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Main research article with the title

**Long-term outcome of porcine skin graft in surgical treatment of recurrent pelvic organ prolapse. An open randomized controlled multicenter study.**

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## **Abstract**

*Objective:* To determine the long-term objective and subjective outcomes of use of a porcine skin graft (Pelvicol™) compared with conventional colporrhaphy in recurrent pelvic organ prolapse surgery and to analyze risk factors and safety.

*Design:* Open randomized controlled multicenter study.

*Setting:* Eight Swedish hospitals.

*Population:* 135 consecutive women with recurrent cystocele and/or rectocele admitted for vaginal prolapse surgery were randomized; 132 completed the study, 64 to conventional colporrhaphy and 68 to Pelvicol.

*Methods:* Conventional anterior and posterior colporrhaphy and colporrhaphy with use of Pelvicol™ mesh reinforcement. Clinical evaluation by means of Pelvic Organ Prolapse Quantification (POP-Q) and symptom questionnaire preoperatively, three months and three years postoperatively.

*Main outcome measures:* Anatomical and subjective outcome. Recurrence was defined as POP-Q  $\geq$  stage 2.

*Results:* At 3-month follow-up early recurrence/surgical failures occurred significantly more often in the Pelvicol™ group, but at the 3-year follow-up the recurrence rates were similar. The recurrence rates in the anterior compartment were 57–62% and 44–23% in the posterior compartment for the colporrhaphy and Pelvicol™ groups, respectively. Symptoms were substantially and equally reduced in the two groups after surgery. Sexual activity and function did not seem to be affected adversely in any group. The complication rate was low. Risk factors for anatomical recurrence were age, body mass index and preoperative stage of the prolapse.

*Conclusions:* Use of Pelvicol™ did not provide advantages to conventional colporrhaphy in recurrent pelvic organ prolapse concerning anatomical and subjective outcomes with the surgical technique used in this study.

**Key words**

Colporrhaphy; Outcome; Pelvicol; Randomized study; Recurrent prolapse

**Abbreviations**

CCG	=	conventional colporrhaphy group
CI	=	confidence interval
OR	=	odds ratio
PG	=	Pelvicol implant group
POP	=	Pelvic Organ Prolapse
POP-Q	=	Pelvic Organ Prolapse Quantification
SUI	=	Stress urinary incontinence

## **Introduction**

Pelvic organ prolapse (POP) is a common condition in women (1). The annual age-related incidence of surgery for POP is in the range of 10 to 30 per 10 000 women (2). Surgical management should aim to provide the most durable repair. The objective outcomes of primary POP surgery vary depending on the site of surgery and the stage of the prolapse. Recurrence rates up to 40-50% have been reported (2,3). Although recurrent prolapse occurs in a substantial proportion of women operated for POP it seems that only a smaller proportion of these undergo reoperation (3-5). Treatment of recurrent POP is a challenge to the medical community. It is the general clinical impression among gynecologists that the outcome of surgical treatment of recurrent POP with traditional vaginal prolapse surgery is usually less favorable than the outcome after primary surgery. However, the outcome of surgery for recurrent POP has not been well investigated and the results to date are ambiguous (6,7). In the Cochrane review of surgical management of pelvic organ prolapse (1) data concerning operations for recurrent POP have not been specifically presented but have been pooled with the data of primary operations.

