

# Serious complications and recurrences after pelvic organ prolapse surgery for 2309 women in the VIGI-MESH registry

Xavier Fritel, Renaud de Tayrac, J Keizer, S Campagne-loiseau, M Cosson, P Ferry, X Deffieux, J-p Lucot, L Wagner, P Debodinance, et al.

## ► To cite this version:

Xavier Fritel, Renaud de Tayrac, J Keizer, S Campagne-loiseau, M Cosson, et al.. Serious complications and recurrences after pelvic organ prolapse surgery for 2309 women in the VIGI-MESH registry. BJOG: An International Journal of Obstetrics and Gynaecology, 2021, Online ahead of print. 10.1111/1471-0528.16892. inserm-03353325

## HAL Id: inserm-03353325 https://inserm.hal.science/inserm-03353325

Submitted on 24 Sep 2021

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers. L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



# Serious complications and recurrences after pelvic organ prolapse surgery for 2309 women in the VIGI-MESH registry

Xavier Fritel, Renaud de Tayrac, J Keizer, S Campagne-loiseau, M Cosson, P Ferry, X Deffieux, J-p Lucot, L Wagner, P Debodinance, et al.

## ► To cite this version:

Xavier Fritel, Renaud de Tayrac, J Keizer, S Campagne-loiseau, M Cosson, et al.. Serious complications and recurrences after pelvic organ prolapse surgery for 2309 women in the VIGI-MESH registry. BJOG: An International Journal of Obstetrics and Gynaecology, Wiley, 2021, Online ahead of print. 10.1111/1471-0528.16892. inserm-03353325

## HAL Id: inserm-03353325 https://www.hal.inserm.fr/inserm-03353325

Submitted on 24 Sep 2021

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers. L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

- 1 Title
- 2 Serious complications and recurrences after pelvic organ prolapse surgery for 2309 women
- 3 in the VIGI-MESH registry
- 4 <u>Authors</u>
- 5 Xavier Fritel, MD, PhD, 1, 2
- 6 Renaud de Tayrac, MD, PhD, 3
- 7 Joe de Keizer, MSc, 2
- 8 Sandrine Campagne-Loiseau, MD, 4
- 9 Michel Cosson, MD, PhD, 5
- 10 Philippe Ferry, MD, 6
- 11 Xavier Deffieux, MD, PhD, 7
- 12 Jean-Philippe Lucot, MD, 8
- 13 Laurent Wagner, MD, 9
- 14 Philippe Debodinance, MD, 10
- 15 Christian Saussine, MD, PhD, 11
- 16 Anne-Cécile Pizzoferrato, MD, PhD, 12
- 17 Caroline Carlier-Guérin, MD, 13
- 18 Thibault Thubert, MD, PhD, 14
- 19 Laure Panel, MD, 15
- 20 Pierre-Olivier Bosset, MD, 16
- 21 Elvis Nkounkou, MD, 17
- 22 Rajeev Ramanah, MD, PhD, 18
- 23 Thomas Boisramé, MD, 19
- 24 Thomas Charles, MD, 20
- 25 Cyril Raiffort, MD, 21
- 26 Amélie Charvériat, MD, MSc, 1
- 27 Stéphanie Ragot, MD, PhD, 2
- 28 Arnaud Fauconnier, MD, PhD, 22
- 29 Institutions
- 30 1. Service de Gynécologie, CHU de Poitiers, Poitiers, France
- 31 2. Université de Poitiers, INSERM CIC 1402, Poitiers, France
- 32 3. Service de Gynécologie, CHU Carémeau, Nîmes, France
- 33 4. Service de Gynécologie, CHU Estaing, Clermont-Ferrand, France
- 34 5. Service de Gynécologie, CHU de Lille, France
- 35 6. Service de Gynécologie, CH de La Rochelle, La Rochelle, France
- 36 7. Service de Gynécologie, APHP Antoine-Béclère, Clamart, France
- 37 8. Service de Gynécologie, Hôpital Saint-Vincent-de-Paul, Lille, France
- 38 9. Service d'Urologie, CHU Carémeau, Nîmes, France
- 39 10. Service de Gynécologie, CH de Dunkerque, Dunkerque, France
- 40 11. Service d'Urologie, CHU de Strasbourg, Strasbourg, France
- 41 12. Service de Gynécologie, CHU de Caen, France
- 42 13. Service de Gynécologie, CH de Châtellerault, Châtellerault, France
- 43 14. Service de Gynécologie, CHU de Nantes, Nantes, France
- 44 15. Service de Gynécologie, Clinique Beau-Soleil, Montpellier, France
- 45 16. Service d'Urologie, Hôpital Foch, Suresnes, France

- 46 17. Service de Gynécologie, CH de Béthune, Béthune, France
- 47 18. Université de Franche-Comté, CHU de Besançon, Besançon, France
- 48 19. Service de Gynécologie, CHU de Strasbourg, Strasbourg, France
- 49 20. Service d'Urologie, CHU de Poitiers, Poitiers, France
- 50 21. Service de Gynécologie, Groupe Hospitalier Diaconesses-Croix-Saint-Simon, Paris, France
- 51 22. Service de Gynécologie, CHI Poissy-Saint-Germain, Poissy, France
- 52 <u>Correspondence:</u>
- 53 Prof. Xavier Fritel, Service de Gynécologie-Obstétrique et Médecine de la Reproduction, 2
- rue de la Milétrie, CHU de Poitiers, F-86000 Poitiers, France.
- 55 +33 549 443 360. xavier.fritel@univ-poitiers.fr
- 56 <u>Running title:</u> Complications after 2309 prolapse surgeries.
- 57 Manuscript word count: 2680

