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Title

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Running title: Complications after 2309 prolapse surgeries.

Manuscript word count: 2680

Abstract

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 repair.

Design: Prospective cohort study using a registry.

Setting: 19 French surgical centres.

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.

Main outcome measures: Serious complications and subsequent reoperations for POP recurrence

Results: Median follow-up was 17.6 months. Surgeries were native tissue vaginal repairs (N=504), transvaginal mesh placements (692), and laparoscopic sacropexies with mesh (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 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 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 sacropexy (0.29, 0.18-0.47) groups.

Conclusions: Our results suggest that native tissue vaginal repairs have the lowest risk of serious complications but the highest risk of reoperation for recurrence. These results are useful for informing women and for shared decision making.

Keywords: registry, longitudinal study, mesh, pelvic organ prolapse, surgical complication.

Tweetable abstract: Laparoscopic sacropexy showed fewer serious complications than transvaginal mesh and fewer reoperations for recurrence than vaginal repair.

Introduction

Pelvic organ prolapse is a frequent disability that leads to surgical repair for around one fifth of all women.[1] 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.[2,3] 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.[4]

The information that surgeons provide before the intervention comes from their own experience and their knowledge of the clinical studies. Surgical trials often include selected and small samples. Subjects included in trials are often younger and at lower risk than their target population.[5,6] This situation should encourage efforts to complete the results of trials with prospective registries implemented to reflect current clinical practice.[7,8]

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.[9] 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.

Methods

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.[9]

This analysis considered three surgical groups: obliterative or vaginal repairs involving native tissue and no mesh (hereafter, vaginal repair), transvaginal placements of mesh (hereafter, transvaginal mesh), and laparoscopic sacropexies, which included colposacropexies (in cases 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 used in high-resource countries.[10] The other, rarer surgical procedures (sacropexy by laparotomy, laparoscopy without mesh, and lateral suspensions) were not included in this analysis as they were rare in our registry.[9] The planned surgical group was used for the analysis; for example, a laparoscopic sacropexy converted to a transvaginal mesh procedure was analysed as a laparoscopic sacropexy.

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).[9] Medical data are

analysed as they are received. Queries to surgeons asked them to confirm and detail any serious complications or reoperations when data for these appeared to be missing.

We used the Clavien-Dindo classification to define serious complications: cancellation of planned mesh repair due to intraoperative injury or subsequent surgical intervention related to complication (Grade III), life-threatening complication (Grade IV), or woman's death (Grade V).[11] Minor adaptations of the classification designated to describe specific POP-surgery complications were those previously used in the PROSPERE trial.[12] Conversion (for example, from laparoscopy to the vaginal route) due to operative difficulties, such as adhesions, was not considered a complication.[13] The complications analysed here, selected together with the steering committee, were those possibly attributable to the surgical 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 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 the reoperations for complication of the prolapse surgery and those for recurrence of the prolapse or for de novo urinary incontinence.

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.

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.[14,15] A multinomial logistic regression was constructed to estimate each woman’s probability of receiving one of the three types of surgeries given her baseline covariates (i.e., the propensity score). Variables of the propensity score model were prespecified before outcome analyses and 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. Stabilized weights were used to estimate the average treatment effect in the entire population, and the extreme weights were truncated.[16] Balance between treatment populations was evaluated by standardised differences of all baseline covariates, with a threshold of 0.1 used to indicate imbalance.[16]

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 for serious complications, one for reoperations for POP recurrence, and one for any reoperation (for complications of POP recurrence or stress urinary incontinence) — were used to compare the three surgical groups. The models included a non-parametric estimation of the baseline hazard, a gamma frailty term for the centre effect, and weights that were based on the propensity score.[17,18]

All statistical tests were two-sided, a *P*-value <0.05 was considered significant. A multiple 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,[19] and 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 performed with the R statistical package, version 3.6.1 or later (The R Foundation for Statistical Computing, https://www.R-project.org/).

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

Results

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).

