

The Association Between Pelvic Organ Prolapse, Pelvic Pain and Pelvic Reconstructive Surgery Using Transvaginal Mesh: A Secondary Analysis of a Prospective Multicenter Observational Cohort Trial

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Abstract

Background: The aims of the study were to examine the type, severity and prevalence of pain in women with pelvic organ prolapse (POP) before and after pelvic floor reconstructive surgery, and to evaluate the effect of POP reconstruction over a period of 2 years.

Methods: The study data were collected in a past multicenter prospective study (Propel-Study; ClinicalTrials.gov. Identifier: NCT00638235), where a total of 281 women with stage 2-4 symptomatic POP underwent prolapse repair using the transvaginal, single-incision “Elevate” technique for anterior/apical and posterior/apical prolapse. The degree of POP repair during a follow-up of 2 years was the primary endpoint of the study and has already evaluated previously. In the Propel trial subjective assessments of presumable POP symptoms before and 6, 12 and 24 months after surgery were registered too utilizing the pelvic floor disorder inventory (PFDI) questionnaire. The investigation of all or specific domains of PFDI symptoms were declared as secondary objectives of that study. The present treatise is concentrated on the evaluation of the PFDI pain symptoms consisting of six questions for describing different types of pain.

Results: Preoperatively, 67% of all POP patients reported moderate-to-severe pain, mainly of visceral character. Pelvic floor reconstructive surgery resulted in significant cure or improvement in all pain

types, intensities and locations, and these improvements were stable over 2 years. The largest reduction in pain symptoms following POP repair was registered for visceral complaints (87%), followed by the anterior (84%) and then the posterior (45%). Patients with cystocele had significantly more pain pre- and postoperatively than those with enterocele/rectocele. The best cure effects overall were achieved in cystocele patients with visceral or anterior pain (> 96%). No correlation was found between POP stage and pain intensity preoperatively. The best pain cure rates after surgery were obtained in patients with pronounced POP and pain in the visceral and anterior areas (> 93%). Surgically induced *de novo* pain improved with time from 16% (6 months) to 11% (12 months) and then 7% (24 months).

Conclusion: POP of stage 2 and greater can be associated with moderate-to-severe pain, which can be improved and cured by mesh-supported prolapse repair. Postoperative *de novo* pain does occur, although its incidence and severity appear to be reduced over time.

Keywords: Chronic pelvic pain; Pelvic organ prolapse; Posterior fornix syndrome; Pelvic floor reconstruction; Pelvic mesh

Introduction

The use of alloplastic materials in pelvic floor reconstruction can produce *de novo* pain [1-4]. Reports of adverse events including pain and missing evidence that the probable benefit of the mesh devices outweighs their probable risks influenced the Federal Drug Administration (FDA) to order that all manufacturers in the United States had to stop selling and distributing surgical meshes for transvaginal repair of anterior compartment prolapse in April 2019 [4]. Introduction of microporous light-weight mesh should reduce tissue reaction and infection rate and presumably pain [5, 6]. It has been suggested that meshes should be avoided in women with pre-existing chronic pain syndromes [7].

On the other hand, pelvic pain is reported to be caused by pelvic organ prolapse (POP) and eventually be cured by adequate pelvic floor surgery [8, 9].

In 1938, Heinrich Martius stated that in approximately

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30% of cases, backaches were attributed to organic factors provoked by damaged suspensory or supportive ligaments of the pelvic organs [10, 11].

In 1993, Petros and Ulmsten described chronic pelvic pain syndrome (CPPS) as being caused by lax uterosacral ligaments as part of the “posterior fornix syndrome” [12], along with other pelvic symptoms such as nocturia, urgency and abnormal emptying. They reported a significant cure rate of CPPS and other posterior fornix symptoms following repair of the uterosacral ligaments and vaginal apical reconstruction [12].

In an extensive review in 2015, Goeschen [8] explained how sympathetic (T12-L2), parasympathetic (S2-S4) and somatic nerves (S2-S4) could be stretched in women with POP and cause different pain qualities and localizations, from lower abdominal and posterior area pain to pelvic pain and vulvodynia.

Despite these publications, definitions of and numerous review papers on chronic pelvic pain (CPP) and bladder pain syndrome (BPS) either fail to mention [13-23] or mention purely peripherally [24] the possible causal relationship between POP and CPP. And in none of these reviews is surgical POP repair identified as a plausible treatment option.

CPP affects many women, and it has been debated to date on whether the existence of POP is an independent risk factor for CPP. In 2004, Williams et al [25] reviewed the existing literature using “chronic pelvic pain” as a keyword and selected articles focusing on the duration, location and definition of CPP. Disappointingly, they found a number of notable omissions within these publications: 93% did not specify the location of pain, 44% did not specify the duration, 74% did not address etiology or pathology in their definitions and 95% did not consider comorbidities.

Meanwhile, there is much more information today about CPP [8, 24]. But even today, numerous CPP conditions are still deemed to be of unknown origin. Due to the numerous possible etiologies for pelvic pain, the definition of CPP is still incongruent and ambiguous in the literature. An extract of the learned society definitions can be summarized as follows: 1) CPP is a chronic or persistent type of pain perceived in structures related to the pelvis [24]; 2) CPP is pain in the pelvic area that lasts for 6 months or longer [26]; 3) CPPS is the occurrence of CPP when there is no proven infection or other obvious local pathology that may account for the pain. CPPS is often associated with negative cognitive, behavioral, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynecological dysfunction [27, 28].

Bearing these controversies in mind, we were prompted to further analyze the data of the Propel study to investigate the interrelationship between POP and pelvic pain before and after surgical POP reconstruction, using the following hypotheses: 1) Women with a POP-defect greater than stage 1 reveal in a considerable proportion pelvic pain symptoms too, which may show some significant differences in their severity when comparing specific subgroups of the sample population; 2) Pelvic pain symptoms can be localized in specific pelvic regions showing characteristic severity profiles both in the total sample population and in some specific subgroups of it; 3) POP repair can significantly remedy type-dependent pain severity for a long time.

The profiles of pain severity from baseline to 2 years follow-up show considerable differences with respect to type of pain complaint as well to position and stage of POP.

Furthermore explorative interest of the study was directed to the incidence of *de novo* pain following mesh-supported POP repair, to the pain severity transitions between pre- and postoperative phase and to the coexistence of other pelvic floor symptoms as well.

Materials and Methods

The Propel study was conducted from 2008 to 2012 by 16 centers in the USA and Europe (urology, urogynecology and gynecology sites proficient in prolapse repair and transvaginal mesh use) to primarily assess the effect of the Elevate single-incision, transvaginal prolapse reconstruction systems (American Medical Systems, Minnetonka, MN, USA) on the anatomical correction of anterior/apical or posterior/apical prolapse stage ≥ 2 , with anatomical success being defined as POP \leq stage 1. Institutional review board (IRB) approval was obtained by all centers. This study was conducted in compliance with the ethical standards of the responsible institutions on human subjects as well as with the Helsinki Declaration.

The various outcome measures, the inclusion and exclusion criteria are reported in the ClinicalTrials registration [29].