The use of meshes in prolapse surgery evolved during the late 1990's, probably mostly due to reports of the high cure rate with use of meshes in hernia repair but also due to the reports of high recurrence rates after conventional vaginal prolapse surgery. Several types of graft material, - synthetic and biologic; non-absorbable and absorbable; auto-, allo- or xenografts, have been used (8). The results have been contradictory and recommendations for the use of meshes in POP surgery vary (9). The synthetic meshes seemed to exhibit a high risk of complications in particular with mesh erosions (10). This side-effect seemed to be significantly less pronounced when using biologic meshes. Thus biologic grafts were considered to be more ideal in POP surgery. Pelvicol™ is a biologic xenograft acellular collagen matrix. It consists of sterile, biocompatible, cross-linked porcine dermal collagen that readily incorporates into host tissue. When Pelvicol™ was introduced in Sweden in 2000 we found it of interest to use this graft in the surgical treatment of recurrent POP. The women with recurrent POP were chosen basically because of the lack of randomized studies on Pelvicol™ in prolapse surgery and a presumed higher efficacy of the mesh on objective outcome measures after reoperation for POP. Besides, from an ethical point of view it seemed acceptable to use reinforcement material in this group of women since conventional treatment had already failed, and a new operation with the conventional technique could be anticipated to give an outcome less favorable than that of the primary operation.

The objectives of this randomized, open, controlled multicenter study were to determine the long-term effectiveness of use of the Pelvicol™ graft in recurrent POP surgery by means of objective and subjective measures and to analyze risk factors and complication rates. We hypothesized that use of Pelvicol™ graft to augment the native fascial structures in POP would improve the objective and subjective outcome compared with use of traditional colporrhaphy in surgery for recurrent POP.

## **Material and methods**

An open randomized controlled multicenter study was conducted comparing conventional colporrhaphy with vaginal repair using porcine dermal implant in women with recurrent POP. Eight Swedish hospitals participated. Women who were admitted to the departments of obstetrics and gynecology in these hospitals for surgical treatment of recurrent POP in the anterior and/or posterior vaginal compartment were eligible. Recurrent POP was defined as a relapse in a site previously operated upon for prolapse. The study was approved by the ethical research committees of Gothenburg University, Örebro University and Linköping University.

The study was performed between November 2003 and April 2010. Sample size was based on the assumption that a 15% difference in objective cure rate after three years between the implant-augmented repair and the traditional anterior/posterior colporrhaphy with 90% power should be significant at a 5%-level. It was estimated that totally 160 women, 80 in each arm, including a drop-out of 10%, were needed.

Randomization was carried out as a block randomization. A computer generated the randomization sequences into blocks of 10 with equal number of the two modes of surgery for each of the eight participating centers. The allocated mode of surgery was written on a label that was sealed in opaque consecutively numbered envelopes. The centers were assigned one to three blocks corresponding to the expected number of eligible patients at the hospital.

The women were required to give informed written consent before entering into the study. At each center the envelopes were opened in consecutive number order of patient inclusion before start of surgery in the operating theatre. The participant received information about the allocated mode of surgery after the surgery.

The prolapse was evaluated by means of the pelvic organ prolapse quantification system (POP-Q) (11) preoperatively, three months and three years postoperatively. The pelvic examination was conducted in the lithotomy position. For the purpose of this study only points Ba and Bp are presented. Objective anatomically cure was defined as POP-Q less than stage 2 in the compartment operated upon. Women who had a relapse of the prolapse after the operation in the study and underwent additional POP surgery during the follow-up period were not followed further, according to the study protocol. In the analyses of the objective outcomes three years after surgery, the POP-Q status evaluated immediately prior to the relapse surgery was used as a substitute for the otherwise lacking measurements at the 3-year follow-up.

In order to assess symptoms the women completed a questionnaire deriving from the validated questionnaire by Mouritsen et al. (12) encompassing questions covering vaginal, urinary and anorectal symptoms and sexual issues. The questions were constructed as simple sentences and the answers were given by placing a cross next to the written alternatives indicating the frequency of occurrence of the symptom or condition.

Surgery was intended to be carried out following standardized procedures. To achieve maximal agreement on surgical technique the participating surgeons met at two workshops before the start of the study. It was allowed to plicate the levator ani muscles and to perform a perineoplasty if the attachments to the perineal body peroperatively were found to be disrupted and if the perineal body was deficient. Apical support was to be secured, if needed, either by fixing the vaginal apex to the sacrouterine ligaments or to the sacrospinous ligament. In case of overt stress urinary incontinence the surgeon was allowed, but was not required, to perform an incontinence operation simultaneously with the prolapse operation. Mode of anesthesia was left to the discretion of the surgeon and anesthesiologist.