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

Median follow-up was 17.6 months (0.4 to 33.8). Complications of Clavien-Dindo grade III or higher occurred to 52 women (Table 2). During surgery or in the first 48 hours, 7 women had an intraoperative injury, 4 a haemorrhage or haematoma, and 1 a cardiac infarct. From 2 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 retention, 7 a haemorrhage or haematoma, 4 ureteral obstruction, 4 pelvic abscess, 1 severe postoperative pain, and 2 vaginal mesh exposure. Between 2 and 12 postoperative months, 20 women required surgical treatment for a complication (5 women had 2 complications 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%).

At 12 months the cumulative weighted incidence of serious complications was 1.8% for vaginal repair (95% CI 0-3.9), 3.9% for transvaginal mesh (95% CI 2.0-5.9), and 2.2% for sacropexy (95% CI 1.1-2.6). Compared with the sacropexy group, the risk of serious complications was higher among women in the transvaginal mesh group (Figure 1, Table 3). A concomitant total hysterectomy was associated with a higher risk of complications (Table 3). A sensitivity analysis was performed by excluding both complications with debatable imputability (one case of appendicitis and one case of an overactive bladder requiring botulinum toxin); both results remained the same. The analysis limited to the women with an anterior defect found similar and significant hazard ratios (Table S3).Due to a recurrence 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 the cumulative weighted incidence of reoperation for prolapse recurrence was 1.5% for 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 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.

Postoperative stress incontinence resulted in reoperation for 61 women (2.6%): 6 after vaginal repair (1.2%), 28 after transvaginal mesh (4.0%), and 27 after sacropexy (2.4%). When we considered the composite criterion of all reoperations (for complications, recurrence of prolapse, or postoperative stress incontinence), 124 women underwent 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 complicated prolapse recurrence or stress urinary incontinence was 3.2% for vaginal repair (95% CI 1.0-5.4), 6.9% for transvaginal mesh (95% CI 4.4-9.3), and 5.3% for sacropexy (95% CI 3.7-6.9). The comparison between the groups shows a significant difference in favour of the vaginal repair group only if we consider the propensity score (weighted HR, Table S4).

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 for prolapse recurrence.

Discussion

Main findings

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

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.[11,12]

Our results must be interpreted considering the absence of randomisation. The surgical groups had different characteristics. It is possible that the type of prolapse influenced the choice of the most appropriate surgical technique. However, we took the women's preoperative characteristics into account with the propensity score to emulate a comparative trial.[14] The data about the construction of the propensity score appear reassuring regarding potential unmeasured confounders that may bias our results. When we consider the variable with the greatest difference between the groups (anterior defect), the results of the analysis limited to the women with an anterior defect were similar to those for

all women. Within each surgical group, there were multiple and different surgical procedures. It is probable that some hysterectomies (especially in the vaginal repair group) were expediency hysterectomies performed to facilitate the intervention, whereas the surgeons appeared to avoid hysterectomies for women in the transvaginal mesh group. We were not able to consider some factors that might have promoted prolapse recurrence, such as family history, prolapse stage 3-4, a large genital hiatus or levator ani avulsion.[20] These limitations are the price of a "real world" study design, which can introduce variance but limits statistical power.

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.[21] Five year after transvaginal mesh placement, another study found that 79% of the mesh exposures occurred during the first postoperative year.[22]

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.

Interpretation

Our results about the relative risk of serious complications are similar to earlier comparative studies, reporting fewer complications with vaginal surgery without mesh.[23,24] The incidence of complications in our registry is lower than that reported in several trials. This difference 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 systematically and regularly verified the information with the hospitals' data departments 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.

Conclusion

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

sacropexy); and transvaginal mesh has a higher risk of serious complications than the other 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 technique most appropriate for them.

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. Renaud de Tayrac reports grants, personal fees or other from Boston Scientific and Coloplast, during the conduct of the study; non-financial support from Wellspect, outside the submitted work. Prof. Michel Cosson reports personal fees from Boston Scientific, Coloplast, Promedon, and AMI, outside the submitted work. Prof. Xavier Deffieux reports personal fees or other from Urgo-Tech, Coloplast, Allergan, Laborie, Hologic, Sanofi, and Nanobiotics, outside the submitted work.