Secondary endpoints included a variety of quality of life (QOL) measures through utilization of the pelvic floor distress inventory (PFDI) questionnaire at baseline and 6, 12 and 24 months postoperatively. This observational study was done to evaluate the effect of POP reconstruction specifically on pain symptoms.

In the Propel study, a total of 281 female patients with POP (\geq stage 2) and a mean age of 63.2 ± 10.6 years were included in the Propel study. Four patients with incomplete data in the PFDI questionnaire were excluded. This study therefore concentrated on 277 patients with anterior/apical POP ($n = 142$) and posterior/apical POP ($n = 135$). According to the POP quantification system (POP-Q), 122 patients had stage 2 POP, and 150 had stage 3 or 4 POP.

Pain-related symptoms were identified by PFDI questions 1 (pressure in the lower abdomen), 2 (pain in the lower abdomen or genital area), 3 (heaviness or dullness in the pelvic area), 6 (pelvic discomfort when standing or upon physical exertion), 7 (pain in the lower posterior area most days) and 46 (abdominal or lower posterior area pain when straining for any reason). The six types of pain symptoms could be well assigned to three complaint areas: “anterior area” (PFDI 1, 2), “visceral area” (PFDI 3, 6) and “posterior area” (PFDI 7, 46). On the PFDI, subjective answers and corresponding scoring related to these pain symptoms with respect to degree of bother include: “no symptoms” = score 0, “yes/not at all bothersome” = score 1, “somewhat bothersome” = score 2, “moderately bothersome” = score 3, or “quite a bit bothersome” = score 4. Values were obtained at baseline, then postoperatively at 6, 12 and 24 months. The hypotheses of the study were predominantly focused on the “moderately or quite a bit” bother of the symptoms or equivalently on symptom-intensity scores ≥ 3 .

Statistical analyses

Given the categorical data structure of the investigated pain symptoms, statistical evaluation was mainly based on frequency analyses related to single or combined (compound) symptom outcomes. To the later belongs the compound outcome “R2” that corresponds to a “moderately or quite a bit” bothersome symptom assessment, and its pedant “R1” that corresponds to a “no symptoms or yes/not at all or somewhat” bothersome symptom assessment.

Towards the pain location regions, statistical analysis was additionally performed on two specific pain events defined as follows: “irrelevant pain complaints” (IPCs), when both symptoms of the corresponding region were evaluated in terms of their severity in patients with R1, and “relevant pain complaints” (RPCs), when at least one of the two symptoms were evaluated in patients with R2. By considering the “complete pelvic area”, to which all pain symptoms (PFDI 1, 2, 3, 6, 7 and 46) belonged, IPC was then defined as pain events occurring in a patient when all symptoms demonstrated R1 severity, while RPC was defined as pain events occurring in a patient when at least one of the six symptoms demonstrated R2 severity.

Group comparisons in terms of the frequency distribution of the symptom outcomes were performed on the basis of χ^2 -tests or Fisher’s exact tests. Associations between symptoms with categorical data structure were also statistically evaluated with the χ^2 -test for independence.

Global and simple effects of POP repair on the incidence of R2 and other specific outcomes/events of the considered pain symptoms were tested for significance with Cochran’s Q tests followed by McNemar localization tests.

Moreover, the effects of POP repair on R2 and regional dependent pain events were investigated under the additional consideration of location and degree of the anatomical POP defect.

Results

Baseline distribution of pain severity

Type-dependent pain

In view of the first hypothesis of the study, statistical analysis was focused on the baseline pain severity distribution within the total sample population and within some interesting sub-samples as well.

Table 1 demonstrates the absolute and relative preoperative frequencies of the four pain intensities: “no or not at all” (symptom-free), “somewhat”, “moderate”, “quite a bit” and the combination of “moderate” or “quite a bit” (R2) for the six PFDI types 1, 2, 3, 6, 7 and 46 in the following groups: 1) total population (tP, n = 277); 2) anterior/apical POP (aaP, n = 142) and posterior/apical POP (paP, n = 135); 3) stage 2 POP (S2P, n = 122) and stage 3 or 4 POP (S34P, n = 150).

In tP group (Table 1), the “symptom-free” outcome of

the six PFDI types had a prevalence rate between 38.6% and 60.3%, a “somewhat” outcome between 15.20% and 22.1%, a “moderate” outcome between 13.4% and 20.9% and a “quite a bit” outcome between 13.04% and 22.7%.

All six pain sensations were found in patients with aaP, paP, S2P and S34P. Regarding R2, PFDI 6 was the most frequent pain type (40.8%), followed by PFDI 7 (37.9%), PFDI 1 (32.9%), PFDI 3 (27.1%), PFDI 46 (24.6%) and PFDI 2 (22.8%).

Patients with paP vs. aaP suffered significantly more from R2 complaints regarding the pain types PFDI 1 (37.0% vs. 28.9%), 2 (28.1% vs. 17.7%), 3 (34.1% vs. 20.5%) and 7 (43.0% vs. 33.1%) (Fisher’s exact tests, $P < 0.05$). Between 35.9% and 67.6% of women with aaP and 40.0-54.8% of women with paP were pain-free preoperatively.

Concerning the various pain types identified by PFDI 1, 2, 3, 6, 7 and 46, S2P vs. S34P patients reported R2 pain frequencies in the range of 23.8-39.4% vs. 21.4-42%. Considering all pain types, 18.4% of S2P patients exhibited “somewhat”, 19.1% “moderately” and 16.9% “quite a bit” complaints. In S34P patients, the average frequency distribution was “somewhat”, “moderately” and “quite a bit” in 18.7%, 6% and 14.3%, respectively. Pain types and intensity were not significantly different.

In summary we can say that about 40% of women with POP stage greater than 1 show in the baseline relevant pain severity (R2) by at least one pain type. When comparing the R2 prevalence of the various pain symptom types between paP and aaP as well as between S2P and S34P we found by four of the six pain symptoms significant differences between paP and aaP.

Location-related pain

In terms of location-related pain, the focus of the statistical analysis was on the two pain events IPC and RPC.

Concerning tP, a breakdown of pain complaint into anterior, visceral or posterior area resulted in RPC frequencies of 37.9%, 46.6% and 44% (Table 2). Evaluating the subgroups, the distribution of pain complaint to anterior, visceral or posterior in aaP was 34.5%, 49.0% and 38.7%; in paP, 41.1%, 50.4% and 49.6%; in S2P, 39.3%, 43.4% and 45.1%; and in S34P, 36.7%, 49.3% and 43.3%.

The anterior vs. visceral/posterior complaints showed the fewest RPC frequencies in tP and subgroups (Table 2). However, statistically significant differences were found entirely between the anterior and visceral complaints in the tP and S34P.

Furthermore, the data showed that aaP vs. paP patients suffered less frequently from RPC in all complaints (anterior + visceral + posterior) (61.2% vs. 74.1%) as well as in the anterior (34.5% vs. 41.5%), visceral (43.0% vs. 50.4%) and posterior (38.7% vs. 49.6%) complaints (Table 2). However, the differences were only statistically significant for all complaints (χ^2 -tests, $P < 0.05$).

Interestingly, POP stage did not significantly influence the frequency of relevant pain in any of the considered pain complaints (Table 2).