## 59 <u>Abstract</u>

- 60 *Objective:* To assess the incidence of serious complications and reoperations for recurrence
- after pelvic organ prolapse (POP) surgery and compare the three most common types of
- 62 repair.
- 63 *Design:* Prospective cohort study using a registry.
- 64 *Setting:* 19 French surgical centres.
- 65 *Population:* 2309 women participated between 2017 and 2019.
- *Methods:* A multivariate analysis including an inverse probability of treatment weighting
   approach was used to obtain three comparable groups.
- 68 *Main outcome measures:* Serious complications and subsequent reoperations for POP 69 recurrence
- 70 *Results:* Median follow-up was 17.6 months. Surgeries were native tissue vaginal repairs
- 71 (N=504), transvaginal mesh placements (692), and laparoscopic sacropexies with mesh
- 72 (1113). Serious complications occurred among 52 women (2.3%), and reoperation for POP
- recurrence was required for 32 (1.4%). At one year, the cumulative weighted incidence of
- 74 serious complications was 1.8% for native tissue vaginal repair, 3.9% for transvaginal mesh,
- and 2.2% for sacropexy; while those rates for reoperation for recurrence were respectively
- 1.5%, 0.7%, and 1.1%. Compared with native tissue vaginal repair, the risk of serious
- complications was higher in the transvaginal mesh group (weighted hazard ratio 3.84, 95% CI
- 78 2.43-6.08), and the sacropexy group (2.48, 1.45-4.23), while the risk of reoperation for
- prolapse recurrence was lower in both the transvaginal mesh (0.22, 0.13-0.39) and
- 80 sacropexy (0.29, 0.18-0.47) groups.
- 81 *Conclusions:* Our results suggest that native tissue vaginal repairs have the lowest risk of
- 82 serious complications but the highest risk of reoperation for recurrence. These results are
- 83 useful for informing women and for shared decision making.

84

- 85 <u>Keywords:</u> registry, longitudinal study, mesh, pelvic organ prolapse, surgical complication.
- 86 <u>Tweetable abstract:</u> Laparoscopic sacropexy showed fewer serious complications than
- 87 transvaginal mesh and fewer reoperations for recurrence than vaginal repair.

#### 89 Introduction

- Pelvic organ prolapse is a frequent disability that leads to surgical repair for around one fifth of all women.<sup>1</sup> About 1.1 woman per 1000 undergoes surgery for this condition in France, and around 3.6-3.8 per 1000 aged 60-79 years in the USA.<sup>2,3</sup> Information about the risks of adverse effects is essential for choosing the procedure most appropriate to the woman's clinical situation and expectations. To promote shared decision-making, this information must include the frequent or serious complications.<sup>4</sup>
- 96 The information that surgeons provide before the intervention comes from their own
  97 experience and their knowledge of the clinical studies. Surgical trials often include selected
  98 and small samples. Subjects included in trials are often younger and at lower risk than their
  99 target population.<sup>5,6</sup> This situation should encourage efforts to complete the results of trials
  100 with prospective registries implemented to reflect current clinical practice.<sup>7,8</sup>
  101 The VIGI-MESH registry prospectively collects data about operations performed to treat
- pelvic organ prolapse and follows them up to track both their serious complications and
  reoperations for recurrence.<sup>9</sup> The registry has now been in operation for three years. We
  anticipate that the incidence of serious complications and of reoperations for recurrence
  might differ by the type of surgical repair planned (native tissue vaginal repair, transvaginal
  mesh placement, or laparoscopic sacropexy with mesh). The objective of our analysis was to
  assess the risks of the different surgical options used in real-world practice for prolapse
  repair.

#### 110 <u>Methods</u>

Participation in the VIGI-MESH registry began after the Comité de Protection des Personnes Ouest III (Institutional Review Board) in February 2017 (IDRBC 2017-A000308-45) approved it and it was posted on Clinicaltrial.gov (NCT03052985). The Agence Nationale de Sécurité du Médicament et des produits de santé (national medicines agency) provided funding for the VIGI-MESH registry, but played no role in data collection or analysis, assessment of the complications, or interpretation of the results. The study had no support or involvement by any manufacturer of mesh.

Participation was offered to all women undergoing surgery for anterior, apical (uterine or
vaginal vault) or posterior vaginal prolapse. Each participating woman received information
about the VIGI-MESH registry and consented. Surgeons described each operation on a
specific case report form. We checked the data collection by comparing surgeons' reports
with mesh deliveries from the hospital pharmacies and the surgical codes of eligible
procedures recorded by each hospital's medical data department.<sup>9</sup>

124 This analysis considered three surgical groups: obliterative or vaginal repairs involving native 125 tissue and no mesh (hereafter, vaginal repair), transvaginal placements of mesh (hereafter, 126 transvaginal mesh), and laparoscopic sacropexies, which included colposacropexies (in cases 127 of previous or associated hysterectomy) or colpohysterosacropexies (when the uterus was left in place) that placed mesh by laparoscopy. These procedures are those most frequently 128 used in high-resource countries.<sup>10</sup> The other, rarer surgical procedures (sacropexy by 129 laparotomy, laparoscopy without mesh, and lateral suspensions) were not included in this 130 analysis as they were rare in our registry.<sup>9</sup> The planned surgical group was used for the 131 analysis; for example, a laparoscopic sacropexy converted to a transvaginal mesh procedure 132 133 was analysed as a laparoscopic sacropexy.

134 Outcomes:

In accordance with the design of the registry, the surgeons reported complications and reoperations on a specific form during follow-up. To ensure the completeness of the surgeons' reports (for complications and reoperations), we checked the data collected by each hospital's data department to link and monitor medical events after the index surgery and surveyed the participating women (annual postal questionnaire).<sup>9</sup> Medical data are analysed as they are received. Queries to surgeons asked them to confirm and detail anyserious complications or reoperations when data for these appeared to be missing.

