

1 A systematic review on reporting outcomes and outcome measures in trials on synthetic
2 mesh procedures for pelvic organ prolapse. Urgent action is needed to improve quality of
3 research.

4

5 **Abstract**

6 The use of synthetic mesh in pelvic organ prolapse surgery is being closely scrutinized
7 because of serious concerns regarding life-changing complications such as erosion, pain,
8 infection, bleeding, dyspareunia, organ perforation and urinary problems. Randomized
9 trials and their syntheses in meta-analysis offer a unique opportunity to assess efficacy
10 and safety. However, outcomes and outcome measures need to be consistently selected,
11 collected, and reported across randomized trials to be effectively combined in systematic
12 reviews.

13 **Aims**

14 We evaluated outcome and outcome measure reporting across randomized controlled
15 trials on surgical interventions using synthetic mesh for pelvic organ prolapse.

16 **Methods**

17 Systematic review of randomized controlled trials using synthetic mesh for the treatment of
18 pelvic organ prolapse. The selected studies were evaluated using Jadad and MOMENT
19 criteria. Outcomes and outcome measures were systematically identified and categorized.

20 **Results**

21 Seventy-one randomized trials were included. Twenty-four different types of mesh were
22 identified. Included trials reported 110 different outcomes and 60 outcome measures.
23 Erosion (40 trials, 78,43%), pain (29 trials, 56,86%), bleeding (31 trials, 60,78%) and
24 dyspareunia (25 trials, 49,02%) were the most frequently reported outcomes. The longest
25 follow up was 74 months.

26 **Conclusions**

27 Most randomized trials evaluating surgical interventions using synthetic mesh for pelvic
28 organ prolapse failed to report on clinically important outcomes and to evaluate efficacy
29 and safety over the medium- and long-term. Developing and implementing a minimum
30 data set, known as a core outcome set, in future vaginal prolapse trials could help address
31 these issues.

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33 Keywords:

34 Core outcome sets

35 Efficacy

36 Outcome variation

37 Pelvic organ prolapse

38 Randomized controlled trials

39 Safety

40 Synthetic mesh

41 Systematic reviews

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53 Introduction

54 Surgical interventions for the treatment of pelvic organ prolapse have been performed
55 extensively . The International Urogynecological Association and the International
56 Continenence Society have defined mesh as ‘a (prosthetic) network fabric or structure used
57 in general for prolapse surgery with synthetic materials’. [1] The Food and Drug
58 Administration has recently reclassified synthetic mesh as a high-risk device. [2] Our
59 specialty has failed many women with pelvic organ prolapse and has not lived up to one of
60 the oldest medical principles “above all, do no harm”.

61

62 Randomized controlled trials and their syntheses in meta-analysis should offer a unique
63 opportunity to assess the efficacy and safety of synthetic mesh for pelvic organ prolapse
64 procedure. Although there is often no hypothesis concerning harms in trials, safety
65 outcomes should be collected and reported as secondary outcomes. Unfortunately, the
66 collection and reporting of safety has drawn limited attention: for example, the
67 Consolidated Standards of Reporting Trials (CONSORT) statement published an
68 extension for harm reporting, five years after the original statement. Without high-quality
69 data relating to the trade-offs between benefits and harms suboptimal decisions may have
70 been made.

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72 The International Urogynecological Association and the International Continenence Society
73 has engaged with standardizing the mesh complication definitions:

- 74 1. Exposure: Condition of displaying, revealing, exhibiting or making accessible;
- 75 2. Extrusion: Passage gradually out of a body structure or tissue; and
- 76 3. Perforation: Abnormal opening into a hollow organ or viscus [1]

77 The next challenge is to address unwarranted, unhelpful and often confusing variation in
78 outcome selection, collection and reporting. The development and use of a core outcome

79 set would help to address this challenge. The first step in core outcome set development
80 requires an evaluation of outcome and outcome reporting across published randomized
81 trials. CHORUS is an International Collaboration for Harmonizing Outcomes, Research
82 and Standards in Urogynaecology and Women's Health (<http://i-chorus.org>), aiming to
83 address such issues in all areas of urogynaecology/female pelvic medicine and
84 reconstructive surgery. We have recently published relevant papers on childbirth trauma
85 and anterior prolapse surgery. [3, 4]

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87 Therefore, the aim of the present study was to assess the consistency in outcome and
88 outcome measure reporting among randomized trials evaluating surgical interventions
89 using synthetic mesh for pelvic organ prolapse.