Contribution to authorship

Study concept and design: Fritel, Fauconnier, Ragot.
Acquisition of data: Fritel, de Tayrac, Campagne-Loiseau, Cosson, Ferry, Hummel, Deffieux, Lucot, Wagner, Debodinance, Saussine, Pizzoferrato, Carlier-Guérin, Thubert, Panel, Bosset, Nkounkou, Ramanah, Boisramé, Charles, Bressler, Charvériat, Raiffort, Fauconnier.
Analysis and interpretation of data: Fritel, Fauconnier, de Keizer, Ragot.
Drafting of the manuscript: Fritel, Fauconnier, Ragot.
Statistical analysis: Fritel, de Keizer, Ragot.
Obtaining funding: Fritel.
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 meet authorship criteria and that no others meeting the criteria have been omitted.
We affirm that our manuscript is an honest, accurate and transparent report of the VIGI-MESH registry; that no important aspects of the registry have been omitted; and that any discrepancies from the registry as originally planned and registered have been explained.

Details of ethics approval

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).

Funding

The national medicines agency (Agence Nationale de Sécurité du Médicament et des 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.

Acknowledgements:

We thank Lucie Merlet (CHU de Poitiers), Aurélie Comptour (CHU Carémeau), Florence Tartarin (CHU de Poitiers), Elodie Migault (CHU de Poitiers), and Pierre-Jean Saulnier (Université de Poitiers) for their support or contribution to collecting and cleaning the data. We thank Jo Ann Cahn for the editing (CHU de Poitiers).

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

379 References

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.

7 Rimmer A. Vaginal mesh procedures need compulsory register, says royal college. BMJ 2018;360:k586.

8 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

11 Dindo D, Demartines N, Clavien PA. Classification of surgical complications. Ann Surg 2004;240:205-13.

12 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

15 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.

16 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.

17 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.

20 Friedman T, Eslick GD, Dietz HP. Risk factors for prolapse recurrence: systematic review and meta-analysis. 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.

22 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).

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.

Baseline characteristics		Vaginal repair N= 504	Transvaginal mesh N= 692	Laparoscopic sacropexy 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)

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).

Grade III or IV complication, n (%)	Vaginal repair N= 504	Transvaginal mesh N= 692	Laparoscopic sacropexy N= 1113	Overall 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)
Surgical group	Vaginal repair	1	1
	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 procedure	Total hysterectomy	2.48 (1.15 to 5.34)	4.13 (2.75 to 6.21)
	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 factors for reoperation for prolapse recurrence. Frailty model with centre as a random effect (N= 2309)

Risk factor		Non-weighted HR (95% CI)	Weighted* HR (95% CI)
Surgical group	Vaginal repair	1	1
	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 procedure	Total hysterectomy	0.14 (0.02 to 1.06)	0.06 (0.01 to 0.27)
	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.

