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Review – Female Urology - Incontinence

Safety and Efficacy of Vaginal Implants in Pelvic Organ Prolapse Surgery: A Meta-analysis of 161 536 Patients

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Abstract

Context: Among the many surgical treatments for pelvic organ prolapse (POP), better results can be achieved with the use of vaginal implants. However, owing to perceived complications, vaginal implant surgeries have been restricted or banned in many countries.

Objective: To assess the real value of vaginal implants in POP surgery and compare the safety and efficacy of operations with and without implants.

Evidence acquisition: A systematic search was performed in three medical databases. Randomised controlled trials and observational studies comparing the safety and efficacy of vaginal POP surgery with implants versus native tissue were included. Safety outcomes were defined as different types of complications (functional and non-functional) and reoperations for complications. Efficacy outcomes were parameters of anatomical success and the rate of reoperations due to recurrence. A multivariate meta-analysis framework was used to estimate pooled odds ratios (ORs) with confidence intervals (CIs) with simultaneous control for study correlations and estimation of multiple correlated outcomes.

Evidence synthesis: We included 50 comparative studies in the analysis. Rates of reoperation for complications (OR 2.15, 95% CI 1.20–3.87), vaginal erosion (OR 14.05, 95% CI 9.07–21.77), vaginal bleeding (OR 1.67, 95% CI 1.25–2.23), and de novo stress urinary incontinence (OR 1.44, 95% CI 1.18–1.75) were significantly higher in the implant group. Rates of anatomical success (OR 3.22, 95% CI 2.06–5.0) and reoperation for recurrence (OR 0.55, 95% CI 0.36–0.85) were superior in the implant group.

Conclusions: POP surgeries with vaginal implants are more effective than surgeries without implants, with acceptable complication rates. Therefore, the complete prohibition of implants for POP surgeries should be reconsidered.

Patient summary: We compared vaginal surgery with and without implants for repair of pelvic organ prolapse. Despite higher complication rates, vaginal implants provide better long-term results overall than surgery without implants.

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1. Introduction

The use of vaginal implants in pelvic organ prolapse (POP) surgeries is currently a controversial issue [1]. Women have an 11% chance of undergoing surgery for vaginal prolapse during their lifetime, and 30% of these patients will require repeat surgery for recurrence [2]. Traditional surgical approaches that use native tissue (NT) are often insufficient, and POP is likely to recur in these cases. For better outcomes, new interventions using implants were introduced, which provided more durable support [3]. As of 2006, however, the US Food and Drug Administration (FDA) has issued several warnings regarding the safety of stress urinary incontinence (SUI) and POP surgeries performed with tape, mesh, or slings due to high complication rates observed with these implants [4,5]. Although no detailed causal exploratory analysis has been performed, the increasing number and severity of perioperative complications initially limited the use of vaginal implants for POP surgeries. Unfortunately, these ill-considered revelations led several countries to completely ban the use of vaginal implants not only for POP but also for SUI [6]. Even in countries that still allow the use of implants, there are no clear recommendations on which POP subpopulation is likely to benefit from implant surgery.

The aim of our study was to analyse the complications and the efficacy of female POP operations with versus without vaginal implants to determine whether implant use poses a greater risk of complications that would outweigh the potentially superior outcomes in comparison to NT surgery. Expert opinion suggests that the effectiveness of POP surgery performed with a vaginal implant is superior to techniques without implants, and the complications are not so serious and frequent to justify exclusion of implants from the surgical repertoire [7]. To test this hypothesis, we performed a comprehensive systematic review and meta-analysis to examine the complication patterns and effectiveness of vaginal POP reconstructions with implants in comparison to NT approaches.

2. Data acquisition

Our systematic review and meta-analysis followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement (PRISMA; Fig. 1) and the Cochrane handbook [8,9]. The review protocol was registered on PROSPERO (CRD42022369386).

2.1. Eligibility criteria

The PICO (Population, Intervention, Comparison, Outcome) framework was used to pose our questions. Studies on females with pelvic organ prolapse (P) who underwent vaginal surgery with implants (I) in comparison to surgery without implants (C) were included. All complications types reported (Outcome 1) and the efficacy (Outcome 2) of the two methods were compared. Complications are reported in terms of number of patients with the complication, the rate of reoperation for complications, and the different complication types. To determine the efficacy, data on anatomical success (based on definitions used by the authors, Pelvic Organ Prolapse Quantification [POPQ] stage, POPQ points) and the rate of reoperation for recurrence were collected. To satisfy the inclusion criteria, studies had to report on both patients undergoing vaginal surgery with implants and patients undergoing vaginal surgery with NT.

Randomised controlled trials (RCTs) and prospective and retrospective cohort studies were eligible. No studies were excluded on the basis of language criteria.

Studies were excluded if they reported on either implant surgeries or on NT surgeries alone, if the data could not be further processed, or if the relevant publication was a conference abstract, review, case series, or case report.

2.2. Information sources

Our systematic search was conducted on November 2, 2022 in the Embase, MEDLINE (via PubMed), and Cochrane Central Register of Controlled Trials (CENTRAL) databases.

2.3. Search strategy

The search key included terms for females who underwent vaginal POP surgery with or without vaginal implants. We did not use filters or other restrictions.