Table 1. Baseline Prevalence of the Four Symptom Outcomes and the Combination R2 Regarding the PFDI Symptoms in Patient Groups

Preoperative pain symptoms	Total population (n = 277)		Posterior/apical (n = 135)		Anterior/apical (n = 142)		POP-Q stage 2 (n = 122)		POP-Q stage 3 or 4 (n = 150)	
	Absolute frequency	Relative frequency	Absolute frequency	Relative frequency	Absolute frequency	Relative frequency	Absolute frequency	Relative frequency	Absolute frequency	Relative frequency
PFDI 1 (pressure in the lower abdomen)										
Symptom-free	131	47.30%	56	41.50%	75	52.80%	55	45.10%	73	48.70%
Somewhat	55	19.90%	29	21.50%	26	18.30%	24	19.70%	30	20.00%
Moderate	47	17.00%	23	17.00%	24	16.90%	20	16.40%	27	18.00%
Quite a bit	44	15.90%	27	20.00%	17	12.00%	23	18.90%	20	13.30%
R2 (moderate or quite a bit)	91	32.90%	50	37.00% ^a	41	28.90% ^a	43	35.30%	47	31.30%
Observed cases	277	100.0%	135	100.0%	142	100.0%	122	100.0%	150	100.0%
PFDI 2 (pain in the lower abdomen or genital area)										
Symptom-free	167	60.30%	74	54.80%	93	65.50%	75	61.50%	90	60.00%
Somewhat	47	17.00%	23	17.00%	24	16.90%	18	14.80%	28	18.70%
Moderate	37	13.40%	25	18.50%	12	8.50%	16	13.10%	19	12.70%
Quite a bit	26	9.40%	13	9.60%	13	9.20%	13	10.70%	13	8.70%
R2 (moderate or quite a bit)	63	22.80%	38	28.10% ^b	25	17.70% ^b	29	23.80%	32	21.40%
Observed cases	277	100.0%	135	100.0%	142	100.0%	122	100.0%	150	100.0%
PFDI 3 (heaviness or dullness in the pelvic area)										
Symptom-free	141	50.90%	63	46.70%	78	54.90%	62	50.80%	77	51.30%
Somewhat	61	22.00%	26	19.30%	35	24.60%	27	22.10%	33	22.00%
Moderate	39	14.10%	24	17.80%	15	10.60%	13	10.70%	25	16.70%
Quite a bit	36	13.00%	22	16.30%	14	9.90%	20	16.40%	15	10.00%
R2 (moderate or quite a bit)	75	27.10%	46	34.10% ^c	29	20.50% ^c	33	27.10%	40	26.70%
Observed cases	277	100.0%	135	100.0%	142	100.0%	122	100.0%	150	100.0%
PFDI 6 (pelvic discomfort during standing or physical exertion)										
Symptom-free	107	38.60%	56	41.50%	51	35.90%	53	43.40%	51	34.00%
Somewhat	57	20.60%	23	17.00%	34	23.90%	21	17.20%	36	24.00%
Moderate	58	20.90%	29	21.50%	29	20.40%	23	18.90%	34	22.70%
Quite a bit	55	19.90%	27	20.00%	28	19.70%	25	20.50%	29	19.30%
R2 (moderate or quite a bit)	113	40.80%	56	41.50%	57	40.10%	48	39.40%	63	42.00%
Observed cases	277	100.0%	135	100.0%	142	100.0%	122	100.0%	150	100.0%
PFDI 7 (pain in lower back most days)										
Symptom-free	126	45.50%	54	40.00%	72	50.70%	56	45.90%	68	45.30%
Somewhat	46	16.60%	23	17.00%	23	16.20%	20	16.40%	24	16.00%
Moderate	42	15.20%	24	17.80%	18	12.70%	15	12.30%	26	17.30%

Table 1. Baseline Prevalence of the Four Symptom Outcomes and the Combination R2 Regarding the PFDI Symptoms in Patient Groups - (continued)

Preoperative pain symptoms	Total population (n = 277)		Posterior/apical (n = 135)		Anterior/apical (n = 142)		POP-Q stage 2 (n = 122)		POP-Q stage 3 or 4 (n = 150)	
	Absolute frequency	Relative frequency	Absolute frequency	Relative frequency	Absolute frequency	Relative frequency	Absolute frequency	Relative frequency	Absolute frequency	Relative frequency
Quite a bit	63	22.70%	34	25.20%	29	20.40%	31	25.40%	32	21.30%
R2 (moderate or quite a bit)	105	37.90%	58	43.00% ^d	47	33.10% ^d	46	37.70%	58	38.60%
Observed cases	277	100.0%	135	100.0%	142	100.0%	122	100.0%	150	100.0%
PFDI 46 (abdominal or lower back pain when straining for any reason)										
Symptom-free	167	60.30%	71	52.60%	96	67.60%	68	55.70%	95	63.30%
Somewhat	42	15.20%	27	20.00%	15	10.60%	25	20.50%	17	11.30%
Moderate	36	13.00%	21	15.60%	15	10.60%	17	13.90%	18	12.00%
Quite a bit	32	11.60%	16	11.90%	16	11.30%	12	9.80%	20	13.30%
R2 (moderate or quite a bit)	68	24.60%	37	27.50%	31	21.90%	29	23.70%	38	25.30%
Observed cases	277	100.0%	135	100.0%	142	100.0%	122	100.0%	150	100.0%

The pairwise superscripts "a", "b", "c" and "d" on the relative frequencies of certain symptoms indicate significant differences between the posterior/apical and anterior/apical groups in terms of the prevalence rates of R2 (Fisher's exact tests, $P < 0.05$). PFDI: pelvic floor disorder inventory; POP-Q: pelvic organ prolapse quantification system.

Surgery and cure-duration effects on pain

POP-repair effects on type-dependent pain in the total sample population

Focusing first on the analysis of R0 ("symptom-free") and R2 outcomes ("moderately" or "quite a bit"), all six pain types (Table 3) in the tP group were significantly reduced 6, 12 and 24 months after surgery. Twenty-four months postoperatively, the R0 state was most noted by PFDI 2 in 92.4%, followed by PFDI 3 in 91.9%, PFDI 6 in 91.4%, PFDI 1 in 88.1%, PFDI 46 in 84.3% and PFDI 7 in 75.1% (Table 3). The R0 outcome was noted in all postoperative phases, while the R2 outcome was reported significantly less than noted at baseline, indicating improvement in pain symptoms (Table 3).

For each single outcome, the ranges of the prevalence rates over the six PFDI pain types showed considerable changes from baseline to 24 months after surgery. Thus, for the "symptom-free" outcome, the preoperative and 24-month postoperative prevalence rates were 38.6-60.3% and 75.1-92.4% respectively; for the "somewhat" outcome, they were 15.2-22.1% and 3.8-6.5%; for the "moderately" outcome, 13.4-20.9% and 1.6-9.2%; and for the "quite a bit" outcome, 13.4-22.7% and 1.1-8.6%. Among the six PFDI pain types, PFDI 6 showed the highest prevalence rates for the "symptom-free" and "quite a bit" outcomes 24 months after surgery (about 80% increase and 94% decrease, respectively).