The conventional anterior and posterior colporrhaphies were performed according to the methods described by Thomson et al. with midline fascial plication (13,14) using interrupted polydioxanon absorbable sutures. The vaginal wall was eventually closed with polyglactin 910 or Polysorb™ absorbable sutures ([www.syneture.com](http://www.syneture.com)).

When Pelvicol™ (BARD, Norden AB, Helsingborg, Sweden) was used, the vaginal wall was opened in a similar way by midline incision. The porcine dermal implant (Pelvicol™) was used as an inlay covering the fascial defect between the vaginal fascial layer and the underlying cysto- or rectocele and with no other reconstructive measure. The size of the implant was adjusted in order to fit the surgical field and to be able to be anchored without tension. The implant was anchored to the vaginal and pelvic fascia with six to eight polydioxanon absorbable sutures. Finally, the vaginal wall was closed with polyglactin 910 or Polysorb™ absorbable sutures. No drainage was used.

### *Statistical analyses*

For statistical analyses the severity of symptoms were dichotomized categorically as presence of symptom once or more per week versus less than once per week and the degree of prolapse as prolapse less than stage 2 or stage 2 or more.

Data are presented as number and percent or median and range. Univariate analyses were executed by means of Mann Whitney U-test for continuous data and Yates' corrected  $\chi^2$  test and Fishers' exact test, when appropriate, for nominal data. A  $p < 0.05$  (two-sided) was

considered significant. Analyses of outcome variables were done by means of multiple logistic regression models. Adjustment was done for known risk factors for prolapse and recurrence: age, number of deliveries, body mass index (BMI) and previous hysterectomy. In the objective outcome variables the preoperative stage of the prolapse was added as a confounder and in the subjective outcome parameters the preoperative occurrence of the specific symptom was included. Results are presented as odds ratios (OR's) and 95% confidence interval (CI). The software StatView<sup>®</sup> for Windows, Copyright©, 1992-1998, Version 5.0.1 (SAS Institute Inc., SAS Campus Drive, Cary, NC 27513, USA) was used for the statistical analyses.

## **Results**

The flow chart of the study participants is shown in Figure 1. Demographic and clinical data at baseline are presented in Table 1. Per- and postoperative data are presented in Table 2. Concomitant vaginal hysterectomy was done significantly more often in the conventional colporrhaphy group (CCG) than in the Pelvicol<sup>TM</sup> implant group (PG). Ten women had additional POP surgery 3 – 35 months after the study operation, 5 in the CCG and 5 in the PG.

### *Anatomic outcome*

The anatomic outcomes regarding recurrence of prolapse of the anterior and posterior compartments at the 3-month and 3-year follow-up are shown in Table 3. Significantly more women in the PG had early recurrence/surgical failures at the 3-month follow-up in the anterior compartment than in the CCG but at the 3-year follow-up the recurrence rates had leveled out and did not differ significantly. Likewise development of de-novo prolapse components at the 3-year follow-up did not differ significantly between the CCG and PG (in the anterior compartment: 15.8% (3/19) vs. 5.0% (1/20), adjusted OR 0.26 (0.02-3.32) and in the posterior compartment: 7.7% (2/26) vs. 11.4% (4/35), adjusted OR 2.17 (0.33-14.29)).

Overall 58% (38/65) of the women in the PG had recurrent prolapse three years after the operation a frequency not significantly different from the 67% (41/61) among the women in the CCG (adjusted OR 0.70 (0.33-1.48)). No significant differences were seen in recurrence rates in relation to the extent of the surgery, i.e. surgery in anterior or posterior compartment only or combined anterior and posterior compartments (data not shown).