142 We used the Clavien-Dindo classification to define serious complications: cancellation of planned mesh repair due to intraoperative injury or subsequent surgical intervention related 143 to complication (Grade III), life-threatening complication (Grade IV), or woman's death 144 (Grade V).<sup>11</sup> Minor adaptations of the classification designated to describe specific POP-145 surgery complications were those previously used in the PROSPERE trial.<sup>12</sup> Conversion (for 146 147 example, from laparoscopy to the vaginal route) due to operative difficulties, such as adhesions, was not considered a complication.<sup>13</sup> The complications analysed here, selected 148 together with the steering committee, were those possibly attributable to the surgical 149 150 procedure. Reoperation for prolapse recurrence was considered a failure but not a complication. For each complication, the operative files of the index surgery and subsequent 151 152 procedures were reviewed by two of the authors (XF and AC). At the request of the reviewers we also analysed the risk of reoperation by creating a composite variable including 153 the reoperations for complication of the prolapse surgery and those for recurrence of the 154 155 prolapse or for de novo urinary incontinence.

156 Statistical analysis:

Baseline comparisons of the three surgical groups for women's characteristics used ANOVA
tests for continuous and Chi-square tests for categorical variables.

159 We used a propensity score approach with inverse probability of treatment weighting to balance the baseline differences between the surgical groups and limit indication bias.<sup>14,15</sup> A 160 multinomial logistic regression was constructed to estimate each woman's probability of 161 receiving one of the three types of surgeries given her baseline covariates (i.e., the 162 propensity score). Variables of the propensity score model were prespecified before 163 164 outcome analyses and included age, body mass index, smoking, diabetes, surgical history (hysterectomy, or surgery for stress urinary incontinence or pelvic organ prolapse), physical 165 166 status score (ASA), menopausal status, and anatomical defect. Stabilized weights were used 167 to estimate the average treatment effect in the entire population, and the extreme weights were truncated.<sup>16</sup> Balance between treatment populations was evaluated by standardised 168 differences of all baseline covariates, with a threshold of 0.1 used to indicate imbalance.<sup>16</sup> 169

170 Survival curves were obtained with the Kaplan-Meier estimator. In the absence of earlier events, we censored events as of 10 December, 2019. Three weighted frailty models - one 171 for serious complications, one for reoperations for POP recurrence, and one for any 172 reoperation (for complications of POP recurrence or stress urinary incontinence) — were 173 used to compare the three surgical groups. The models included a non-parametric 174 175 estimation of the baseline hazard, a gamma frailty term for the centre effect, and weights that were based on the propensity score.<sup>17,18</sup> 176 177 All statistical tests were two-sided, a P-value <0.05 was considered significant. A multiple 178 imputation (R mice package) strategy was used to deal with the missing data. We have verified the random character of the missing data; they are indeed missing at random,<sup>19</sup> and 179 180 found no difference between patients with completely observed data and those with incomplete data; all imputed values fell in the range expected. All statistical analyses were 181 performed with the R statistical package, version 3.6.1 or later (The R Foundation for 182 Statistical Computing, https://www.R-project.org/). 183

Patients were not involved in the development of the VIGI-MESH registry. No core outcomesets were used.

#### 187 <u>Results</u>

Between February 2017 and November 2019, 2309 women underwent a surgical repair for pelvic organ prolapse by 110 surgeons in 19 centres, agreed to participate in the registry and were included in the analysis. We estimate that the surgical procedures included in the analysis represent about 76.6% of eligible procedures for POP repair performed during the study period in the 19 centres (Table S1).

The vaginal repair group included 504 women (including 36 with obliterative repairs), the transvaginal mesh group 692, and the laparoscopic sacropexy group 1113 (including 128 with robotic assistance; Table S2). Eight women in the laparoscopic sacropexy group needed a conversion (0.7%): three times to a laparotomic sacropexy, twice to laparoscopic lateral attachment, twice to transvaginal mesh, and once to vaginal repair. One or more other surgical procedures were associated with prolapse surgery, including midurethral sling placement and hysterectomy (Table S2).

200 The surgical groups differed in terms of age, body mass index, diabetes, menopausal status, 201 smoking, previous hysterectomy, previous surgery for stress urinary incontinence or for 202 pelvic organ prolapse, and anatomical defect (Table 1). Seven of the 12 covariates in the 203 planned propensity score had weighted maximum standardised differences below 10%, 204 while 5 (age, menopausal status, history of POP surgery, history of hysterectomy, and 205 anatomical anterior defect) exceeded the threshold by a maximum of 4% (Figure S1). 206 Despite the differences observed for the mean age of the surgical groups, the age 207 distribution showed a large overlap between them (Figure S2).

208 Median follow-up was 17.6 months (0.4 to 33.8). Complications of Clavien-Dindo grade III or 209 higher occurred to 52 women (Table 2). During surgery or in the first 48 hours, 7 women had 210 an intraoperative injury, 4 a haemorrhage or haematoma, and 1 a cardiac infarct. From 2 211 days to 2 months, 18 women required surgical treatment of complications (some women had more than one type): 1 had peritonitis, 1 appendicitis, 1 wound dehiscence, 1 bladder 212 213 retention, 7 a haemorrhage or haematoma, 4 ureteral obstruction, 4 pelvic abscess, 1 severe 214 postoperative pain, and 2 vaginal mesh exposure. Between 2 and 12 postoperative months, 215 20 women required surgical treatment for a complication (5 women had 2 complications 216 each): 11 had vaginal mesh exposure, 1 bladder mesh exposure, 3 severe chronic pain, 2

ureteral obstruction, 2 an incisional hernia and 3 a vaginal granuloma. Two women returned
to the operating room more than a year after the prolapse surgery: 1 for an incisional hernia,
and 1 for toxin injection. Complications necessitated 16 interventions to remove the mesh
totally or partially (0.9%).

