthetic non-absorbable mesh	AC & biological mesh	-0.20	-1.29	0.86	0.30	-0.48	1.11	0.14	-0.47	0.76
AC & synthetic non-absorbable mesh	AC & synthetic partially absorbable mesh	-0.26	-1.84	1.31	-0.43	-1.61	0.78	-0.36	-1.26	0.55
AC & synthetic non-absorbable mesh	AC & synthetic absorbable mesh				0.85	-0.60	2.34	0.85	-0.60	2.34
AC & synthetic non-absorbable mesh	Paravaginal repair & synthetic non-absorbable mesh				-0.43	-2.20	1.27	-0.43	-2.20	1.27
AC & synthetic non-absorbable mesh	Paravaginal defect repair (abdominal)				1.12	-1.03	3.31	1.12	-1.03	3.31
AC & synthetic non-absorbable mesh	Paravaginal repair & biological mesh				0.80	-0.76	2.39	0.80	-0.76	2.39
AC & biological mesh	AC & synthetic partially absorbable mesh				-0.49	-1.50	0.49	-0.49	-1.50	0.49
AC & biological mesh	AC & synthetic absorbable mesh				0.71	-0.78	2.21	0.71	-0.78	2.21
AC & biological mesh	Paravaginal repair & synthetic non-absorbable mesh				-0.57	-2.36	1.14	-0.57	-2.36	1.14
AC & biological mesh	Paravaginal defect repair (abdominal)				0.98	-1.20	3.19	0.98	-1.20	3.19
AC & biological mesh	Paravaginal repair & biological mesh				0.66	-0.94	2.26	0.66	-0.94	2.26
AC & synthetic partially absorbable mesh	AC & synthetic absorbable mesh				1.20	-0.42	2.86	1.20	-0.42	2.86
AC & synthetic partially absorbable mesh	Paravaginal repair & synthetic non-absorbable mesh				-0.08	-1.98	1.77	-0.08	-1.98	1.77
AC & synthetic partially absorbable mesh	Paravaginal defect repair (abdominal)				1.48	-0.80	3.79	1.48	-0.80	3.79
AC & synthetic partially absorbable mesh	Paravaginal repair & biological mesh				1.15	-0.57	2.91	1.15	-0.57	2.91
AC & synthetic absorbable mesh	Paravaginal repair & synthetic non-absorbable mesh				-1.29	-3.50	0.86	-1.29	-3.50	0.86
AC & synthetic absorbable mesh	Paravaginal defect repair (abdominal)				0.28	-1.33	1.89	0.28	-1.33	1.89
AC & synthetic absorbable mesh	Paravaginal repair & biological mesh				-0.05	-2.12	2.01	-0.05	-2.12	2.01
Paravaginal repair & synthetic non-absorbable mesh	Paravaginal defect repair (abdominal)				1.56	-1.12	4.30	1.56	-1.12	4.30
Paravaginal repair & synthetic non-absorbable mesh	Paravaginal repair & biological mesh				1.23	-0.41	2.96	1.23	-0.41	2.96
Paravaginal defect repair (abdominal)	Paravaginal repair & biological mesh				-0.32	-2.94	2.28	-0.32	-2.94	2.28

[a] *Direct estimates presented when available*

[b] *Indirect estimates obtained from node-splitting models when direct evidence is available, otherwise equal to NMA estimates*

[c] *Network meta-analysis (NMA) estimates obtained from random effects model, assuming consistency*