### *Symptom outcome*

The prevalence of symptoms is shown in Figure 2. No significant differences for any of the symptoms were observed preoperatively between the two groups. The prevalence of the prolapse-related symptoms pelvic pressure and heaviness, and feeling of a vaginal lump decreased considerably after surgery. At the 3-year follow-up the feeling of a vaginal lump occurred significantly more often in women in the PG than in the CCG (adjusted OR 7.75 (1.27-47.62)) whereas no significant differences were observed between the groups as concerned prevalence of pelvic pressure and heaviness, urinary and fecal incontinence, digitations, being sexually active or dyspareunia.

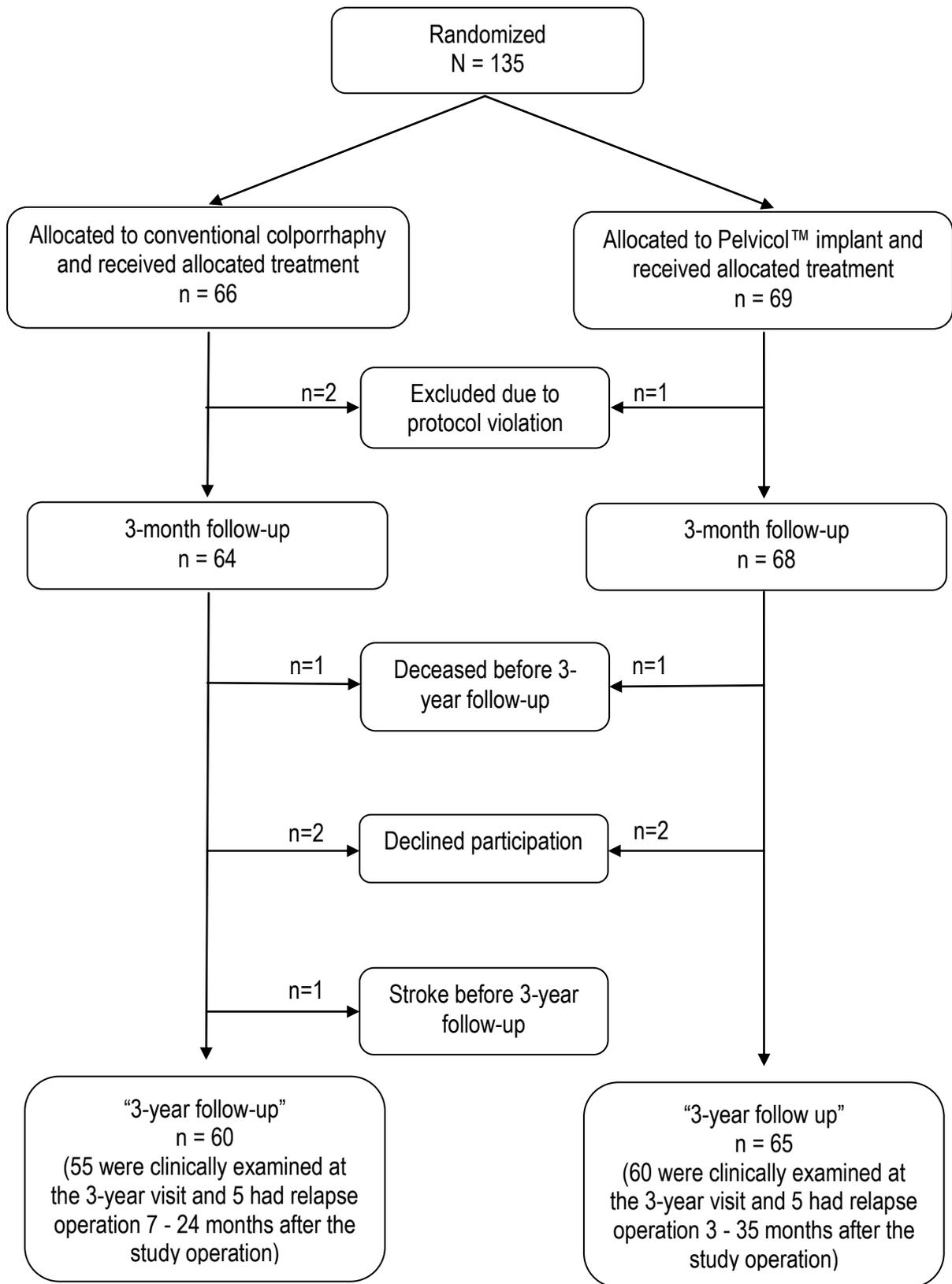


Figure 1. Flow chart of participants in the study.