2.4. Selection process

EndNote version 20.0 (Clarivate Analytics, Philadelphia, PA, USA) and rayyan.ai (Rayyan Systems, Cambridge, MA, USA) were used for the study selection process. After automatic and manual removal of duplicates, the selection was independently performed by two pairs of authors (J.Á. and B. S.; J.Á. and M.T.) at the title and abstract level and then review of the full text. Disagreements were resolved at each level by a third author for each pair (N.Á. and P.N.). Cohen's κ coefficient was calculated after each step to measure inter-rater reliability.

2.5. Data collection process

Data were collected from the eligible articles by two authors (J.Á. and B.S.) independently and entered into a predetermined data table.

2.6. Data items

The following data were extracted: first author, year of publication, study period, number of participants, age, body mass index, previous vaginal surgeries, menopausal status, implant type, vaginal compartment being reconstructed, study type, intraoperative complications, postoperative complications (functional, nonfunctional), reoperations, rate of anatomical success, POPQ stage, and POPQ points.

Subgroup analyses were carried out by study type (RCT vs observational) and for operations that were only on the anterior vaginal compartment.

2.7. Study risk-of-bias assessment

Two review authors (J.Á. and M.T.) assessed the risk of bias independently using the Quality in Prognostic Studies (QUIPS) tool for retrospective and prospective studies, and Risk of Bias 2 (RoB2) tool for randomised trials. For QUIPS, the risk assessment categories were predefined for each domain (Supplementary material). Another two authors (P.N. and N.Á.) resolved disagreements. To assess the quality

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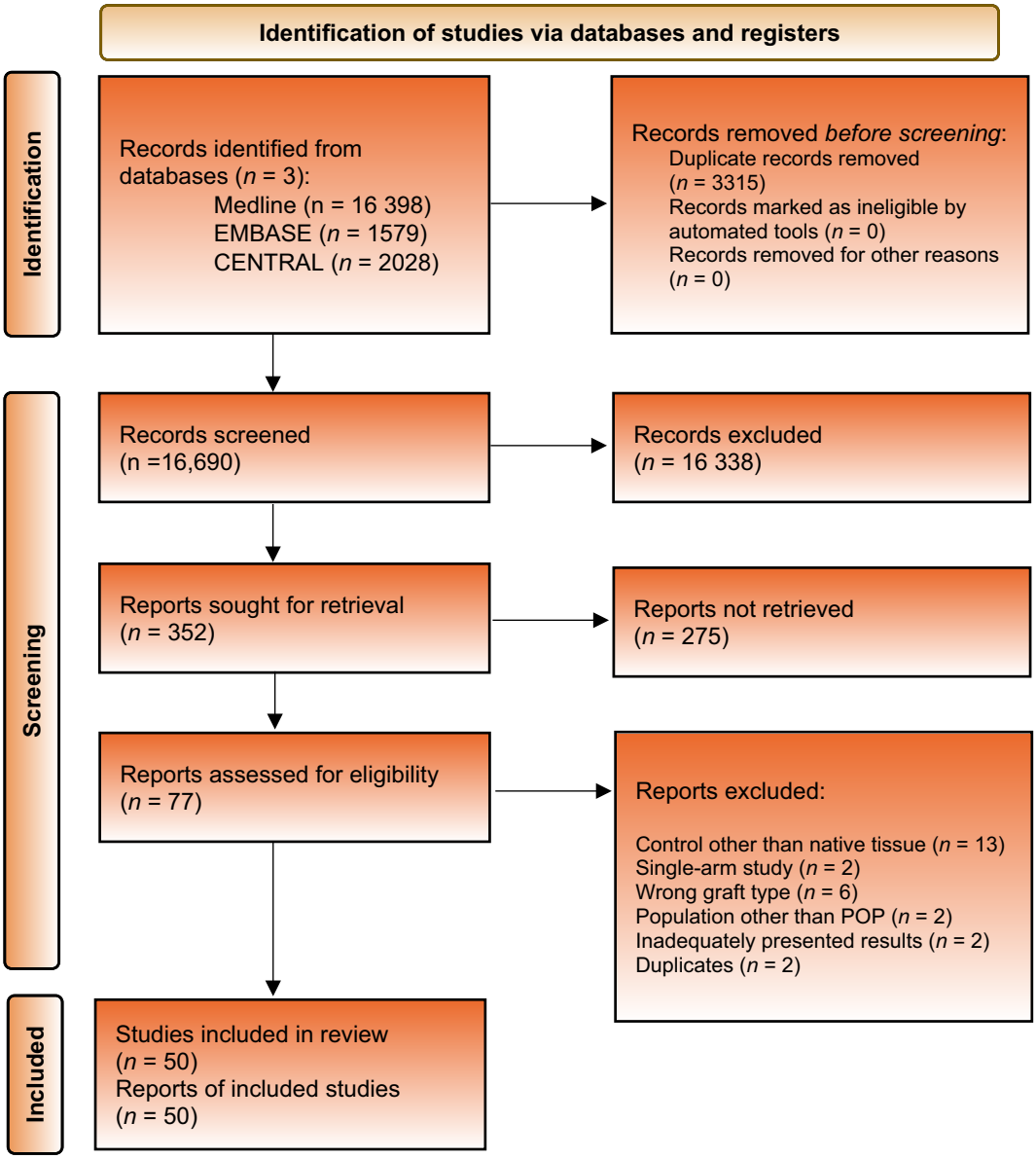

Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 flowchart of the study selection process.

of the evidence, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) recommendations were followed [10].