Table A4: Summary of sensitivity analysis

Surgical approach	Original random effects model		Random effects model excluding duplicate study (Delroy 2013)	
	median	95% CrI	median	95% CrI
Paravaginal repair & biological mesh	0.84	(0.18, 3.82)	0.84	(0.18, 3.96)
Paravaginal defect repair (abdominal)	1.17	(0.14, 9.80)	1.16	(0.13, 10.44)
Paravaginal repair & synthetic non-absorbable mesh	0.25	(0.04, 1.26)	0.24	(0.04, 1.30)
AC & synthetic absorbable mesh	0.89	(0.22, 3.52)	0.89	(0.21, 3.72)
AC & synthetic partially absorbable mesh	0.27	(0.11, 0.62)	0.27	(0.11, 0.63)
AC & biological mesh*	0.44	(0.26, 0.73)	0.44	(0.25, 0.74)
AC & synthetic non-absorbable mesh*	0.38	(0.24, 0.59)	0.39	(0.23, 0.62)
Paravaginal repair & biological mesh*	0.84	(0.18, 3.82)	0.84	(0.18, 3.96)

Surgical treatments compared in the cost-effectiveness analysis

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

We developed a de novo Markov model to estimate the cost-effectiveness of surgical procedures over 15 years using the data obtained from the NMA. The model was run in yearly cycles and included the following health states: 'well' (that is, successfully managed POP), 'failure/recurrence', and 'complications'. (See Figure A3).

Within each year, women could remain in the same state or move from one state to another. The model considered only one further recurrence following the primary repair given that very few women have more than two repairs.[1]

In the model after their initial surgical treatment, women then move into one of the health states. They may enter the 'well' health state defined as women who are not experiencing complications or recurrence. Women might stay in the 'well' state for the duration of the model. However, at the end of each yearly cycle women may also transition from 'well' state if they experience recurrence or complications.

Women who experience a recurrence and require further repeat POP surgery entered a tunnel health state for the duration of three years to account for the time between the initial and repeat POP repair.[2] During the time between the initial and subsequent repair women received conservative management. Following the secondary repair women go through a similar model process as those following primary repair.

Women who suffer a recurrence and require only conservative management stay in this recurrence health state for the duration of the model. However, at the end of each yearly cycle they may also transition from this state if they experience mesh complications. Women in whom the recurrent POP is not severe enough and requires no further treatment go through a similar model process.

At any point, women may experience complications following their surgery. If a woman experiences complications, she enters the 'complications' health state and receives

treatment. A woman who experiences complications might have these resolved during a single cycle or might remain in the 'complications' health state until the complications resolve. This allowed to capture the potential impact of persistent complications that require long-term management, and have important consequences in terms of health-related quality of life and health care costs.

The time horizon of the analysis was determined by the availability of clinical data and was 15 years, which allowed the assessment of longer-term costs and benefits associated with surgical treatments. A half-cycle correction was applied; practically this means that all events in the model occurred in the middle of each cycle.

Figure A3. Markov model for comparison of different surgical procedures for women with anterior POP.
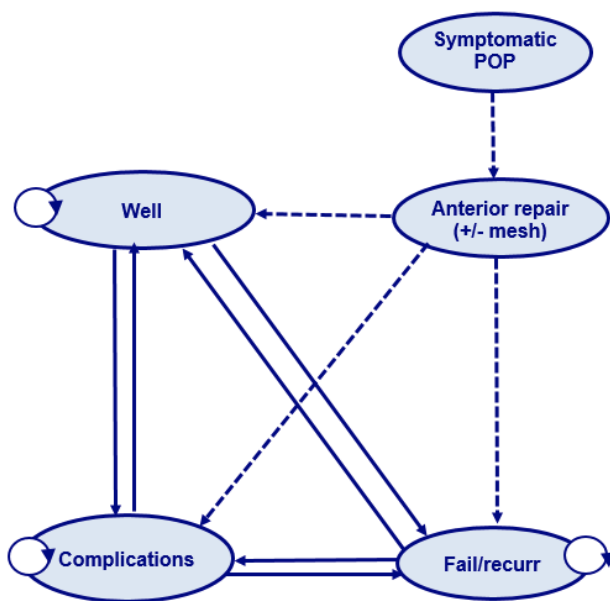
POP: pelvic organ prolapse

References

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