221 At 12 months the cumulative weighted incidence of serious complications was 1.8% for 222 vaginal repair (95% CI 0-3.9), 3.9% for transvaginal mesh (95% CI 2.0-5.9), and 2.2% for 223 sacropexy (95% CI 1.1-2.6). Compared with the sacropexy group, the risk of serious 224 complications was higher among women in the transvaginal mesh group (Figure 1, Table 3). 225 A concomitant total hysterectomy was associated with a higher risk of complications (Table 226 3). A sensitivity analysis was performed by excluding both complications with debatable 227 imputability (one case of appendicitis and one case of an overactive bladder requiring 228 botulinum toxin); both results remained the same. The analysis limited to the women with 229 an anterior defect found similar and significant hazard ratios (Table S3). Due to a recurrence 230 of the prolapse, a second intervention was required for 32 women (1.4%): 14 after vaginal repair (2.8%), 6 after transvaginal mesh (0.9%), and 12 after sacropexy (1.1%). At 12 months 231 232 the cumulative weighted incidence of reoperation for prolapse recurrence was 1.5% for 233 vaginal repair (95% CI 0.4-2.5), 0.7% for transvaginal mesh (95% CI 0-1.4), and 1.1% for sacropexy (95% CI 0.3-1.9). Compared with the vaginal repair group, the risk of reoperation 234 235 for prolapse recurrence was reduced in the transvaginal mesh and sacropexy groups (Figure 2, Table 4), with no significant differences between the latter two groups. 236

237 Postoperative stress incontinence resulted in reoperation for 61 women (2.6%): 6 after 238 vaginal repair (1.2%), 28 after transvaginal mesh (4.0%), and 27 after sacropexy (2.4%). 239 When we considered the composite criterion of all reoperations (for complications, 240 recurrence of prolapse, or postoperative stress incontinence), 124 women underwent 241 reoperations (5.4%): 23 after vaginal repair (4.6%), 48 after transvaginal mesh (6.9%), and 53 after sacropexy (4.8%). At 12 months the cumulative weighted incidence of reoperation for 242 243 complicated prolapse recurrence or stress urinary incontinence was 3.2% for vaginal repair 244 (95% CI 1.0-5.4), 6.9% for transvaginal mesh (95% CI 4.4-9.3), and 5.3% for sacropexy (95% CI 245 3.7-6.9). The comparison between the groups shows a significant difference in favour of the 246 vaginal repair group only if we consider the propensity score (weighted HR, Table S4).

- 247 The women included in 2017 and 2018 received a postal questionnaire (about complication
- and recurrence) and 61% of 1575 responded. The responses showed that 96.3% of the
- serious complications were already listed in the registry as were 94.1% of the reoperations
- 250 for prolapse recurrence.
- 251

#### 252 <u>Discussion</u>

#### 253 Main findings

We report an analysis of data collected from routine care to compare the short-term efficacy 254 and safety of the three most common surgical procedures for pelvic organ prolapse repair in 255 256 a population of 2309 women. The events were uncommon: at 1 year the women in the 257 vaginal repair group were exposed to the lowest risk of serious complications and the 258 highest risk of reoperation for recurrence (1.5%), the women in the transvaginal mesh group 259 to the highest risk of serious complications (3.9%) and the lowest risk of reoperation for recurrence (0.7%), and the women in the laparoscopic sacropexy group to an intermediate 260 risk of serious complications (2.2%) and a low risk of reoperation for recurrence (1.1%), as 261 262 were those in the transvaginal mesh group.

#### 263 Strengths and limitations

The strengths of our study are its large prospective registry including 19 centres and numerous surgeons; these features enable the detection of rare events. The analysis covers operations performed in real-life situations: complex clinical situations were not excluded. Indeed, a high proportion of our population would not have been included in a randomised trial, because they were too old or had prolapse recurrence after previous surgery or various comorbidities. The regular and routine verification of the information from the hospitals databases and from the participants is evidence of validity.

Our primary outcome was based on a robust criterion, as the modified Clavien–Dindo
 classification has been found to be a valid and reproducible classification of complications in
 various surgical domains.<sup>11,12</sup>

274 Our results must be interpreted considering the absence of randomisation. The surgical 275 groups had different characteristics. It is possible that the type of prolapse influenced the 276 choice of the most appropriate surgical technique. However, we took the women's preoperative characteristics into account with the propensity score to emulate a 277 comparative trial.<sup>14</sup> The data about the construction of the propensity score appear 278 reassuring regarding potential unmeasured confounders that may bias our results. When we 279 280 consider the variable with the greatest difference between the groups (anterior defect), the 281 results of the analysis limited to the women with an anterior defect were similar to those for 282 all women. Within each surgical group, there were multiple and different surgical 283 procedures. It is probable that some hysterectomies (especially in the vaginal repair group) were expediency hysterectomies performed to facilitate the intervention, whereas the 284 surgeons appeared to avoid hysterectomies for women in the transvaginal mesh group. We 285 were not able to consider some factors that might have promoted prolapse recurrence, such 286 as family history, prolapse stage 3-4, a large genital hiatus or levator ani avulsion.<sup>20</sup> These 287 limitations are the price of a "real world" study design, which can introduce variance but 288 limits statistical power. 289

Another limitation is the shortness of the follow-up (median 17 months). However, a Finnish
cohort found that most complications of POP surgery occurred within the first two
postoperative months.<sup>21</sup> Five year after transvaginal mesh placement, another study found
that 79% of the mesh exposures occurred during the first postoperative year.<sup>22</sup>
The number of events observed limited the number of explanatory variables we were able to

add to the multivariate models. We were unable to specify some technical surgical details
(such as the type of mesh or the sutures used), or the experience of both surgeons and
centres, which may reduce the risk of complication. Assessing these factors may be useful
for improving the procedures or determining if some procedures should be reserved to
expert centres.