90

91 Material and methods

92 This systematic review has been undertaken by CHORUS: An International Collaboration
93 for Harmonizing Outcomes, Research and Standards in Urogynecology and Women's
94 Health and has been registered with the Prospective Register of Systematic Reviews
95 (PROSPERO), registration number CRD42017062456. A protocol including explicitly
96 defined objectives, study selection criteria, and data extraction methods was developed.
97 Ethical approval for this study was not required.

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99 Search strategy

100 The search strategy was performed in accordance to PRISMA criteria. The review was
101 undertaken by searching the Cochrane Central register of Controlled Trials (CENTRAL),
102 EMBASE and MEDLINE, from their inception to June 2018 using MeSH words pelvic
103 organ prolapse, vaginal prolapse, bladder prolapse, cystocele, bowel prolapse, rectocele,
104 enterocele, uterine prolapse and vault prolapse. Two researchers independently screened

105 each potentially relevant record on the basis of its title and abstract, and subsequently
106 reviewed the full text of each selected study to assess eligibility. Discrepancies in initial
107 screening between the two researchers were resolved by consensus.

108

109 We included randomized controlled trials evaluating surgical interventions using synthetic
110 mesh for pelvic organ prolapse in English language. Non-randomized studies,
111 observational studies, and case reports were excluded.

112

113 Two researchers independently extracted study characteristics, including methodological
114 quality and quality of outcomes, interventions and reported outcomes. Again, any
115 discrepancies between the researchers were resolved by consensus among the authors.

116

117 The methodological quality of the selected studies was evaluated according to modified
118 Jadad score. This is a 5-point scale that scores 1 point for each description:
119 randomisation; adequate method for randomisation; blinded trial described; adequate
120 method for blinding and if the trial accounts for the patients selected. [5] The outcome
121 quality was scored according to the MOMENT criteria (Management of otitis media with
122 effusion in cleft palate score system), in a 6-point scale. It sums 1 point for the state of a
123 primary outcome; if the primary outcome is defined for reproducible measures; the state of
124 a second outcome; if the second outcome is defined as for reproducible measures; if the
125 choice of outcome is explained and if the methods used are designed to improve
126 appropriately the quality of measures. [6] High quality was determined for studies that
127 reached score 4 or more in these criteria.

128

129 An inventory of outcomes reported in each study was developed. They were then
130 organized into thematic domains by the researchers.

131

132 Articles that used the same population and intervention (secondary analyses) were defined
133 as follow up studies and duplicated outcomes for the same population were considered
134 only once. Year and Journal of publication were also listed and Journal impact factor was
135 reported according to Thomson Reuters' (NY, USA) citation reports for obstetrics and
136 gynecology. Descriptive statistics were used to characterize the trials included in the
137 review, mapping outcomes and their methods of definition or measurement across
138 included trials. These data were managed in Excel 2013 (Microsoft Corporation, WA, USA)

139

140 Results

141 In total, 2567 titles and abstracts were screened, and 234 potentially relevant studies were
142 examined in detail (Figure 1). Fifty-one randomized trials met the inclusion criteria. Twenty
143 published follow-up studies were included. Quality of studies and outcomes are presented
144 in Table 1. Year of publication ranged from 2000-2017 in vaginal and 2003-2015 in
145 abdominal studies. The mean JADAD and MOMENT score among all studies were 3.59
146 and 4.63 respectively. (Table 1) Description of interventions and mesh used are displayed
147 in Tables 2 and 3. The longest patient follow up was reported as 74 months. The mean
148 follow up was 19.34 months.