POP-repair effects on location-dependent pain in the total sample population

In the tP group, the RPC frequency regarding the complete pelvic area was reduced from 67.5% preoperatively to 24.9% 24 months postoperatively, which was equivalent to a success rate of 63.1% (Table 4). The success rate for anterior was 84.4%, for visceral 87.3% and for posterior area complaints 45.2%. The postoperative prevalence rates in all three areas were significantly lower than preoperatively. Furthermore, RPC occurred significantly less often in the anterior and visceral complaints compared to the posterior 6, 12 and 24 months after surgery. And the cure rates for pain with anterior vs. posterior and visceral vs. posterior complaints were also significantly better (Table 4).

The findings of the above two sections confirm the first three hypotheses formulated in the introduction.

POP-repair effects on location-dependent pain in different subsamples

Repair effects in the aaP and paP groups

The pre- and 24-month postoperative prevalence rates of RPC in the paP subgroup were as follows: all pain complaints 74.1% vs. 31.8% (cure rate (cr) = 57.0%), anterior 41.5% vs. 9.1% (cr = 78.0%), visceral 50.4% vs. 9.1% (cr = 81.9%) and posterior 49.6% vs. 26.4% (cr = 50.4%) (Table 5).

Table 2. Absolute and Relative Frequencies of the IPCs and RPCs in the Anterior, Visceral, Posterior and the Whole Pain Complaint Area (All Areas) for Different Patient Samples Preoperatively

Location of pain symptoms	Prevalences of the irrelevant and relevant pain complaints in the front, visceral, back and all areas into different samples in the baseline											
	Total sample (n = 277)		Posterior/apical (n = 135)		Anterior/apical (n = 142)		X ² -tests for testing posterior/apical vs. anterior/apical (P-values)		POP-Q stage 2 (n = 122)		POP-Q stage 3 or 4 (n = 150)	
	Absolute frequency	Relative frequency	Absolute frequency	Relative frequency	Absolute frequency	Relative frequency	Absolute frequency	Relative frequency	Absolute frequency	Relative frequency	Absolute frequency	Relative frequency
Anterior area (PFDI 1 and PFDI 2)												
IPCs (IPC: PFDI 1 = R1 and PFDI 2 = R1)	172	62.10%	79	58.50%	93	65.50%	X ² (1) = 1.43	74	60.70%	95	63.30%	X ² (1) = 0.20
RPCs (RPC: PFDI 1 = R2 or PFDI 2 = R2)	105	37.90%	56	41.50%	49	34.50%	P = 0.231	48	39.30%	55	36.70%	P = 0.650
Total cases	277	100.00%	135	100.00%	142	100.00%		122	100.00%	150	100.00%	
Visceral area (PFDI 3 and PFDI 6)												
IPCs (IPC: PFDI 3 = R1 and PFDI 6 = R1)	148	53.40%	67	49.60%	81	57.00%	X ² (1) = 1.52	69	56.60%	76	50.70%	X ² (1) = 0.93
RPCs (RPC: PFDI 3 = R2 or PFDI 6 = R2)	129	46.60%	68	50.40%	61	43.00%	P = 0.216	53	43.40%	74	49.30%	P = 0.332
Total cases	277	100.00%	135	100.00%	142	100.00%		122	100.00%	150	100.00%	
Posterior area (PFDI 7 and PFDI 46)												
IPCs (IPC: PFDI 7 = R1 and PFDI 46 = R1)	155	56.00%	68	50.40%	87	61.30%	X ² (1) = 3.33	67	54.90%	85	56.70%	X ² (1) = 0.08
RPCs (RPC: PFDI 7 = R2 or PFDI 46 = R2)	122	44.00%	67	49.60%	55	38.70%	P = 0.067	55	45.10%	65	43.30%	P = 0.772
Total cases	277	100.00%	135	100.00%	142	100.00%		122	100.00%	150	100.00%	
Testing global and simple differences in the occurrence of relevant complaints between regions (Cochran's Q- and McNemar tests)												
		Q _(DF=2) = 6.92	Q _(DF=2) = 3.97	Q _(DF=2) = 3.32	Q _(DF=2) = 1.25	Q _(DF=2) = 7.97						
		P = 0.0314 ⁺	P = 0.137	P = 0.189	P = 0.533	P = 0.0186 ⁺						
	F/V											
All areas												
IPCs (PFDI: 1, 2, 3, 6, 7 and 46, all PFDIs = R1)	90	32.50%	35	25.90%	55	39.70%	X ² (1) = 5.52	37	21.30%	51	34.00%	X ² (1) = 1.41
RPCs (at least one of the PFDIs = R2)	187	67.50%	100	74.10%	87	61.30%	P = 0.018 ⁺	85	69.70%	99	66.00%	P = 0.519
Total cases	277	100.00%	135	100.00%	142	100.00%		122	100.00%	150	100.00%	

When considering all complaints, more than 61.30% of the female patients revealed at least one relevant pain symptom, irrespective of the affiliation sample. The area with the least frequent RPCs was the anterior area. For each considered sample, Cochran's Q-tests followed by the McNemar tests were applied for testing differences between the three areas: anterior area (F), visceral (V) and posterior (B), in terms of the prevalence rates of RPCs, whereas differences in the prevalence rates of PRC between the "pap" and "aap" groups as well as between the "S2P" and "S34P" groups were tested about significance for each considered area (symptom domain) with X²-test. "+" indicates significant (marginally significant) area or group differences at a Bonferroni corrected level of significance (nominal level of significance $\alpha = 0.05$). POP-Q: pelvic organ prolapse quantification system; PFDI: pelvic floor

Table 3. Absolute and Relative Frequencies of the Four Symptom Outcomes and the Combined Outcome R2 Before and 6, 12 and 24 Months After POP Reconstruction in the Total Population