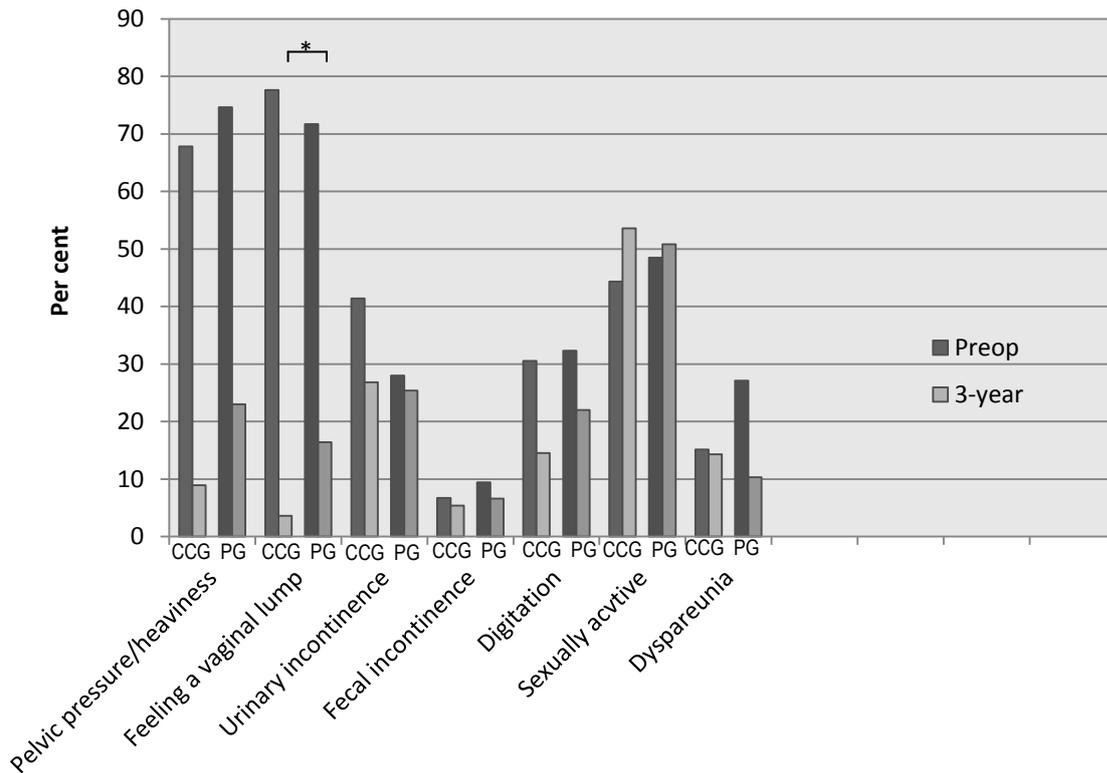


Figure 2. Prevalence of symptoms preoperatively and at the 3-year follow-up in the Conventional colporrhaphy group (CCG) and the Pelvicol™ implant group (PG). \* indicates significant difference between CCG and PG,

Eighty four percent of the women in the PG and 85% in the CCG declared at the 3-year follow-up that the operation had improved or cured their pelvic symptoms.