149

150 Reported outcomes

151 In total, 110 different outcomes were identified. They were divided into domains (adverse
152 events, clinical effectiveness, efficacy and cost effectiveness) and described in Table 4.
153 The most common outcomes were mesh exposure (40 studies, 78.43%), operative time
154 (38 studies, 74.50%), blood loss and hospital stay (32 studies each, 62.74%).

155

156 Twenty-four different meshes were described in the included studies. Studies on vaginal

157 meshes reported more voiding symptoms and dysfunction (21 times documented in the
158 studies) than the ones on abdominal approach (6 times). Stress urinary incontinence was
159 the most frequently reported outcome for urinary incontinence (26 studies, 50.98%), 3
160 times more in vaginal than abdominal route. Also, vaginal studies presented more on
161 sexuality in women after the procedure, and dyspareunia was 4.2-fold more cited in
162 vaginal than in abdominal mesh studies (21 and 5 studies, respectively).

163

164 Mesh-related outcomes

165 In relation to mesh, there were 20 different outcomes. Mesh related outcomes were much
166 more frequently reported in studies on vaginal mesh compared to those on abdominal
167 insertion of mesh (87 times and 25 times respectively). Emphasis on mesh excision, mesh
168 exposure and mesh removal were much more often observed in studies evaluating
169 prolapse repairs using mesh via vaginal route.

170

171 A high number of studies presented data as length of hospital stay (32 studies, 62.74%)
172 and operative time (38 studies, 74.50%). These outcomes were more frequently reported
173 than bladder injury (20 studies, 39.21%) and abdominal and pelvic pain (30 studies,
174 58.82%).

175

176 Variations in outcomes measures

177 Sixty outcome measures are listed in Table 5. Visual Analogue Scale (VAS) was used in
178 32% of the studies for different purposes (pain, patient satisfaction, degree of bother). Only
179 72.54% of the studies reported POP-Q measurement for treatment effectiveness
180 evaluation. Baden-Walker scale was reported in 2 studies. Eighteen studies described
181 physical examination as a part of the evaluation (35.29%).

182

183 A few studies reported on the amount of intraoperative bleeding, but there was no variation
184 on this measurement. Only in one study the weighing of towels was used to measure
185 bleeding, while 6 studies used hemoglobin or haematocrit.

186

187 Efficacy outcomes

188 Outcomes reported efficacy as “cure” or “success” (27 studies, 52.94%) or “failure” (10
189 studies, 19.60%). Some studies evaluated success or failure only anatomically, while
190 others included patient satisfaction. Some used the term ‘cure’ to show optimal results,
191 making the anatomical evaluation variable between optimal and satisfactory success
192 outcome. POP-Q assessment was used in all studies to evaluate outcome of surgery
193 (success if POP-Q < stage 2, failure if POP-Q ≥ stage 2). A reported measure of success
194 was the lack of prolapse recurrence indirectly evaluated as no need for operation.

195

196 Quality of life evaluation

197 Quality of life was assessed by validated questionnaires and scores in the majority of
198 studies. All the questionnaires used are listed in Table 4. We identified 34 different tools,
199 and questionnaires being part of another questionnaire (as CRADI belongs to PFDI). The
200 most commonly used questionnaire was the Pelvic Organ Prolapse/Urinary Incontinence
201 Sexual Questionnaire (PISQ-12), featured 14 times (28%), followed by Pelvic Floor
202 Distress Inventory (PFDI) and Pelvic Floor Impact Questionnaire (PFIQ), identified in 11
203 (22%) and 10 (20%) studies, respectively.

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205 Discussion

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207 Summary of main findings

208

209 Our systematic review demonstrated a wide variation both in reported outcomes and
210 outcome measures in most trials on POP surgery. Among the reported outcomes, mesh-
211 related, intraoperative data and complications and anatomic results were the most variable
212 ones. Post-operative urinary symptoms and functional outcomes were more extensively
213 presented in studies on vaginal procedures.

214

215 Interpretation

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217 It is clear that the identified variations in outcomes would preclude comparisons and
218 combinations of the findings in a meta-analysis. In addition, these wide variations may be
219 responsible at least partly for the inconsistent and often conflicting evidence and
220 controversies around mesh research evidence.