Pre- and postoperative pain symptoms (total population, n = 277)	Baseline (phase 0)		6 months after surgery (phase 1)		12 months after surgery (phase 2)		24 months after surgery (phase 3)		Cochran's Q-tests for testing global effects (P-values)	McNemar tests for testing simple effects (phase pairs with significant differences)
	Absolute frequency	Relative frequency	Absolute frequency	Relative frequency	Absolute frequency	Relative frequency	Absolute frequency	Relative frequency		
PFDI 1 (pressure in the lower abdomen)										
Symptom-free	131	47.30%	213	82.90%	213	85.90%	163	88.10%	P < 0.00001*	0/1, 0/2, 0/3
Somewhat	55	19.90%	23	8.90%	18	7.30%	12	6.50%		
Moderate	47	17.00%	14	5.40%	9	3.60%	8	4.30%		
Quite a bit	44	15.90%	7	2.70%	8	3.20%	2	1.10%		
R2 (moderate or quite a bit)	91	32.90%	21	8.10%	17	6.80%	10	5.40%	P < 0.00001*	0/1, 0/2, 0/3
Observed cases	277	100.00%	257	100.00%	248	100.00%	185	100.00%		
PFDI 2 (pain in the lower abdomen or genital area)										
Symptom-free	167	60.30%	217	84.40%	218	87.90%	171	92.40%	P < 0.00001*	0/1, 0/2, 0/3
Somewhat	47	17.00%	18	7.00%	16	6.50%	9	4.90%		
Moderate	37	13.40%	15	5.80%	8	3.20%	3	1.60%		
Quite a bit	26	9.40%	7	2.70%	6	2.40%	2	1.10%		
R2 (moderate or quite a bit)	63	22.80%	22	8.50%	14	5.60%	5	2.70%	P < 0.00001*	0/1, 0/2, 0/3
Observed cases	277	100.00%	257	100.00%	248	100.00%	185	100.00%		
PFDI 3 (heaviness or dullness in the pelvic area)										
Symptom-free	141	50.90%	226	87.90%	223	89.90%	170	91.90%	P < 0.00001*	0/1, 0/2, 0/3
Somewhat	61	22.00%	22	8.60%	13	5.20%	10	5.40%		
Moderate	39	14.10%	5	1.90%	6	2.40%	3	1.60%		
Quite a bit	36	13.00%	4	1.60%	6	2.40%	2	1.10%		
R2 (moderate or quite a bit)	75	27.10%	9	3.50%	12	4.80%	5	2.70%	P < 0.00001*	0/1, 0/2, 0/3
Observed cases	277	100.00%	257	100.00%	248	100.00%	185	100.00%		
PFDI 6 (pelvic discomfort during standing or physically exerting)										
Symptom-free	107	38.60%	218	84.80%	224	90.30%	169	91.40%	P < 0.00001*	0/1, 0/2, 0/3
Somewhat	57	20.60%	19	7.40%	9	3.60%	7	3.80%		
Moderate	58	20.90%	13	5.10%	12	4.80%	7	3.80%		
Quite a bit	55	19.90%	7	2.70%	3	1.20%	2	1.10%		
R2 (moderate or quite a bit)	113	40.80%	20	7.80%	15	6.00%	9	4.90%	P < 0.00001*	0/1, 0/2, 0/3
Observed cases	277	100.00%	257	100.00%	248	100.00%	185	100.00%		
PFDI 7 (pain in lower back most days)										
Symptom-free	126	45.50%	182	70.80%	178	71.80%	139	75.10%	P < 0.00001*	0/1, 0/2, 0/3
Somewhat	46	16.60%	25	9.70%	22	8.90%	13	7.00%		
Moderate	42	15.20%	25	9.70%	19	7.70%	17	9.20%		
Quite a bit	63	22.70%	25	9.70%	29	11.70%	16	8.60%		

Table 3. Absolute and Relative Frequencies of the Four Symptom Outcomes and the Combined Outcome R2 Before and 6, 12 and 24 Months After POP Reconstruction in the Total Population - (continued)

Pre- and postoperative pain symptoms (total population, n = 277)	Baseline (phase 0)		6 months after surgery (phase 1)		12 months after surgery (phase 2)		24 months after surgery (phase 3)		Cochran's Q-tests for testing global effects (P-values)	McNemar tests for testing simple effects (phase pairs with significant differences)
	Absolute frequency	Relative frequency	Absolute frequency	Relative frequency	Absolute frequency	Relative frequency	Absolute frequency	Relative frequency		
R2 (moderate or quite a bit)	105	37.90%	50	19.40%	48	19.40%	33	17.80%	P < 0.00001*	0/1, 0/2, 0/3
Observed cases	277	100.00%	257	100.00%	248	100.00%	185	100.00%		
PFDI 46 (abdominal or lower back pain when straining for any reason)										
Symptom-free	167	60.30%	210	81.70%	205	82.70%	156	84.30%	P < 0.00001*	0/1, 0/2, 0/3
Somewhat	42	15.20%	16	6.20%	13	5.20%	10	5.40%		
Moderate	36	13.00%	15	5.80%	18	7.30%	10	5.40%		
Quite a bit	32	11.60%	16	6.20%	12	4.80%	9	4.90%		
R2 (moderate or quite a bit)	68	24.60%	31	12.00%	30	12.10%	19	10.30%	P < 0.00001*	0/1, 0/2, 0/3
Observed cases	277	100.00%	257	100.00%	248	100.00%	185	100.00%		

Frequencies at each postoperative stage refer to the number of patients who were observed in this stage. The global time effects on the prevalence rates of R2 and of the "symptom-free" outcome were tested for significance with Cochran's Q-tests. Whenever significant global effects were revealed, McNemar tests were subsequently performed to test the simple effects, i.e., for identifying the phase pairs with significant differences in the investigated prevalence rates. ***(number pairs) indicates significant global effects on (phase pairs with significant differences in) the investigated prevalence rates at a Bonferroni corrected level of significance α^* (where $\alpha^* < \alpha (= 0.05)$). POP: pelvic organ prolapse; PFDI: pelvic floor disorder inventory.

In the aaP subgroup, the pre- vs. 24-month postoperative prevalence rates of RPC were as follows: all pain complaints 61.3% vs. 14.7% (cr = 76.0%), anterior 34.5% vs. 1.3% (cr = 96.2%), visceral 43.0% vs. 1.3% (cr = 96.9%) and posterior 44% vs. 13.3% (cr = 65.6%). The paP patients as well as the aaP patients suffered significantly less often from RPC in each postoperative phase than at baseline, irrespective of the region where the RPC occurred. Comparing the aforementioned 24-month cure rates of aaP patients with those of paP patients in the three pelvic areas, better cure rates were found for aaP patients. All pain complaints noted 76.0% vs. 57.0% (19.0% better), anterior 96.2% vs. 78.0% (18.2% better), visceral 96.9% vs. 81.9% (15.0% better) and posterior 65.6% vs. 50.4% (15.2% better), respectively. The best cure effect was achieved in aaP patients with RPC visceral (96.9%) or anterior pains (96.2%), while the least cure effect was seen in paP patients with posterior pain (50.4%).

The inferential comparisons of aaP vs. paP patients in terms of the different pelvic areas supplied the following results. Preoperatively, paP vs. aaP patients suffered significantly more from RPC for anterior, visceral, posterior and all complaints. Twelve and 24 months after surgery, paP vs aaP patients had significantly lower RPC prevalence rates for any complaint (X²-tests, P < 0.05).

Repair effects in the S2P and S34P groups

The pre- and 24-month postoperative RPC prevalence and cure rates were as follows (Table 6): S2P: all complaints 45.1% vs. 35.2% (cr = 21.9%), anterior 39.3% vs. 9.9% (cr = 74.8%), visceral 43.4% vs. 8.8% (cr = 79.7%) and posterior 43.4% vs. 29.7% (cr = 31.5%) (Table 6); S34P: all complaints 43.3% vs. 15.7% (cr = 63.7%), anterior 36.7% vs. 2.2% (cr = 94.0%), visceral 49.3% vs. 3.4% (cr = 93.1%) and posterior 49.3% vs. 13.5% (cr = 72.6%).

The comparison of the S34P vs. S2P groups in terms of the RPC cure rates after 24 months revealed the following differences (improvements): all complaints 63.7% vs. 21.9% (41.8% improvement), anterior 94.0% vs. 74.8% (19.2% improvement), visceral 93.1% vs. 79.7% (13.4% improvement) and posterior 72.6% vs. 31.5% (41.1% improvement). The best cure effect was achieved in the S34P patients with RPC anterior pain (94.0%) or visceral pain (93.1%), and the least cure effect was found in S2P patients with posterior pain (31.5%). Similar to the aaP and paP patients, the S2P as well as the S34P patients suffered significantly less often from RPC in each postoperative phase than at baseline, irrespective of pain region.