2.8. Synthesis and statistical analysis

The odds ratio (OR) with 95% confidence interval (CI) were calculated for the effect size measures. To pool the effect sizes for the sum of intraoperative complications (as reported in the papers), individual intraoperative complication types, total reoperations, reoperations for recurrence, and reoperations for complications, the Mantel-Haenszel method with Hartnung Knapp adjustments was used in random-effect meta-analysis [11]. Heterogeneity was assessed using Higgins and Thompson I^2 statistics.

To pool the ORs for various functional complications, nonfunctional complications, and anatomical success outcomes, we used a multivariate model framework [12]. This allowed us to control for intrastudy and interstudy correlations and to simultaneously test moderator effects in a model. We used sandwich-type cluster-robust estimates of a variance-covariance matrix of the model coefficients and CIs [13].

Small-study publication bias was assessed via visual inspection of funnel plots, while outliers were detected via visual inspection of Baujat plots and leave-one-out analysis according to the recommendations of Harrer et al. [11].

3. Evidence synthesis

3.1. Search and selection

The systematic search yielded 20 005 articles. After duplicate removal, 16 690 articles were screened by title and abstract. Full-text review of 77 reports revealed that 50 studies (19 RCTs, 31 observational studies) involving 161 536 patients were eligible. The screening and selection processes are summarised in a PRISMA flowchart in Figure 1.

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3.2. Basic characteristics

Baseline characteristics of the studies included are detailed in Supplementary Table 1 and the surgical parameters are summarised in Supplementary Table 2. Median follow-up was 1 yr (range 2 mo–10 yr). The mean patient age was 74.2 ± 8.9 yr in the implant group and 62.7 ± 9.7 yr in the NT group. The majority of women were postmenopausal. Most commonly, surgery was performed on the anterior vaginal compartment; however, in many cases more than one compartment was reconstructed. Some 41% of the studies (23/50) were conducted after the FDA warning in 2011 about serious complications. The eligibility criteria in the studies are summarised in Supplementary Table 3.

3.3. Safety parameters

Intraoperative complications were rare and only the incidence of bladder perforation was significantly higher for the implant group (Supplementary Figs. 4–7).

The odds of postoperative complications were significantly higher in the implant group (OR 1.71, 95% CI 1.19–2.47); however, the studies for this pooled analysis included only one RCT (Supplementary Fig. 9).

There was no significant difference in total reoperations between the two groups (OR 1.13, 95% CI 0.79–1.63; Supplementary Fig. 8). However, the odds of reoperation for complications were significantly higher in the implant group among randomised trials (OR 2.15, 95% CI 1.20–3.87) and nonrandomised trials (OR 3.42, 95% CI 1.28–9.13; Fig. 2).

Regarding postoperative nonfunctional complications, vaginal bleeding (OR 1.67, 95% CI 1.15–2.40) and erosion (OR 14.05, 95% CI 7.96–24.80) were significantly more frequent in the implant group, whereas buttock pain was more common in the NT group (OR 0.34, 95% CI 0.17–0.70). There were no clinically relevant or statistically significant differences between the implant and NT groups in the odds of groin pain, haematoma, pelvic abscess formation, pelvic pain, postoperative fever, thrombosis, urinary tract infection, vaginal adhesion or stenosis, or vaginal discharge (Fig. 3). In the anterior compartment subgroup, the odds of erosion (OR 9.76, 95% CI 4.73–20.15), bleeding (OR 1.71, 95% CI 1.32–2.23), and groin pain (OR 13.74, 95% CI 5.74–32.89) were significantly higher in the implant cohort (Supplementary Fig. 1).

Among postoperative functional complications, the odds for de novo SUI development were significantly higher (OR 1.44, 95% CI 1.189–1.75) in the implant group. The difference in odds for the remaining functional complications (de novo dyspareunia, de novo overactive bladder, de novo urgency, defecation difficulties, micturition difficulties, and urinary retention) were not statistically significant (Fig. 4). In the anterior compartment subgroup, there were no significant differences in functional complications (Supplementary Fig. 2).

3.4. Efficacy parameters

The odds of achieving an anatomically successful reconstruction were 3.22 times higher (95% CI 2.06–5.01) in the vaginal implant group, while the probability of presenting with POPQ stage 3 at the end of follow-up was 69% higher (OR 0.31, 95% CI 0.16–0.62) in the NT group. There were no significant differences between the groups for POPQ stages 0, 1, 2, and 4 (Fig. 5). For the anterior compartment, the odds of anatomical success were 3.92 times higher (95% CI 1.87–8.22) for the implant group. POPQ stage 0 was also significantly more likely to occur with mesh implantation (OR 3.18, 95% CI 1.49–6.77); however, POPQ stage 2 was more frequent in the NT group (OR 0.21, 95% CI 0.06–0.73; Supplementary Fig. 3).

Furthermore, among RCTs the reoperation rate for recurrence was higher in the NT group (OR 0.55, 95% CI 0.36–0.85; Fig. 6). Univariate analysis results for clinical recurrence (POPQ stage $\geq$2) and POPQ points are detailed in Supplementary Figures 10–31.

3.5. Risk-of-bias assessment

Results for the risk-of-bias assessment for the studies are presented in Supplementary Table 4 and the Supplementary material. The studies included in the meta-analysis were mainly at moderate risk of bias. Domains at low risk of bias included deviations from the planned intervention, missing outcome data, and the selection of reported outcome ranges.