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222 Variations in outcomes may be secondary to several inherent methodological factors in
223 surgical trials, including surgical techniques, surgeon's skills, type of instruments and
224 material used as well as demographic characteristics of the patients. However,
225 superimposing these often unavoidable variations with additional heterogeneity based on
226 the selection of outcomes and outcome measures, will inevitably result in an unnecessarily
227 compounded overall heterogeneity of the primary trials.

228

229 Certainly, the results may also be somehow affected by the significant and rapid changes
230 in reconstructive pelvic surgery which have occurred in the last two decades, moving
231 towards minimally invasive surgery (laparoscopic/robotic). The outcomes reflect also
232 surgical routes and techniques. Studies on laparoscopic procedures may report outcomes
233 related to length of hospitalization more than those on open abdominal techniques.

234

235 Strengths and limitations

236

237 To our knowledge, this is the first systematic review evaluating the quality of randomized
238 controlled trials and analyzing these outcomes and outcome measures. We followed a
239 rigorous search strategy and the assessment of the studies was as standardized as
240 possible following the methodology of previous publications in this field. [3, 7]

241

242 However, as most studies of this type, we acknowledge the limitation of missing out
243 reported outcomes from non-randomized trials which were excluded from our study. The
244 rationale for analyzing outcomes of randomized and non-randomized studies separately
245 follows the conventional approach of performing meta-analysis and systematic reviews of
246 randomized and non-randomized studies separately. Moreover, only studies in English
247 language were included as this criterion was predefined in the present systematic review.
248 One of the main reasons involves possible complexities arising from terminology and
249 definitions in the area of pelvic medicine across different languages, which would possibly
250 influence the taxonomy and classifications of outcomes in thematic groups, without adding
251 much essential weight into our findings given that the vast majority of randomized
252 controlled trials would be in English language.

253

254 Categorization of outcomes and outcome domains can be undertaken through different
255 approaches and therefore interpretation of the different groups of outcomes may vary. We
256 did not differentiate specific outcomes to studies on specific anatomical compartment as
257 our aim was to have a uniform approach to all prolapse trials using mesh and ideally focus
258 on mesh related outcomes rather than creating smaller subsets with limited weight of
259 evidence.

260

261 Recommendations

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263 While the development of Core Outcome sets in the area of POP is still under way, we
264 would recommend as an interim consensus the use of a short list of the most commonly
265 reported outcomes based on our findings as a minimum set. These outcomes and
266 outcome measures could be the three or four most commonly reported ones in each
267 domain, including a separate domain specific for mesh. Future studies should use
268 validated questionnaires for Quality of Life, such as Pelvic Floor Distress Inventory (PFDI),
269 Pelvic Floor Impact Questionnaire (PFIQ) and Pelvic Organ Prolapse/Urinary Incontinence
270 Sexual Questionnaire (PISQ). All patients after a prolapse surgery with mesh
271 augmentation should undergo physical examination and POP-Q measurement ideally in a
272 long-term follow up assessment, which would facilitate the establishment of the definition
273 of anatomical success or failure of each procedure.

274

275 Long term follow-ups for prolapse interventions using mesh have been recommended. The
276 post-operative interval to law suits is 5.3 years for prolapse treatment with synthetic mesh.
277 In patients treated with sling tapes concomitantly to prolapse the interval is 4.8 years. [2]

278

279 The establishment of an interim minimum set of core outcomes and outcome measures
280 based on this review may well differ from the final set as patient involvement as well as a
281 wider stakeholder participation is essential in this development and may influence the
282 agreed core outcome sets.

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284 Conclusion

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286 Interventions for pelvic organ prolapse using synthetic mesh require additional attention for

287 complications and postoperative symptoms and outcomes. They are not free from failure
288 and recurrence. Vaginal and abdominal procedures may have different success and failure
289 rates. Their outcomes should be comparable. The development of core outcome sets for
290 these procedures will facilitate the design of future studies and promote high quality
291 evidence that will advise patient centered clinical practice.

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295

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