Compared with X²-tests of the RPC prevalence rates of S2P vs. S34P patients in each region, the results demonstrate that S34P patients vs. S2P patients showed a significantly stronger reduction in RPC for anterior, posterior and all complaints at 12 and 24 months after surgery, but interestingly not at 6 months postoperatively.

Surgery effects concerning pain severity changes

To obtain a better impression of the severity changes for each

Table 4. Pre- and Postoperative Observed Cases and Occurrences of RPCs in the Anterior, Visceral, Posterior and All Complaint Areas in the Total Population (n = 277)

Location of pain symptoms	Baseline (phase 0)		6 m after surgery (phase 1)		12 m after surgery (phase 2)		24 m after surgery (phase 3)		Cochran's Q-tests for testing global effects (Q-values and corresponding P-values)	McNemar tests for testing simple effects (phase pairs with significant differences)
	Absolute frequency	Relative frequency	Absolute frequency	Relative frequency	Absolute frequency	Relative frequency	Absolute frequency	Relative frequency		
Front area (PFDI 1 and PFDI 2)										
Observed cases	277		257		248		185		$Q_{(DF=3)} = 136.56$	
RPCs	105	37.90%	30	11.70%	23	9.30%	11	5.90%	$P < 0.00001^*$	0/1, 0/2, 0/3
Cure rates of the RPC		69.13%		75.46%		84.43%		84.43%		
OR of the RPC		0.216		0.167		0.104		0.104		
95% CI of OR		0.14 - 0.34		0.10 - 0.27		0.05 - 0.20		0.05 - 0.20		
Visceral area (PFDI 3 and PFDI 6)										
Observed cases	277		257		248		185		$Q_{(DF=3)} = 193.41$	
RPCs	129	46.60%	22	8.60%	18	7.30%	11	5.90%	$P < 0.00001^*$	0/1, 0/2, 0/3
Cure rates of the RPC		81.55%		84.33%		87.34%		87.34%		
OR of the RPC		0.107		0.090		0.073		0.073		
95% CI of OR		0.07 - 0.17		0.05 - 0.15		0.04 - 0.13		0.04 - 0.13		
Posterior area (PFDI 7 and PFDI 46)										
Observed cases	277		257		248		185		$Q_{(DF=3)} = 37.44$	
RPCs	122	44.00%	62	24.10%	56	22.60%	39	24.10%	$P < 0.00001^*$	0/1, 0/2, 0/3
Cure rates of the RPC		45.23%		48.64%		45.23%		45.23%		
OR of the RPC		0.403		0.370		0.339		0.339		
95% CI of OR		0.28 - 0.57		0.26 - 0.53		0.23 - 0.51		0.23 - 0.51		
Testing global and simple differences in the occurrence of relevant complaints between areas (Cochran's Q- and McNemar tests)										
All areas (PFDI 1, 2, 3, 6, 7 and 46)		$Q_{(DF=2)} = 6.92$ $P = 0.0314^+$ F/V		$Q_{(DF=2)} = 37.33$ $P < 0.00001^*$ F/B, V/B		$Q_{(DF=2)} = 44.10$ $P < 0.00001^*$ F/B, V/B		$Q_{(DF=2)} = 36.46$ $P < 0.00001^*$ F/B, V/B		
Observed cases	277		257		248		185		$Q_{(DF=3)} = 122.20$	
RPCs	187	67.50%	80	31.10%	67	27.00%	46	24.90%	$P < 0.00001^*$	0/1, 0/2, 0/3
Cure rates of the RPC		53.93%		59.98%		63.11%		63.11%		
OR of the RPC		0.218		0.178		0.159		0.159		
95% CI of OR		0.16 - 0.30		0.13 - 0.25		0.11 - 0.23		0.11 - 0.23		

Additionally, the cure rates, ORs and 95% CIs of the ORs, when comparing the postoperative prevalence rates of RPCs with those at baseline, were entered. OR is the chance of symptom occurrence in an experimental condition (say A) divided by the chance of symptom occurrence in another experimental condition (say B). An OR equal to 1 means identical chances for symptom occurrence in both experimental conditions. Cochran's Q-tests followed by McNemar tests were applied for testing global and simple effects of the surgery on the occurrence of RPCs in each complaint area. The same tests were also performed to test global and local complaint-area differences in the occurrence of RPC at baseline as well as at each postoperative phase (6, 12 and 24 months after surgery). ***(+)" indicates significant global surgery or region effects at a Bonferroni corrected level of significance (at the nominal level of significance $\alpha = 0.05$). Number (capital letter) pairs characterize significant differences between corresponding phase or complaint-area pairs. Note that the analysis of single effects with the McNemar tests was only performed when the prior applied Cochran's tests supply significant global effects. RPC: relevant pain complaint; OR: odds ratio; CI: confidence interval; PFDI: pelvic floor disorder inventory.

Table 5. Absolute and Relative Frequencies (Prevalence Rates) of RPCs for Patients With Posterior/Apical POP (Group paP; n = 135) and Those With Anterior/Apical POP (Group aaP; n = 142)