300 Interpretation

Our results about the relative risk of serious complications are similar to earlier comparative 301 studies, reporting fewer complications with vaginal surgery without mesh.<sup>23,24</sup> The incidence 302 of complications in our registry is lower than that reported in several trials. This difference 303 304 may be explained by the definition used for complications, which considered only serious Clavien-Dindo complications. The risk of reporting failure seems marginal, as we 305 306 systematically and regularly verified the information with the hospitals' data departments 307 and with the women. Most participating hospitals are teaching hospital centres specialised in management of recurrent prolapse. This point may explain the low complication rate. 308

309 <u>Conclusion</u>

Of the three types of prolapse repair analysed, native tissue vaginal repair had a higher riskof reoperation for recurrence than the techniques with mesh (transvaginal mesh and

- 312 sacropexy); and transvaginal mesh has a higher risk of serious complications than the other
- 313 two (vaginal repair and sacropexy). As concerns about mesh safety abound, our results offer
- real-world information for women that can enable them to participate in the choice of
- 315 technique most appropriate for them.
- 316

## 317 Disclosure of interests

- All authors completed the ICMJE uniform disclosure form. XF, JK, SCL, PF, JPL, LW, PD, CS,
- ACP, CCG, TT, LP, POB, EN, RR, TB, TC, CR, AC, SR, and AF have nothing to disclose. Prof.
- 320 Renaud de Tayrac reports grants, personal fees or other from Boston Scientific and
- 321 Coloplast, during the conduct of the study; non-financial support from Wellspect, outside
- 322 the submitted work. Prof. Michel Cosson reports personal fees from Boston Scientific,
- 323 Coloplast, Promedon, and AMI, outside the submitted work. Prof. Xavier Deffieux reports
- 324 personal fees or other from Urgo-Tech, Coloplast, Allergan, Laborie, Hologic, Sanofi, and
- 325 Nanobiotics, outside the submitted work.

## 326 Contribution to authorship

- 327 Study concept and design: Fritel, Fauconnier, Ragot.
- Acquisition of data: Fritel, de Tayrac, Campagne-Loiseau, Cosson, Ferry, Hummel, Deffieux,
- 329 Lucot, Wagner, Debodinance, Saussine, Pizzoferrato, Carlier-Guérin, Thubert, Panel, Bosset,
- 330 Nkounkou, Ramanah, Boisramé, Charles, Bressler, Charvériat, Raiffort, Fauconnier.
- Analysis and interpretation of data: Fritel, Fauconnier, de Keizer, Ragot.
- 332 Drafting of the manuscript: Fritel, Fauconnier, Ragot.
- 333 Statistical analysis: Fritel, de Keizer, Ragot.
- 334 Obtaining funding: Fritel.
- 335 Xavier Fritel had full access to all the data in the study and takes responsibility for the
- integrity of the data and the accuracy of the data analysis. He attests that all listed authors
- 337 meet authorship criteria and that no others meeting the criteria have been omitted.
- 338 We affirm that our manuscript is an honest, accurate and transparent report of the VIGI-
- 339 MESH registry; that no important aspects of the registry have been omitted; and that any
- 340 discrepancies from the registry as originally planned and registered have been explained.
- 341 Details of ethics approval
- 342 Our study complies with French law. The Institutional Review Board (Comité de Protection
- des Personnes Ouest III) approved the protocol on 9 February 2017 (IDRBC 2017-A000308-
- 45), and the study was registered by the national data protection authority (Commission
- Nationale Informatique et Libertés, CNIL) on 16 August 2017 (DR-2017-245).

## 346 <u>Funding</u>

- 347 The national medicines agency (Agence Nationale de Sécurité du Médicament et des
- 348 produits de santé, ANSM) provided the funding for the study, but played no role in data
- collection or analysis, assessment of the complications, or interpretation of the results.
- 350 Acknowledgements:
- 351 We thank Lucie Merlet (CHU de Poitiers), Aurélie Comptour (CHU Carémeau), Florence
- 352 Tartarin (CHU de Poitiers), Elodie Migault (CHU de Poitiers), and Pierre-Jean Saulnier
- 353 (Université de Poitiers) for their support or contribution to collecting and cleaning the data.
- 354 We thank Jo Ann Cahn for the editing (CHU de Poitiers).