3.6. Publication bias and heterogeneity

Only randomised trials were used in the multivariate analysis, so overall heterogeneity can be considered low. Heterogeneity was high for most outcomes and can be attributed to different study types, heterogeneous populations, and differences in surgical approach and expertise.

3.7. Discussion

The aim of this review was to determine the complication rates and effectiveness of the two types of vaginal POP surgeries and assess whether these outcomes support the FDA warnings. Several studies have investigated complications associated with mesh surgeries; however, there has been no comprehensive comparative study analysing all compartments, different implant types, surgical parameters, and anatomical success of implant versus NT POP surgery.

In the past 10 yr, meta-analyses have compared vaginal mesh to NT surgeries with a sole focus on the anterior compartment [14–17], postoperative sexual function [18], or potential risk factors for mesh erosion [19], but none has addressed a combination of all the parameters of interest. To the best of our knowledge, our review is the most comprehensive on the subject, providing a detailed summary of all complications along with the efficacy of implant versus NT POP surgeries for all vaginal compartments, and including RCTs and observational studies. Given the complexity of the scope, we also built a special multivariate statistical model to control potential confounding factors. Our meta-analysis yielded pooled results for RCTs and for observational studies. However, in view of the high degree of heterogeneity observed in the nonrandomised studies, we included only RCTs involving more homogeneous patient groups in the statistical model built for multivariate analysis.

Our assessment of the rates of reoperation for complications and our comparison of different complication types provide an objective overview of the safety of POP surgeries. In several studies, the incidence of reoperation for

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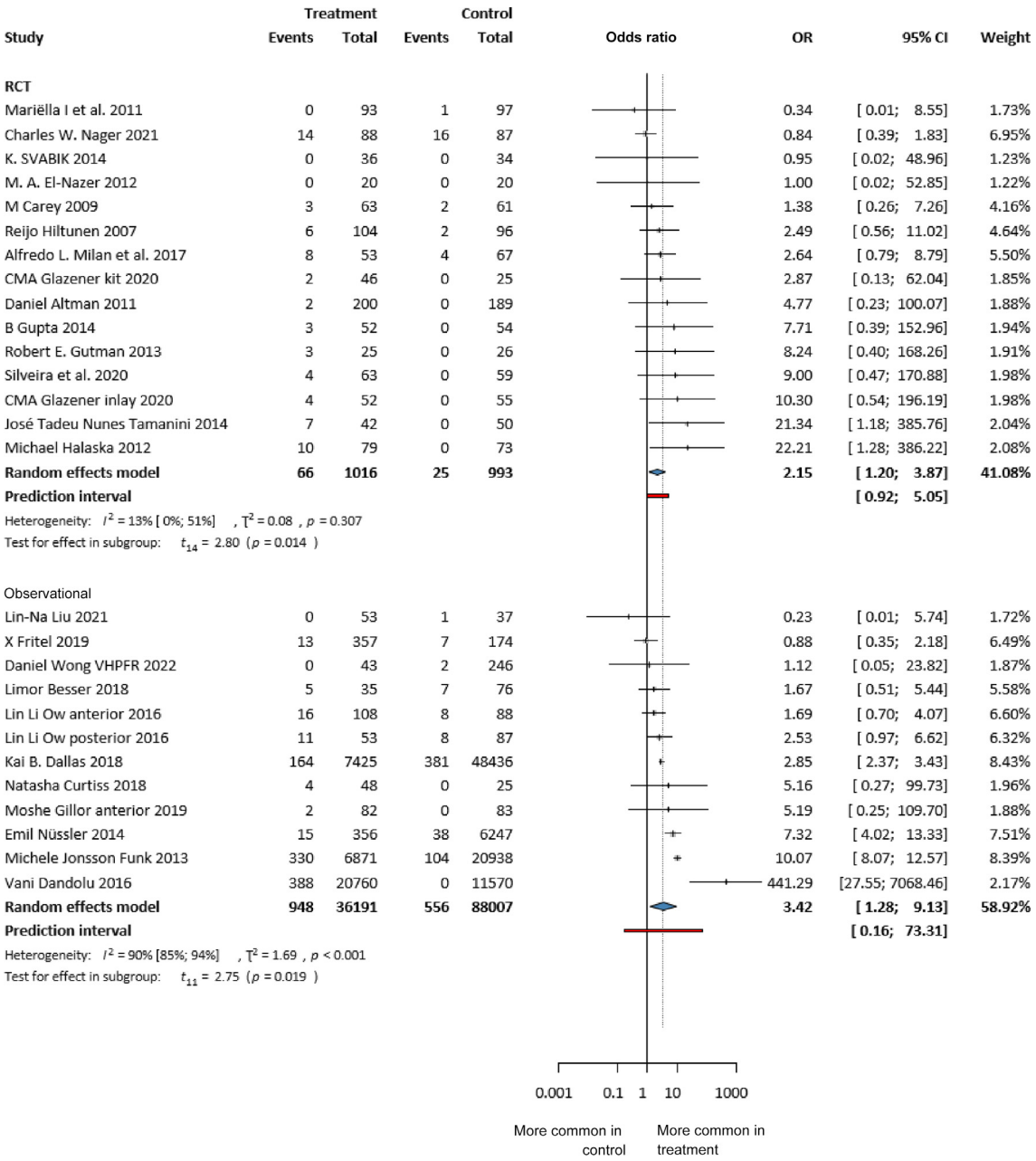