Regional dependent pain (posterior/apical (n = 135) versus anterior/apical (n = 142))	Comparisons of postoperative RPCs in the front, visceral, back and all areas between patients with posterior/apical and anterior/apical POP-Q defect									
	Baseline (phase 0)		6 m after surgery (phase 1)		12 m after surgery (phase 2)		24 m after surgery (phase 3)		Cochran's Q-tests for testing global effects	McNemar tests for testing simple effects
	Absolute frequency	Relative frequency	Absolute frequency	Relative frequency	Absolute frequency	Relative frequency	Absolute frequency	Relative frequency		
Front area (PFDI 1 and PFDI 2) (RPC: "PFDI 1 = R2 or PFDI 2 = R2")										
RPC in the posterior/apical sample	56	41.50%	15	11.80%	16	13.00%	10	9.10%	$Q_{(DF=3)} = 67.37$	0/1, 0/2, 0/3
Total cases	135		127		123		110		$P < 0.00001^*$	
RPC in the anterior/apical sample	49	34.50%	15	11.50%	7	5.60%	1	1.30%	$Q_{(DF=3)} = 72.73$	0/1, 0/2, 0/3
Total cases	142		130		125		75		$P < 0.00001^*$	
X^2 -tests for testing posterior/apical vs. anterior/apical										
	$X^2(1) = 1.43$		$X^2(1) = 0.004$		$X^2(1) = 4.04$		$X^2(1) = 4.79$		$P = 0.028^+$	
	$P = 0.231$		$P = 0.945$		$P = 0.044^+$		$P = 0.028^+$			
Visceral area (PFDI 3 and PFDI 6) (RPC: "PFDI 3 = R2 or PFDI 6 = R2")										
RPC in the posterior/apical sample	68	50.40%	14	11.00%	14	11.40%	10	9.10%	$Q_{(DF=3)} = 136.56$	0/1, 0/2, 0/3
Total cases	135		127		123		110		$P < 0.00001^*$	
RPC in the anterior/apical sample	61	43.00%	8	6.20%	4	3.20%	1	1.30%	$Q_{(DF=3)} = 93.23$	0/1, 0/2, 0/3
Total cases	142		130		125		75		$P < 0.00001^*$	
X^2 -tests for testing posterior/apical vs. anterior/apical										
	$X^2(1) = 1.52$		$X^2(1) = 1.94$		$X^2(1) = 6.16$		$X^2(1) = 4.79$		$P = 0.028^+$	
	$P = 0.256$		$P = 0.162$		$P = 0.013^+$		$P = 0.028^+$			
Posterior area (PFDI 7 and PFDI 46) (RPC: "PFDI 7 = R2 or PFDI 46 = R2")										
RPC in the posterior/apical sample	67	49.60%	37	29.10%	39	31.70%	29	26.40%	$Q_{(DF=3)} = 19.21$	0/1, 0/2, 0/3
Total cases	135		127		123		110		$P = 0.0002^*$	
RPC in the anterior/apical sample	55	38.70%	25	19.20%	17	13.60%	10	13.30%	$Q_{(DF=3)} = 21.98$	0/1, 0/2, 0/3
Total cases	142		130		125		75		$P = 0.0001^*$	
X^2 -tests for testing posterior/apical vs. anterior/apical										
	$X^2(1) = 3.33$		$X^2(1) = 3.44$		$X^2(1) = 11.62$		$X^2(1) = 4.55$		$P = 0.032^+$	
	$P = 0.067$		$P = 0.063$		$P < 0.0001^*$		$P = 0.032^+$			
All areas (PFDI: 1, 2, 3, 6, 7 and 46) (RPC: "at least one of the PFDIs = R2")										
RPC in the posterior/apical sample	100	74.10%	45	35.40%	48	39.00%	35	31.80%	$Q_{(DF=3)} = 65.15$	0/1, 0/2, 0/3
Total cases	135		127		123		110		$P < 0.00001^*$	
RPC in the anterior/apical sample	87	61.30%	35	26.90%	19	15.20%	11	14.70%	$Q_{(DF=3)} = 61.42$	0/1, 0/2, 0/3
Total cases	142		130		125		75		$P < 0.00001^*$	
X^2 -tests for testing posterior/apical vs. anterior/apical										
	$X^2(1) = 5.52$		$X^2(1) = 2.17$		$X^2(1) = 17.84$		$X^2(1) = 7.02$		$P = 0.008^*$	
	$P = 0.018^+$		$P = 0.140$		$P < 0.0001^*$		$P = 0.008^*$			

*** ("+") indicates significant global surgery or group effects on the prevalence of RPC at a Bonferroni corrected level of significance (at the nominal level of significance $\alpha = 0.05$). Number pairs characterize significant differences between the corresponding phases. The prevalence rates of RPCs were significantly reduced after surgery in both groups and that for each complaint area (anterior, visceral, posterior and all areas (Cochran's Q-tests, followed by McNemar tests, $P < \alpha^*$, where α^* = Bonferroni corrected α ($\alpha^* < \alpha = 0.05$)). Comparisons of the RPC frequencies between "paP" and "aaP" patients into each phase (baseline and 6, 12, 24 months after surgery) and in each complaint area showed that "aaP" patients had significantly more pain reduction than "paP" patients 6 and 24 months after surgery and that in any complaint area (X^2 -tests, P-values significant at the nominal α ($= 0.05$) or at a Bonferroni corrected level of significance α^* , where $\alpha^* < \alpha$). RPC: relevant pain complaint; POP-Q: pelvic organ prolapse quantification system; PFDI: pelvic floor disorder inventory.

Table 6. Absolute and Relative RPC Frequencies (Prevalence Rates) of Patients With Stage 2 POP-Q (Group S2P; n = 122) and Stage 3 or 4 POP-Q Stage (Group S34P; n = 150)

Comparisons of postoperative RPCs in the front, visceral, back and all areas between patients with POP-Q stage 2 and POP-Q stage 3 or 4									
Regional dependent pain (POP-Q stage 2 (n = 122) versus POP-Q stage 3 or 4 (n = 150))	Baseline (phase 0)		6 m after surgery (phase 1)		12 m after surgery (phase 2)		24 m after surgery (phase 3)		McNemar tests for testing simple effects
	Absolute frequency	Relative frequency	Absolute frequency	Relative frequency	Absolute frequency	Relative frequency	Absolute frequency	Relative frequency	
Front area (PFDI 1 and PFDI 2) (RPC: "PFDI 1 = R2 or PFDI 2 = R2")									
RPC in the "POP-Q stage 2" sample	48	39.30%	13	11.60%	16	14.30%	9	9.90%	$Q_{(DF=3)} = 49.25$ $P < 0.00001^*$
Total cases	122		112		112		91		
RPC in the "POP-Q stage 3/4" sample	55	36.70%	17	12.10%	6	4.60%	2	2.20%	$Q_{(DF=3)} = 86.28$ $P < 0.00001^*$
Total cases	150		140		131		89		
χ^2 -tests for testing POP-Q stage 2 vs. POP-Q stage 3 or 4	$\chi^2(1) = 0.20$ $P = 0.650$		$\chi^2(1) = 0.02$ $P = 0.896$		$\chi^2(1) = 6.90$ $P = 0.008^*$		$\chi^2(1) = 4.58$ $P = 0.032^+$		
Visceral area (PFDI 3 and PFDI 6) (RPC: "PFDI 3 = R2 or PFDI 6 = R2")									
RPC in the "POP-Q stage 2" sample	53	43.40%	13	11.60%	12	10.70%	8	8.80%	$Q_{(DF=3)} = 65.26$ $P < 0.00001^*$
Total cases	122		112		112		91		
RPC in the "POP-Q stage 3/4" sample	74	49.30%	9	6.40%	6	4.60%	3	3.40%	$Q_{(DF=3)} = 124.70$ $P < 0.00001^*$
Total cases	150		140		131		89		
χ^2 -tests for testing POP-Q stage 2 vs. POP-Q stage 3 or 4	$\chi^2(1) = 0.93$ $P = 0.332$		$\chi^2(1) = 2.09$ $P = 0.146$		$\chi^2(1) = 3.31$ $P = 0.068$		$\chi^2(1) = 2.30$ $P = 0.129$		
Posterior area (PFDI 7 and PFDI 46) (RPC: "PFDI 7 = R2 or PFDI 46 = R2")									
RPC in the "POP-Q stage 2" sample	55	43.40%	32	28.60%	36	32.10%	27	29.70%	$Q_{(DF=3)} = 11.24$ $P = 0.0105^+$
Total cases	122		112		112		91		
RPC in the "POP-Q stage 3/4" sample	74	49.30%	30	21.40%	20	15.30%	12	13.50%	$Q_{(DF=3)} = 25.96$ $P < 0.00001^*$
Total cases	150		140		131		89		
χ^2 -tests for testing POP-Q stage 2 vs. POP-Q stage 3 or 4	$\chi^2(1) = 0.08$ $P = 0.772$		$\chi^2(1) = 1.71$ $P = 0.190$		$\chi^2(1) = 9.69$ $P = 0.002^*$		$\chi^2(1) = 6.94$ $P = 0.008^*$		
All areas (PFDI: 1, 2, 3, 6, 7 and 46) (RPC: "at least one of the PFDIs = R2")									
RPC in the "POP-Q stage 2" sample	55	45.10%	39	34.80%	44	39.30%	32	35.20%	$Q_{(DF=3)} = 39.64$ $P < 0.00001^*$
Total cases	122		112		112		91		
RPC in the "POP-Q stage 3/4" sample	65	43.30%	41	29.30%	22	16.80%	14	15.70%	$Q_{(DF=3)} = 81.38$ $P < 0.00001^*$
Total cases	150		140		131		89		
χ^2 -tests for testing POP-Q stage 2 vs. POP-Q stage 3 or 4	$\chi^2(1) = 1.41$ $P = 0.559$		$\chi^2(1) = 0.87$ $P = 0.348$		$\chi^2(1) = 15.43$ $P < 0.0001^*$		$\chi^2(1) = 8.93$ $P = 0.002^*$		