### Risk factors

Of the analyzed confounding factors used in the multiple logistic regression models, BMI was found to be an independent risk factor for feeling of a vaginal lump (OR 1.36 (1.11-1.67)), pelvic pressure and heaviness (OR 1.24 (1.05-1.45)) and not being sexually active (OR 1.27 (1.06-1.51)). Age was an independent risk factor for pelvic pressure and heaviness (OR 1.08 (1.01-1.16)), and for not being sexually active (OR 1.25 (1.13-1.38)). The preoperative stage of the prolapse and preoperative state for all the symptoms that were evaluated except pelvic pressure and heaviness and feeling a vaginal lump were strong independent risk factors with OR's ranging from 4.02 to 489.00. Experience of pelvic pressure and heaviness and feeling a

vaginal lump three years after the operation were not associated with the corresponding symptom preoperatively.

*Complications*

Two women in the PG presented with minor mesh erosion (4.4%) two weeks and three months, respectively, after the operation. These were treated conservatively and healed spontaneously. Two women in the PG and one in the CCG developed local infection postoperatively; all treated successfully with one course of antibiotics per orally. Four women in the PG and one in the CCG developed transient urinary retention postoperatively. Three women in the PG developed vaginal stenosis that was treated with dilatation in two of the cases and plastic operation in the last case. None of these three women had had perineoplasty, but plication of the levator ani muscles had been performed in one.

## **Discussion**

This study showed that the use of porcine dermal graft in recurrent pelvic organ prolapse surgery did not reveal superiority in objective and subjective outcomes compared with conventional colporrhaphy. It seemed that early recurrence/surgical failure was more common in women who had the porcine dermal graft, in particular in the anterior vaginal compartment, but this was made up for after three years. Prolapse symptoms decreased considerably after surgery in both groups, but the feeling of a vaginal lump was significantly more often experienced after Pelvicol™ graft implant. Complication rates were low and no serious or severe complications were seen.

This study is to the best of our knowledge the first randomized study that compares Pelvicol™ with conventional colporrhaphy in recurrent POP surgery. The strengths of the study are in addition to the randomized design the multicenter approach, which makes the results more likely to represent the general everyday work experience in the clinics. There are however, some methodological limitations. The study is open and it is therefore possible that the patient's knowledge of the method used could bias the subjective outcomes, but hardly the objective outcomes. The study material is heterogeneous concerning size and extent of prolapse. We included women with recurrent prolapse in the anterior and/or posterior compartment and it may therefore be more difficult to interpret the results. However, due to the fact that only a selected group of women with recurrent POP was admitted for recurrent surgery it was difficult to obtain a homogenous population concerning size and extent of prolapse of sufficient size in a reasonable time span.

Recruitment of the planned number of women was anticipated to take two years. Due to a much lower number of patients admitted to the clinics with recurrent prolapse than anticipated we decided to close the recruitment after four years of inclusion. At that time 135 women were included in the study. Prior to this decision we considered to include more centers in the study in order to obtain the planned number of patients in the study. However, it was not practically possible to do this since new devices with synthetic meshes in prolapse surgery (as for instance Gynecare Prolift™, [www.ethicon360.com](http://www.ethicon360.com)) had been introduced and gained wide acceptance among urogynecologists during the study period. We were as result not able to reach the estimated power of 90% in the study. However, given the same constraints and with 130 participants the study would have had an estimated power of more than 80%. The sample size estimation was based on a comparison between colporrhaphy and Pelvicol™ graft implant. Ideally consideration in the power calculation should have been

taken to the subgroups of combinations of surgical procedures, and size and extent of the prolapse.

A few women had a concomitant operation in a compartment that was preoperatively classified as stage 0-1. The decision about that intervention was made by the surgeon during surgery if the prolapse was considered larger than at the preoperative examination and a weakness was found in the compartment and the patient simultaneously had symptoms.

Vaginal hysterectomy was executed significantly more often in the CCG compared with the PG. This probably reflects a selection bias. The surgeons might be more prone to avoid the more extensive surgery and thereby increased risks of infection when an implant was to be put in place.