Fig. 2 – Forest plot of the odds ratios (ORs) for reoperation for complications in implant (treatment) versus native tissue (control) groups in randomised controlled trials (RCTs) and observational studies. Reference details for the studies are included in the Supplementary material. CI = confidence interval.

complications was higher in the implant group, although it is important to mention that the erosion rate was also higher in these studies [20]. Mesh erosion was the main reason for reoperation, but this complication is primarily influenced by surgical practice and correct indication criteria [21]. Our meta-analysis confirmed that the rate of reoperation for complications was significantly higher in the implant group, but the difference in event rates (6.5% in implant vs 2.5% in NT groups in RCTs) between the groups was clinically irrelevant. Among postoperative nonfunctional complications, only bleeding, vaginal discharge, urinary tract infection, and erosion had an incidence rate of >5% and could therefore potentially be considered clinically relevant. Vaginal erosion was the only undeniably implant-dependent complication, and was also the most common implant-related complication, occurring in 3–20% of cases [22–25]. According to our meta-analysis, the odds of erosion occurrence were 14 times higher following mesh surgery, although much lower rates have been reported in some studies [26]. In the anterior subgroup, the odds of erosion were nine times higher for the implant cohort. It should be mentioned that mesh-related complications, especially vaginal wall erosion, were detected only in the implant group. The major reason for the FDA imposition of restrictions was the high rate of vaginal erosion [27]. Deng et al. [19] also highlighted the need for careful patient selection, taking into account risk factors such as younger age, a greater number of parities, premenopausal oestrogen replacement therapy, diabetes mellitus, smoking, and concomitant hysterectomy, as well as inadequate surgical experience. Postoperative bleeding also

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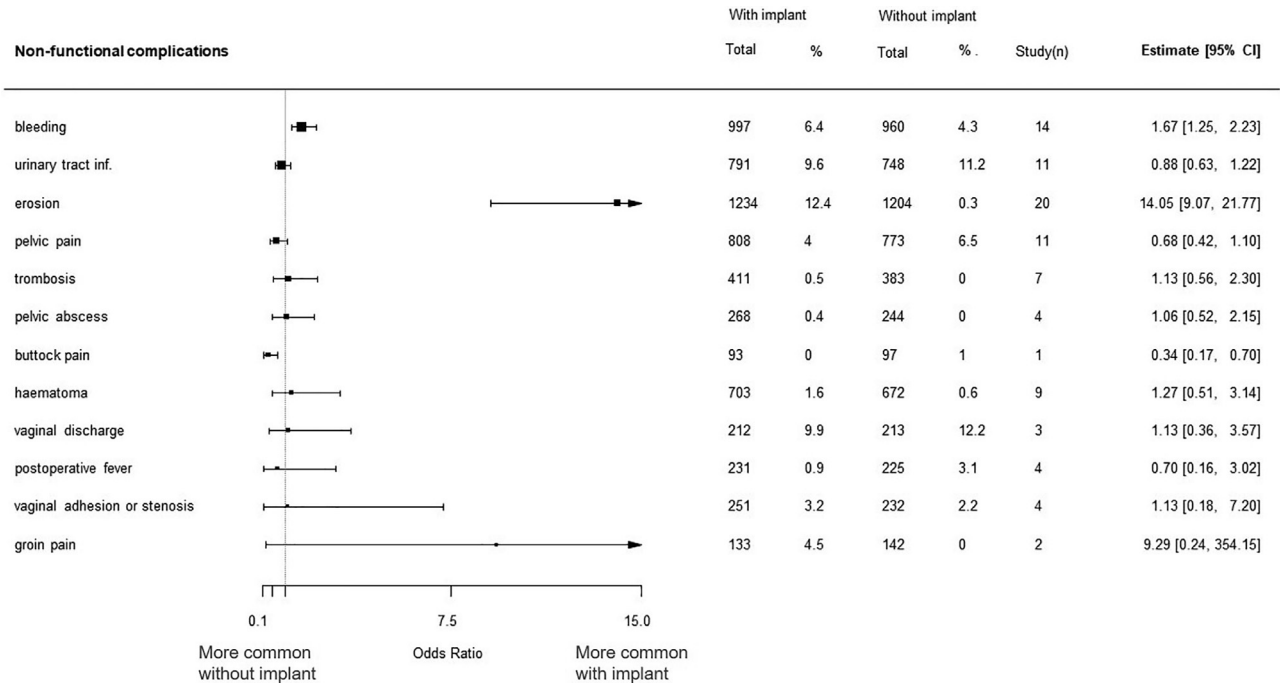

Fig. 3 – Forest plot of the odds ratios on multivariate analysis for nonfunctional complications in the implant versus native tissue groups. Reference details for the studies are included in the Supplementary material. CI = confidence interval.