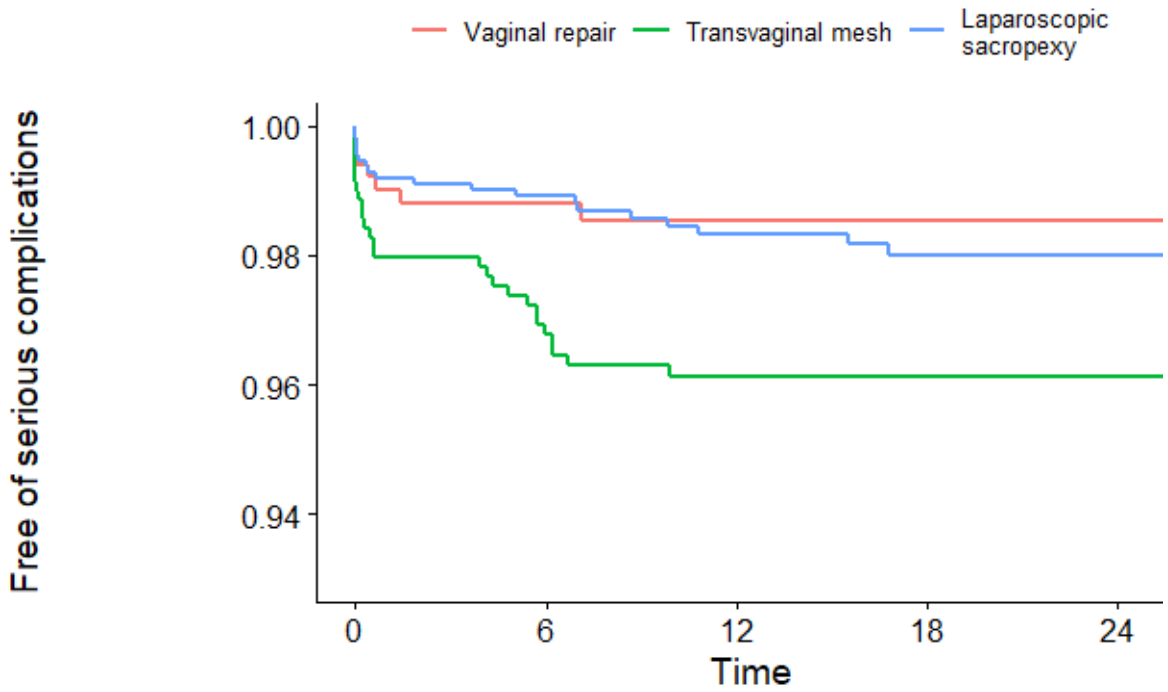

Figure 1. Kaplan-Meier curve free of serious complication (Clavien-Dindo grade III or more) as a function of time (months) and of surgical group (2309 women).

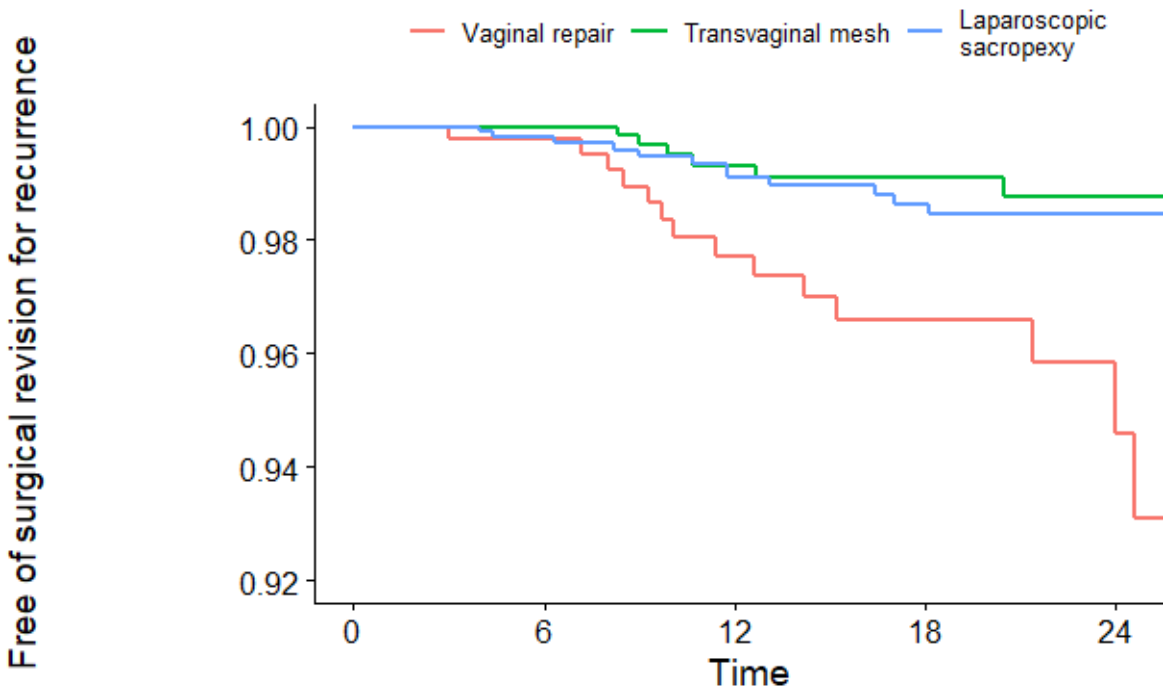

Figure 2. Kaplan-Meier curve free of reoperation for prolapse recurrence as a function of time (months) and of surgical group (2309 women).