355 We thank the 110 surgeons of the VIGI-MESH Group who enrolled patients into the registry: Adnan Aboukassem, Chérif Akladios, Emmanuelle Arsène, Jean-Sébastien Aucouturier, 356 Georges Bader, Emmanuel Bailly, Jean-Jacques Baldauf, Stéphanie Bartolo, Marie-Line 357 Barussaud, Fanny Béchard, Simon Bernardeau, Clément Biscans, Thomas Boisramé, Deepak 358 Boodhun, Pierre-Olivier Bosset, Revaz Botchorishvili, Michel Boukaram, Aude Brams, Laurent 359 360 Bressler, Clément Bruhat, Sandrine Campagne-Loiseau, Michel Canis, Caroline Carlier-Guérin, Victor Cavillon, Olivier Celhay, Thomas Charles, Amélie Charvériat, Armand Chevrot, Pierre 361 Collinet, Arnaud Cornille, Michel Cosson, Pierre Costa, Christophe Courtieu, Laurent 362 363 Courtois, Sandra Curinier, Eric Darnis, Renaud de Tayrac, Philippe Debodinance, Xavier 364 Deffieux, Pierre-Olivier Delpech, Véronique Delporte, Anne Dubois, Emilie Faller, Brigitte 365 Fatton, Arnaud Fauconnier, Philippe Ferry, Cécile Féyeux, Xavier Fritel, Victor Gabriele, Pierre Gadonneix, Olivier Garbin, Florent Genty, Géraldine Giraudet, Pascale Gres, Pauline 366 Gueudry, Jean-François Haab, Audrey Hedde, Aline Host, Michel Hummel, Estelle Jean dit 367 Gautier, Aminata Kane, Sophie Le Gouic, Isabelle Le Teuff, Gil Lebreton, Lise Lecointre, 368 369 Grégoire Léon, Jean-Philippe Lucot, Yolande Maisonnette, Lucile Martin, Aurore Marx, Pascal Mouracade, Elvis Nkounkou, Corinne Palamara, Laure Panel, Petit Nicolas, Caroline 370 371 Pettenati, Laurence Peyrat, Pierre Pillot, Anne-Cécile Pizzoferrato, Jean-Luc Pouly, Clothilde Poupon, Michel Prudhomme, Benoît Rabishong, Rajeev Ramanah, Hélène Ricard, Jérémie 372 373 Ripoche, Géraldine Rivaux, Jennifer Salerno, Delphine Salet-Lizée, Richard Sarfati, Maxence 374 Sarradin, Christian Saussine, Elodie Schuller, An Segaert, François Stoll, Yannick Thirouard, 375 Thibault Thubert, Caroline Trichot, Mélusine Turck, David Vandendriessche, Edouard Vaucel, 376 Sarah Vieillefosse, Anne Villot, Denis Vinatier, Etienne Vincens, Marie Vinchant, Béatrice 377 Vinson-Bonnet, Laurent Wagner, Soraya Wapler, and Sophie Warembourg.

#### 379 <u>References</u>

1 Smith FJ, Holman CD, Moorin RE, Tsokos N. Lifetime Risk of undergoing surgery for pelvic organ prolapse. Obstet Gynecol 2010;116:1096-100.

2 Subramanian D, Szwarcensztein K, Mauskopf JA, Slack MC. Rate, type, and cost of pelvic organ prolapse surgery in Germany, France, and England. Eur J Obstet Gynecol Reprod Biol 2009;144:177-81.

3 Wu JM, MD, Matthews CA, Conover MM, Pate V, Funk MJ. Lifetime Risk of Stress Incontinence or Pelvic Organ Prolapse Surgery. Obstet Gynecol 2014;123:1201-6.

4 Barber MD. Mesh use in surgery for pelvic organ prolapse, Despite many advances, outcomes after surgery remain far from perfect. BMJ 2015;350:h2910

5 Hofmann R, James SK, Jernberg T, Lindahl B, Erlinge D, Witt N, Arefalk G, Frick M, Alfredsson J, Nilsson L, Ravn-Fischer A, Omerovic E, Kellerth T, Sparv D, Ekelund U, Linder R, Ekström M, Lauermann J, Haaga U, Pernow J, Östlund O, Herlitz J, Svensson L; DETO2X–SWEDEHEART Investigators. Oxygen Therapy in Suspected Acute Myocardial Infarction. N Engl J Med 2017;377:1240-9.

6 Lindsay WA, Murphy MM, Almghairbi DS, Moppett IK. Age, sex, race and ethnicity representativeness of randomised controlled trials in peri-operative medicine. Anaesthesia 2020;75:809-15.

Rimmer A. Vaginal mesh procedures need compulsory register, says royal college. BMJ 2018;360:k586.
 Fritel X. Evidence about surgical revision for MUS complications will come from large retrospective cohorts and prospective registers. BJOG 2020;127:1034.

9 Fritel X, Campagne-Loiseau S, Cosson M, Ferry P, Saussine C, Lucot JP, Salet-Lizee D, Barussaud ML, Boisramé T, Carlier-Guérin C, Charles T, Debodinance P, Deffieux X, Pizzoferrato AC, Curinier S, Ragot S, Ringa V, de Tayrac R, Fauconnier A. Complications after pelvic floor repair surgery (with and without mesh): short-term incidence after 1873 inclusions in the French VIGI-MESH registry. BJOG 2020;127:88-97.

10 Haya N, Baessler K, Christmann-Schmid C, de Tayrac R, Dietz V, Guldberg R, Mascarenhas T, Nusller E, Ballard E, Ankardal M, Boudemaghe T, Wu JM, Maher CF. Prolapse and continence surgery in countries of the Organization for Economic Cooperation and Development in 2012. Am J Obstet Gynecol 2015;212:755.e1-27

Dindo D, Demartines N, Clavien PA. Classification of surgical complications. Ann Surg 2004;240:205-13.
 Lucot JP, Cosson M, Bader G, Debodinance P, Akladios C, Salet-Lizée D, Delporte P, Savary D, Ferry P,
 Deffieux X, Campagne-Loiseau S, de Tayrac R, Blanc S, Fournet S, Wattiez A, Villet R, Ravit M, Jacquetin B, Fritel X, Fauconnier A. Safety of Vaginal Mesh Surgery Versus Laparoscopic Mesh Sacropexy for Cystocele Repair:
 Results of the Prosthetic Pelvic Floor Repair Randomized Controlled Trial. Eur Urol 2018;74:167-76.

13 Twijnstra AR, Blikkendaal MD, van Zwet EW, Jansen FW. Clinical relevance of conversion rate and its evaluation in laparoscopic hysterectomy. J Minim Invasive Gynecol 2013;20:64-72.

14 Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology 2000;11:550-60

Lunceford JK, Davidian M. Stratification and weighting via the propensity score in estimation of causal treatment effects: a comparative study. Stat Med 2004;23:2937-60.