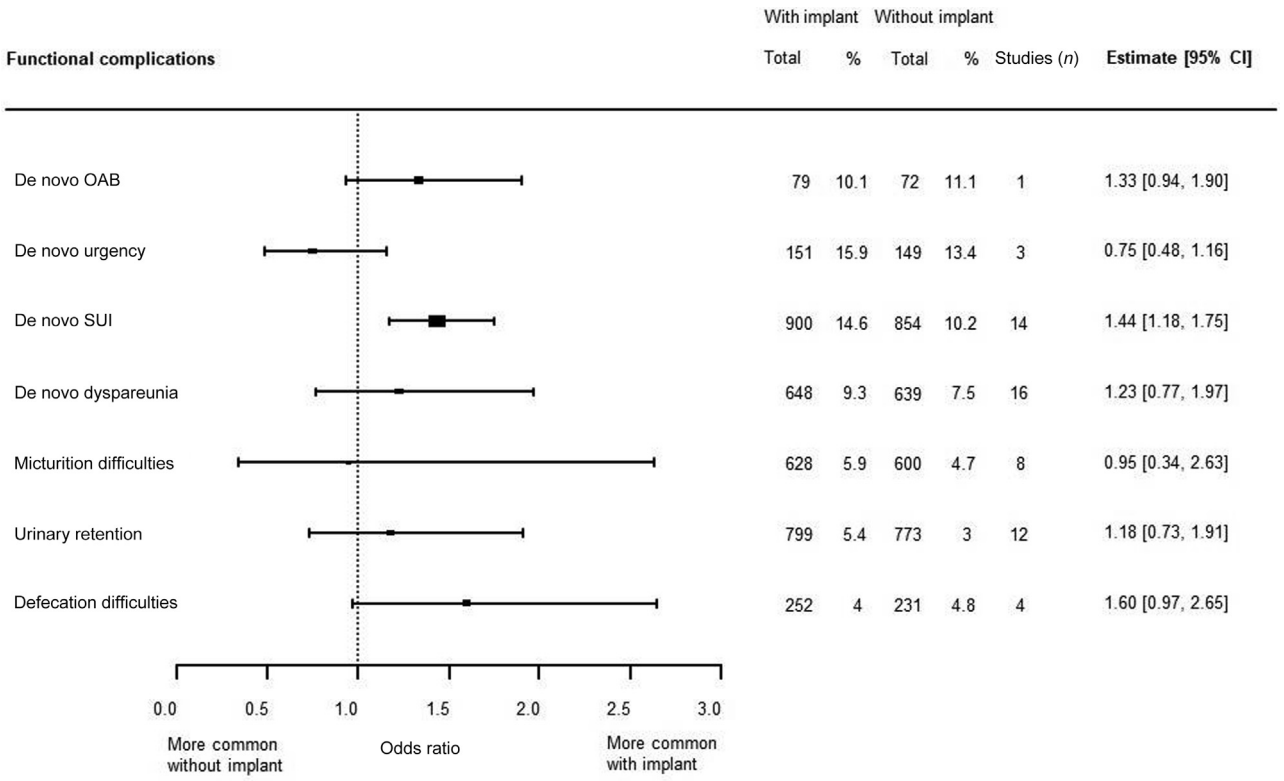

Fig. 4 – Forest plot of the odds ratios on multivariate analysis for functional complications in the implant versus native tissue groups. Reference details for the studies are included in the Supplementary material. CI = confidence interval; OAB = overactive bladder; SUI = stress urinary incontinence.

occurred at a significantly higher rate in the implant group, although bleeding was not clinically relevant, requiring no intervention in most cases. It should be mentioned that vaginal bleeding could be related to erosion, and thus was considered in the design of our statistical model. Buttock pain, which is an unusual complication, was more frequent in

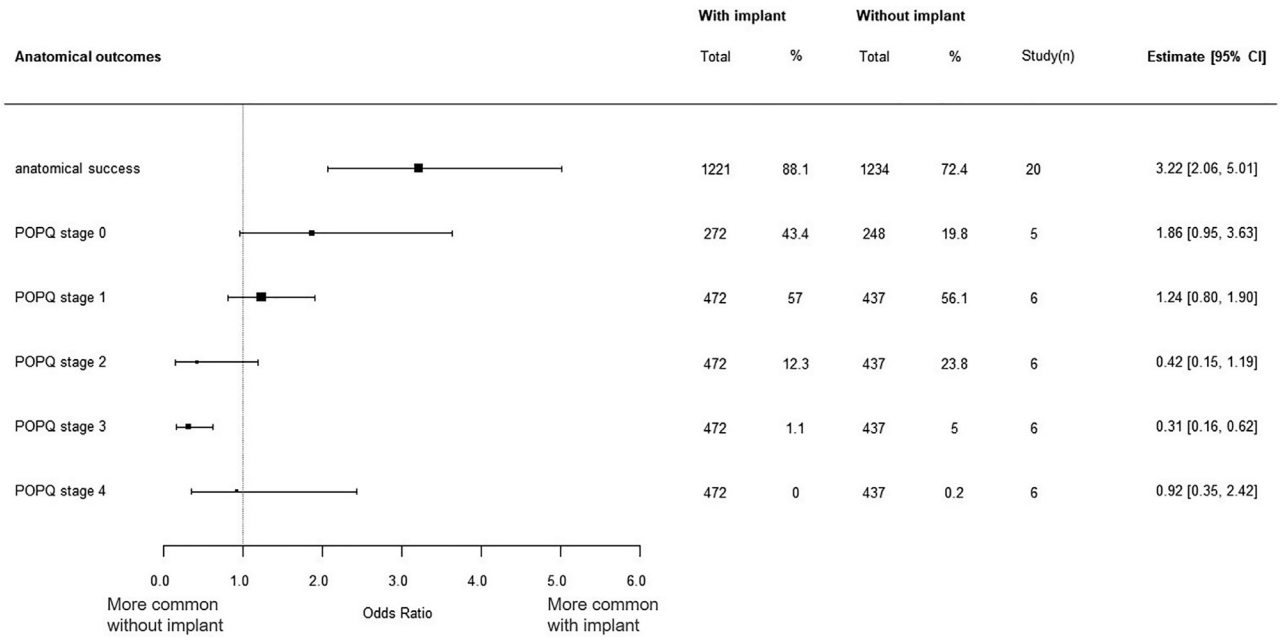

Fig. 5 – Forest plot of the odds ratios on multivariate analysis for efficacy in the implant versus native tissue groups. Reference details for the studies are included in the Supplementary material. CI = confidence interval; POPQ = Pelvic Organ Prolapse Quantification.