Since we started the study two randomized studies have been published presenting results of primary POP surgery comparing traditional colporrhaphy with Pelvicol™ reinforcement (15,16). The results of these two studies were contradictory. One of the studies reported a benefit in anatomical outcome after Pelvicol (15) whereas in the other no difference in anatomical outcome was found (16). However, the surgical technique differed significantly concerning the Pelvicol group which may explain in whole or in part the different outcomes. Meschia et al. plicated the vaginal fascia before applying and anchoring the Pelvicol™ mesh (15) whereas Hvid et al. refrained from this and anchored the graft laterally to the pubocervical fascia and distally to the cardinal ligament/cervix (16). Thus in the former study the mesh was used as a support in an anterior colporrhaphy whereas in the latter it was used as a substitute for a defective fascia, i.e. as a direct hammock. In the present study we used a similar technique as that described by Hvid et al.. Whether the technique described by Mechia et al (15) using the Pelvicol™ as an support of a colporrhaphy also would be superior to conventional colporrhaphy in recurrent POP surgery is not known.

The recurrence rates after primary surgery with use of Pelvicol vary from 7- 46 % . (15-19). In the present study the anatomical recurrence rates in the anterior and posterior compartments were high in both groups; 57 – 62% in the anterior compartment and 17 – 40% in the posterior compartment. However, the recurrence rates vary between 28-70 % (20-23) after primary prolapse surgery with anterior colporrhaphy and after posterior colporrhaphy in 8-24% (20,22,24-26). Recently, Peterson et al. presented a retrospective case–control study of recurrent prolapse surgery with anterior colporrhaphy showing a recurrence rate of cystocele of 57% compared with 29% for women with primary surgery (6). The reason for the high recurrence rate in anatomical outcomes in our study is most likely multifactorial with a combination of surgical related and pathophysiological factors as main causes.

Symptoms related to prolapse were reduced substantially by the surgery, independent of mode of surgery, in spite of a high anatomical recurrence rate. It is well known that there are disagreements between stage and symptoms of prolapse (27,28). Miedel et al. found a high anatomical recurrence rate but less than one-fourth of the women with recurrence were symptomatic (22). Tegerstedt et al. stated that an unsatisfactory anatomic outcome of prolapse surgery was not necessarily associated with symptoms (3). Our study seemed to support this. The reason for the discrepancy in anatomical outcome and symptoms is still unknown. In accordance with other studies sexual life did not seem to be influenced negatively by use of Pelvicol (15,17,26). Besides, the women who had conventional colporrhaphy did not seem to be adversely affected in sexual activity either. This is in accordance with the findings by Abramov et al. (25) and probably reflects restricted use of levator ani muscle plication.

The analyses showed that age, BMI and POP stage were risk factors for a poor outcome of recurrent POP surgery. These factors are all known risk factors even in primary POP surgery and seem to be factors reflecting systemic pathophysiological conditions for developing pelvic floor insufficiency (29). How the risk factors can be used as preventive measures, i.e. to obtain better outcome after primary as well as recurrent prolapse surgery, is still unclear. Should obese women with POP undergo weight reduction prior to surgery? Or should women with POP be advised to undergo surgery at a lower age before the symptoms becomes too severe or the prolapse becomes too large? These questions need to be addressed in well conducted studies.

The complication rate was low after use of Pelvicol™. In particular troublesome mesh erosion was not seen and no rejection of the implant occurred which is in accordance with findings presented by others (15,16,18,19).

In conclusion, Pelvicol™ does not seem to improve anatomical or subjective outcomes more than traditional colporrhaphy in recurrent POP surgery with the surgical technique used in this study. The results of this study illustrate and emphasize the importance of scientific evaluation before new surgical methods are introduced in clinical practice. More studies are needed using biomesh, - Pelvicol™ or others, as reinforcement after suturing of existing fascia defects and with more focus on standardization of surgical technique and directly comparable treatment arms by surgical procedure.

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**Disclosure of Interests**

None of the authors or “RPOP-Pelvicol Study Group” members has any conflicts of interest to declare.