Austin PC. The performance of different propensity-score methods for estimating differences in proportions (risk differences or absolute risk reductions) in observational studies. Stat Med 2010;29:2137-48.
 Duchateau L, Janssen P, Lindsey P, Legrand C, Nguti R, Sylvester R. The shared frailty model and the power for heterogeneity tests in multicenter trials. Computational Statistics & Data Analysis 2002;40:603-20.

18 Gutierrez RG. Parametric frailty and shared frailty survival models. The Stata Journal 2002;2:22-44.

19 Nguyen C, Carlin JB, Lee KJ. Model checking in multiple imputation: an overview and case study. Emerg Themes Epidemiol 2017;14:8.

Friedman T, Eslick GD, Dietz HP. Risk factors for prolapse recurrence: systematic review and metaanalysis. Int Urogynecol J 2018;29:13-21.

21 Wihersaari O, Karjalainen P, Tolppanen A-M, Mattsson N, Jalkanen J, Nieminen K. Complications of Pelvic Organ Prolapse Surgery in the 2015 Finnish Pelvic Organ Prolapse Surgery Survey Study. Obstet Gynecol 2020;136:1135-44.

Jacquetin B, Hinoul P, Gauld J, Fatton B, Rosenthal C, Clavé H, Garbin O, Berrocal J, Villet R, Salet-Lizée D, Debodinance P, Cosson M. Total transvaginal mesh (TVM) technique for treatment of pelvic organ prolapse: a 5-year prospective follow-up study. Int Urogynecol J 2013;24:1679–86.

23 Siddiqui NY, Cara L. Grimes CL, Casiano ER, Abed HT, Jeppson PC, Olivera CK, Sanses TV, Steinberg AC, South MM, Balk EM, Sung VW. Mesh Sacrocolpopexy Compared With Native Tissue Vaginal Repair, A Systematic Review and Meta-analysis. Obstet Gynecol 2015;125:44–55. 24 Maher C, Feiner B, Baessler K, Christmann-Schmid C, Haya N, Brown J. Surgery for women with anterior compartment prolapse. Cochrane Database of Systematic Reviews 2016, Issue 11. Art. No.: CD004014.

## Figure and table legends

Figure 1. Kaplan-Meier curve free of serious complication (Clavien-Dindo grade III or more) as a function of time (months) and of surgical group (2309 women).

Figure 2. Kaplan-Meier curve free of reoperation for prolapse recurrence as a function of time (months) and of surgical group (2309 women).

Table 1. Women's baseline characteristics at the time of the index surgery for pelvic organ prolapse (N= 2309). Comparison between surgical groups with ANOVA tests for continuous and Chi-square tests for categorical variables.

Table 2. Description of serious complications (Clavien-Dindo Grade III or more) among 52 women by type, time to revision after POP surgery, and type of care for complication (some women may have more than one type of complication).

Table 3. Risk factors for serious complication (Clavien-Dindo grade III or more). Frailty model with centre as a random effect (N= 2309).

Table 4. Risk factors for reoperation for prolapse recurrence. Frailty model with centre as a random effect (N= 2309).

## **Online supporting information**

Figure S1. Standardized differences between surgical groups before and after adjustment.

Figure S2. Age distribution in each surgical group.

Table S1. Detail of inclusions in each centre.

Table S2. Surgical procedures for pelvic organ prolapse (N= 2309).

Table S3. Risk factors for serious complication after POP surgery in women with preoperative anterior defect (N= 1836).

Table S4. Risk factors for reoperation for serious complication, prolapse recurrence, or stress urinary incontinence. Frailty model with centre as a random effect (N= 2309).

		Vaginal	Transvaginal	Laparoscopic
		repair	mesh	sacropexy
Baseline characterist	ics	N= 504	N= 692	N= 1113
	Age, mean (sd), md= 2	67.0 (13.2)	69.5 (7.6)	61.8 (10.4)
	BMI, mean (sd), md= 12	26.2 (4.9)	26.4 (4.5)	25.2 (4.0)
	Smoking, (n %), md= 39	33 (6.5)	34 (4.9)	90 (8.0)
	Diabetes, n (%), md= 28	48 (9.5)	82 (11.8)	74 (6.6)
Menopausal status, n (%), md= 7		433 (85.9)	679 (98.1)	896 (80.5)
Physical status score (ASA), mean (sd), md= 82		1.8 (0.6)	1.9 (0.6)	1.7 (0.6)
	Hysterectomy, n (%), md= 18	132 (26.2)	145 (21.0)	140 (12.6)
Surgical history	SUI surgery, n (%), md= 27	64 (12.7)	77 (11.1)	71 (6.4)
	POP surgery, n (%), md= 34	111 (22.0)	151 (21.8)	136 (12.2)
	Anterior, n (%), md= 2	254 (50.4)	616 (89.0)	965 (86.7)
Anatomical defect	Apical, n (%), md= 2	255 (50.6)	429 (62.0)	754 (67.8)
	Posterior, n (%), md= 2	309 (61.3)	271 (39.2)	425 (38.2)

Table 1. Women's baseline characteristics at the time of the index surgery for pelvic organ prolapse (N= 2309). Comparison between surgical groups with ANOVA tests for continuous and Chi-square tests for categorical variables.

Significant differences between groups for each characteristic with P<0.0001 except smoking (P=0.03) and diabetes (P=0.0008).

sd: standard deviation; md: number of missing data; BMI = body mass index; ASA = American Society of Anaesthesiologists patient classification status; SUI = stress urinary incontinence; POP = pelvic organ prolapse

Table 2. Description of serious complications (Clavien-Dindo Grade III or more) among 52 women by type, time to revision after POP surgery, and type of care for complication (some women may have more than one type of complication).