the NT group. This pain may be because neurological damage caused by insertion of the sacrospinous ligament suspension suture [28]. In the majority of previous meta-analyses, only the anterior compartment was investigated in terms of erosion or erosion-associated complications [15,17,29,30]. It is also important to discuss the implant material in relation to complications. Among the studies included in our analysis, polypropylene mesh was the most common material used. It is known that in comparison to first-generation meshes, next-generation macroporous, ultralight meshes cause fewer complications. The mechanical and physicochemical properties of polypropylene materials hinder full tissue integration of the mesh, potentially contributing to the development of erosion and chronic pain. Newly developed advanced materials (eg, polycaprolactone, graphene-based nanocomposite copolymers, polycarbonate, polydimethylsiloxane, and polyvinyl plastics [31]) have more tissue-compatible properties with potentially lower complication rates. These materials are being developed for vaginal implants and many show promise; therefore, their inclusion in upcoming studies should be a priority.

With the exception of erosion, there was no clinically relevant difference between the two groups in other nonfunctional complications in our analysis.

Among functional complications, de novo urgency, de novo SUI, de novo dyspareunia, and micturition difficulties exceeded a relative frequency of 5%. Significant differences between the groups were only found for de novo SUI. Our results are concordant with previous meta-analyses, which showed that there was no difference in the rates of de novo dyspareunia and de novo urgency between groups with and without mesh [15,30]. The higher incidence of de novo SUI is a consequence of the anatomical success achieved by the surgery, as more extensive prolapse results in artificial lower urinary tract obstruction due to compression of the urethra, which then disappears on reconstruction [32]. Assessment of functional complications is a challenge in elderly women because of age-related changes (eg, vaginal dryness, vaginal narrowing, impaired bladder function) and lower sexual activity; therefore, it is difficult to show a causal relationship between vaginal mesh surgery and functional complications [33]. This difficulty notwithstanding, the above-mentioned functional complaints are generally observed more frequently for aging female patients. The global incidence of de novo dyspareunia following transvaginal mesh surgery is 13.9% [34]. Several studies confirmed that sexual function improved following POP surgery, but such surgery may also predispose patients to dyspareunia [35–37]. We expected dyspareunia to be more frequent in the implant group; however, there was no significant difference in the occurrence of de novo dyspareunia, which can be attributed in part to the older age of patients in the implant group (mean age 74.2 ± 8.9 yr vs 62.7 ± 9.7 yr in the NT group).

Perhaps the most objective measure of efficacy is the reoperation rate for recurrence, with overall rates of 6.4% in the NT group and 2.5% in the implant group among the RCTs. Studies indicate that the number of reoperations for recurrence increases over time and is significantly higher for patients without implants [38,39]. Altman et al. [40] reported that at 1-yr follow-up there were no reoperations for recurrence in the implant group and only one in the NT group. In a study by Milani et al. [41] with longer follow-up of 7 yr, 7% of implant and 82% of NT cases required reoperations for recurrence.

Other studies have defined efficacy as anatomical success according to POPQ stage and POPQ points reported by the surgeon [4,42–44]. It has been shown that alloplastic implants provide significantly better anatomical corrections and more successful results in the long run than NT [45]. We used POPQ stage $\geq$2 as the cutoff for clinical recurrence in our univariate analysis [2,46,47]; using this cutoff, the probability of recurrence was 73% higher in the NT group.