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## **Legends to Tables and Figures**

Table 1. Demographic and clinical data at baseline.

Table 2. Per- and postoperative data.

Table 3. Recurrence rates three months and three years following prolapse surgery with conventional colporrhaphy (the Conventional Colporrhaphy Group (CCG)) or implant with Pelvicol<sup>TM</sup> (the Pelvicol<sup>TM</sup> Group (PG)).

Figure 1. Flow chart of participants in the study.

Figure 2. Prevalence of symptoms preoperatively and at the 3-year follow-up in the Conventional colporrhaphy group (CCG) and the Pelvicol<sup>TM</sup> implant group (PG). \* indicate significant difference between CCG and PG.



Table 2. Per- and postoperative data.

	Conventional colporrhaphy group n = 64		Pelvicol™ implant group n = 68		p-value
Mode of anesthesia:					
General anesthesia	22	34%	23	34%	0.384#
Spinal anesthesia	42	66%	43	63%	
Local anesthesia	0	0%	2	3%	
Site of prolapse surgery:					
Anterior compartment	26	41%	36	53%	0.201#
Posterior compartment	20	31%	21	31%	
Ant. and post. compartment	18	28%	11	16%	
Levator ani muscle plication	7	11%	6	9%	0.908##
Perineoplasty	18	29%	14	21%	0.390##
Concomitant vaginal hysterectomy *	12	30%	4	11%	0.045†
Concomitant vaginopexy**	11	17%	7	10%	0.348##
Concomitant surgery for SUI	2	3%	5	7%	0.443†
Per-operative bleeding volume (mL)	50	0-500	50	0-100	0.182¥
Transurethral catheter (days)	1.0	0-3	1.0	0-7	0.802¥
Time in hospital (days)	2.0	0-5	2.0	0-6	0.610¥
POP-Q at 3.month follow-up:	n=64		n=68		
Point Ba (cm)	-2.0	-3-1	-1.5	-3-2.5	0.395¥
Point Bp (cm)	-2.5	-3-1	-2.3	-3-4	0.732¥
POP-Q at 3-year follow up:	n=61		n=65		
Point Ba (cm)	-1.0	-3-3	-1.5	-3-5	0.996¥
Point Bp (cm)	-2.0	-3-2	-2.5	-3-4	0.220¥

Figures indicate number and % or median and range. SUI = stress urinary incontinence

\* Percent of those who had a uterus. \*\* Sacrouterine or sacrospinous ligament fixation.

# Yates' corrected  $\chi^2_{df=2}$ ; ## Yates' corrected  $\chi^2_{df=1}$ ; † Fishers' exact test; ¥ Mann Whitney U-test.

Table 3. Recurrence rates three months and three years following prolapse surgery with conventional colporrhaphy (the Conventional Colporrhaphy Group (CCG)) or implant with Pelvicol™ (the Pelvicol™ Group (PG)).

	CCG % (proportion†)	PG % (proportion †)	OR (95% CI)	Adjusted OR (95% CI)*
3-month follow-up				
Ba ≥ -1 cm	39% (17/44)	57% (27/47)	2.14 (0.93 -4.96)	2.53 (1.03-6.25)
Bp ≥ -1 cm	26% (10/38)	16% (5/32)	0.52 ( 0.16-1.72)	0.40 (0.11-1.53)
3-year follow-up				
Ba ≥ -1 cm	57% (24/42)	62% (28/45)	1.24 (0.52-2.91)	1.41 (0.57-3.45)
Bp ≥ -1 cm	40% (14/35)	17% (5/30)	0.30 (0.09-0.97)	0.43 (0.12-1.56)

† Number of recurrences/the number of women having operation in the compartment

\* Adjusted for age, parity, BMI, hysterectomy and preoperative POP stage.

## **Appendix**

Besides the authors the Recurrent Pelvic Organ Prolapse (RPOP) - Pelvicol Study Group consisted of:

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