		Transvaginal	Laparoscopic	
	Vaginal repair	mesh	sacropexy	Overall
Grade III or IV complication, n (%)	N= 504	N= 692	N= 1113	N= 2309
Intraoperative injury	-	5 (0.7)	2 (0.2)	7 (0.3)
Cardiac infarct	1 (0.2)	-	-	1 (0.0)
Haemorrhage/haematoma	4 (0.8)	6 (0.9)	1 (0.1)	11 (0.5)
Visceral complication	-	-	3 (0.3)	3 (0.1)
Pelvic abscess	-	2 (0.3)	2 (0.2)	4 (0.2)
Retention or obstructed micturition	-	2 (0.3)	1 (0.1)	3 (0.1)
Overactive bladder	-	1 (0.1)	1 (0.1)	2 (0.1)
Ureteral obstruction	1 (0.2)	4 (0.6)	1 (0.1)	6 (0.3)
Mesh exposure	-	9 (1.3)	5 (0.4)	14 (0.8)*
Vaginal granuloma	1 (0.2)	2 (0.3)	-	3 (0.1)
Incisional hernia or dehiscence	-	-	4 (0.4)	4 (0.4)*
Other severe postoperative or chronic pain	1 (0.2)	-	3 (0.3)	4 (0.2)
Time to revision				
T1: 0 to 48 hours	3 (0.6)	7 (1.0)	2 (0.2)	12 (0.5)
T2: day 2 to month 2	3 (0.6)	7 (1.0)	8 (0.7)	18 (0.8)
T3: month 2 to month 12	1 (0.2)*	12 (1.7)*	7 (0.6)*	20 (0.9)*
T4: > 12 months	-	-	2 (0.3)*	2 (0.1)*
Care for complication				
Mesh placement cancelled	-	4 (0.6)	2 (0.2)	6 (0.3)*
Intensive care unit	1 (0.2)	2 (0.3)	-	3 (0.1)
Surgery for haemostasis/drainage	4 (0.8)	6 (0.9)	1 (0.1)	11 (0.5)
Appendicitis/peritonitis surgical cure	-	-	2 (0.2)	2 (0.1)
Mesh surgical ablation	-	9 (1.3)	7 (0.6)	16 (0.9)*
Upper urinary tract surgical procedure	-	2 (0.3)	1 (0.1)	3 (0.1)
Stitch surgical removal	1 (0.2)	1 (0.1)	-	2 (0.1)
Vaginal surgical revision	1 (0.2)	5 (0.7)	1 (0.1)	7 (0.3)
Hernia or dehiscence surgical repair	-	-	4 (0.4)	4 (0.4)*
Pudendal surgical infiltration	-	-	1 (0.1)	1 (0.0)
Bladder botulinum toxin injection	-	-	1 (0.1)	1 (0.0)
Reoperation for serious complication	6 (1.2)	21 (3.0)	17 (1.5)	44 (1.9)
Overall (Grade III and IV complications)	7 (1.4)	26 (3.8)	19 (1.7)	52 (2.3)

\* related to the number of women at risk.

Table 3. Risk factors for serious complication (Clavien-Dindo grade III or more). Frailty model with centre as a random effect (N= 2309)

Risk factor		Non-weighted HR (95% CI)	Weighted* HR (95% CI)
	Vaginal repair	1	1
Surgical group	Transvaginal mesh	3.21 (1.35 to 7.62)	3.84 (2.43 to 6.08)
	Laparoscopic sacropexy	1.61 (0.64 to 4.07)	2.48 (1.45 to 4.23)
Concomitant	Total hysterectomy	2.48 (1.15 to 5.34)	4.13 (2.75 to 6.21)
procedure	Midurethral sling	1.26 (0.59 to 2.67)	0.88 (0.54 to 1.43)

HR = hazard ratio; CI = confidence interval.

\*Weights based on the propensity score which included age, body mass index, smoking, diabetes, surgical history (hysterectomy, or surgery for stress urinary incontinence or pelvic organ prolapse), physical status score (ASA), menopausal status, and anatomical defect.

Exclusion of the two complications with arguable imputability (one case of appendicitis and one case of overactive bladder needing botulinum toxin) did not change the results (weighted HR for transvaginal mesh 3.76, 95% CI 2.38 to 5.95 and for laparoscopic sacropexy 2.23, 95% CI 1.29 to 3.84).

Table 4	. Risk facto	rs for re	operation fo	or prolapse	recurrence.	Frailty ı	model w	ith ce	entre a	as a
random	n effect (N=	= 2309)								

Risk factor		Non-weighted HR (95% CI)	Weighted* HR (95% CI)
	Vaginal repair	1	1
Surgical group	Transvaginal mesh	0.18 (0.07 to 0.47)	0.22 (0.13 to 0.39)
	Laparoscopic sacropexy	0.23 (0.10 to 0.50)	0.29 (0.18 to 0.47)
Concomitant	Total hysterectomy	0.14 (0.02 to 1.06)	0.06 (0.01 to 0.27)
procedure	Midurethral sling	0.45 (0.14 to 1.50)	0.59 (0.32 to 1.09)

HR = hazard ratio; CI = confidence interval.

\*Weights based on the propensity score which included age, body mass index, smoking, diabetes, surgical history (hysterectomy, or surgery for stress urinary incontinence or pelvic organ prolapse), physical status score (ASA), menopausal status, and anatomical defect.



Figure 1. Kaplan-Meier curve free of serious complication (Clavien-Dindo grade III or more) as a function of time (months) and of surgical group (2309 women).



Figure 2. Kaplan-Meier curve free of reoperation for prolapse recurrence as a function of time (months) and of surgical group (2309 women).