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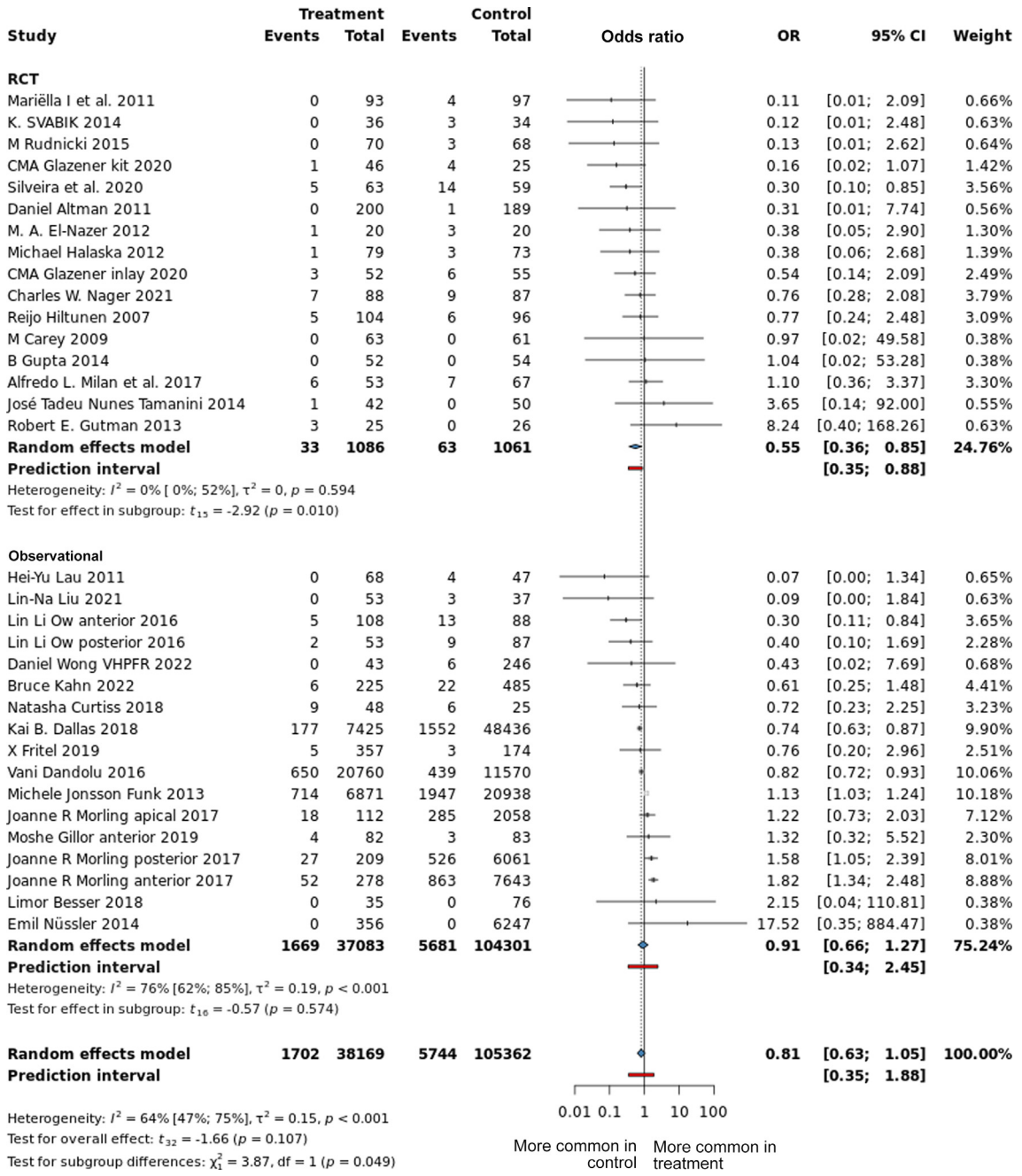

Fig. 6 – Forest plot of the odds ratios (ORs) for reoperation for recurrence in the implant (treatment) versus native tissue (control) groups in randomised controlled trials (RCTs) and observational studies. Reference details for the studies are included in the Supplementary material. CI = confidence interval.

A high recurrence rate for surgery without implants was also reported for other studies, reaching 19% for surgery on multiple compartments, and the incidence of reoperation for recurrence exceeded 17% considering all compartments [23,48].

3.8. *Strengths and limitations*

Regarding its strengths, our analysis was extensive and included all complications studied. We applied a rigorous methodology and included a large number of studies with high patient numbers. Besides conventional random-effect models, our multivariate statistical modelling framework facilitated control of interstudy and intrastudy correlations, thus allowing for more precise estimates.

In terms of limitations, relatively high heterogeneity was observed. This can be attributed to the different implant types used and the different vaginal compartments on which surgery was performed. Other limitations include the wide range for follow-up duration and the limited incidence of certain complication types, which constrains the applicability of some the findings.

3.9. *Implications for practice and research*

Our results indicate that the ban on the use of vaginal alloplastic (polypropylene) implants for POP surgery should be

revised. For ideal results using current implants, more precise indications must be defined, there should be more careful patient selection after obtaining detailed patient information, and the operations should only be performed at high-volume centres. As an implication for research, there should be a focus on further development of graphene-based nanocomposite and other potentially more tissue-friendly materials as alternatives to polypropylene [39].

RCTs with longer follow-up, different mesh materials (including newly developed advanced meshes), and large patient numbers would be required to accurately assess both types of surgery and their advantages and drawbacks. Prompt implementation of these findings would play a pivotal role in delivering benefits to the community and, most importantly, POP patients [49,50].

4. Conclusions

POP surgery with vaginal implants is a more effective approach than surgery without implants, with complication rates and severity that are clinically acceptable. Vaginal wall erosion is the only complication with high clinical relevance, but its occurrence could potentially be reduced with better patient selection, advanced implant material, and surgical technique. Our findings indicate that the ban on implants for POP surgeries should be reconsidered.

Author contributions: Attila Majoros 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.

Study concept and design: J. Ács, Szabó, Skribek, Tenke, Szarvas, Hegyi, Nyirády, N. Ács, Majoros.
Acquisition of data: J. Ács, Skribek, Tenke.
Analysis and interpretation of data: J. Ács, Szabó, Majoros.
Drafting of the manuscript: J. Ács, Szabó, Szarvas, Nyirády, N. Ács, Hegyi, Majoros.
Critical revision of the manuscript for important intellectual content: Majoros, Hegyi, Szabó.
Statistical analysis: Fehérvári, Harnos.
Obtaining funding: Majoros, Hegyi.
Administrative, technical, or material support: J. Ács, Szabó, Skribek, Tenke.
Supervision: Majoros.
Other: None.

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Appendix A. Supplementary data

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