"*" ("+") indicates significant global surgery or group effects on the prevalence of RPC at a Bonferroni corrected level of significance (at the nominal level of significance $\alpha = 0.05$). Number pairs characterize significant (or marginal significant differences whenever provided with the superscript "+") differences between the corresponding phases. The prevalence rates of RPCs were significantly reduced after surgery in both groups and that for each complaint area (anterior, visceral, posterior and all complaints) (Cochran's Q-tests, followed by McNemar tests, $P < \alpha^*$, where α^* a Bonferroni corrected α ($\alpha^* < \alpha = 0.05$)). Comparisons of the RPC frequencies between "S2P" and "S34P" patients into each phase (baseline and 6, 12, 24 months after surgery) and in each complaint area showed that "S34P" patients had significantly more pain reduction than "S2P" patients 6 and 24 months after surgery in the anterior, posterior and the whole area (χ^2 -tests, P-values significant at the nominal α ($= 0.05$) or at a Bonferroni corrected level of significance α^* , where $\alpha^* < \alpha$). POP-Q: pelvic organ prolapse quantification system; RPC: relevant pain complaint; PFDI: pelvic floor disorder inventory.

type of pain, a particular look at the “quite a bit” outcome shows the following results (Table 3).

Calculating the cure rates of the “quite a bit” severity before and 24 months after surgery for the various PFDI types in tP (calculations were based on the prevalence rates at these phases), we obtained 93.1% for PFDI 1, 88.3% for PFDI 2, 91.5% for PFDI 3, 94.5% for PFDI 6, 62.1% for PFDI 7 and 57.0% for PFDI 46. The prevalence rates of “somewhat” and “moderately” intensity outcomes were also reduced. The prevalence rates of the “symptom-free” outcome (Table 3) increased significantly from baseline to 24 months after surgery. These facts provide evidence for the curative power of POP reconstruction with respect to pain symptoms.

Pain severity transitions between pre- and postoperative phases

Figure 1 illustrates the transition structure for IPC and RPC between these states in the anterior, visceral and posterior area when passing over from baseline to one of the three postoperative phases. According to its definition, RPC means that at least one of the pair symptoms belonging to the aforementioned pain complaint areas show the outcome R2.

Surgery-induced neo-pain

Preoperatively, 55 patients had no RPCs, whereas 6 months after surgery, nine patients (16.3%) suffered from RPCs, six (10.9%) patients 12 months after surgery and only four patients (7.2%) 24 months after surgery. This demonstrates that operatively induced pain decreases to a low level over time.

Associations and comorbidities

By testing the association between POP stage and pain intensity with χ^2 -independence tests, no significant correlation among any of the considered pain types was found. Regarding the R2 outcome group and the presence of coexisting pelvic floor symptoms preoperatively, “daytime urinary frequency” was seen in 48.0% of the patients, “urgency” in 47.3%, “urgency incontinence” in 38.2%, “nocturia” in 48.7%, bladder emptying problems in 31.4%, stress urinary incontinence in 19.9%, fecal incontinence in 17.7% and stool outlet obstruction in 6.1%. The cure rates for these coexisting symptoms noted at 24 months after surgery ranged between 59% and 84%, as previously reported [23].

Discussion

The aim of this article was not to list all the numerous causes for CPP but to note the relationship between POP and pelvic pain and the potential resolution of that pain following reconstructive POP surgery. In the Propel study, the primary endpoint was confirmed noting that reconstructive POP surgery with the use of mesh restored normal anatomy ($\text{POP-Q} \leq 1$) in

a statistically significant percentage of patients [30, 31]. The secondary study endpoints were likewise illustrated, as POP-induced bladder and anorectal symptoms were often improved or cured by surgical POP repair [9, 32]. The tertiary, so far not evaluated endpoint presented in this paper was to determine the relationship between POP and pain before and after reconstructive surgery, with respect to type, location, severity and frequency.

The preoperative data evaluation showed that two-thirds of all POP patients (67.5%) had RPCs in the complete pelvic area, while only one-third did not. In the tP as well as in the subgroups, the visceral complaints were the main pain, followed by the posterior and anterior.

An explanation for this finding seems to be that the upright position of human beings forces the sacrum to curve in an age-dependent manner [33]. The more the sacrum curves, the more the pelvic floor comes in a horizontal position. Since the inclination angle of the pelvic floor determines the degree of the forces acting on it, the center of the now horizontal shape is increasingly under pressure and gives way to prolapse. And if pressure becomes stronger, then overstretched connective tissue, ligaments, nerves and muscles react with pain [33].

There are two pathways of pain transmission for CPP described by Martius [34]: a visceral and a mechanical pathway. The visceral pathway is transmitted from Frankenhauser's plexus, located in the middle of the pelvis in the parametrium, approximately 2 cm lateral to the cervix. The paired ganglia undergo permanent stimulation, if the uterus or vagina descend, and can cause serious pain, similar to pain during childbirth [2]. The pain radiates mainly to the anterior and lateral abdominal wall, the inguinal region and the thighs. This is the pathway for visceral and anterior pain. The mechanical pathway is transmitted by deficient, overstretched suspensory ligaments or support from the pelvic floor leading to increased tension against the sacral plexus, thereby causing pain.

In this context, in 2015, Goeschen [8] pointed out that mechanical support of the uterus and vagina by restoration of the supportive and suspensory structures should be able to stop the permanent stimulation of the paired ganglia. These patients should be free of prolapse-related pain unless the supporting system gives way again.

The results of this study are in line with the prior considerations of Goeschen [8]. The postoperative data showed the following. In the total population, all six pain types were significantly reduced 6, 12 and 24 months after reconstructive POP surgery. The visceral symptom area had the highest pain reduction rate (87.3%), followed by the anterior (84.4%) and the posterior area (45.2%) after surgical POP repair. The most bothersome pain complaint category, “quite a bit”, noted the highest improvement rate of 80.5%.

The cure rates for visceral/anterior vs. posterior pain complaints were significantly better with very small odds ratios of RPCs, indicating a very low risk for recurrence.

Cystocele/rectocele

Patients with cystocele (aaP) vs. recto/enterocele (paP) had

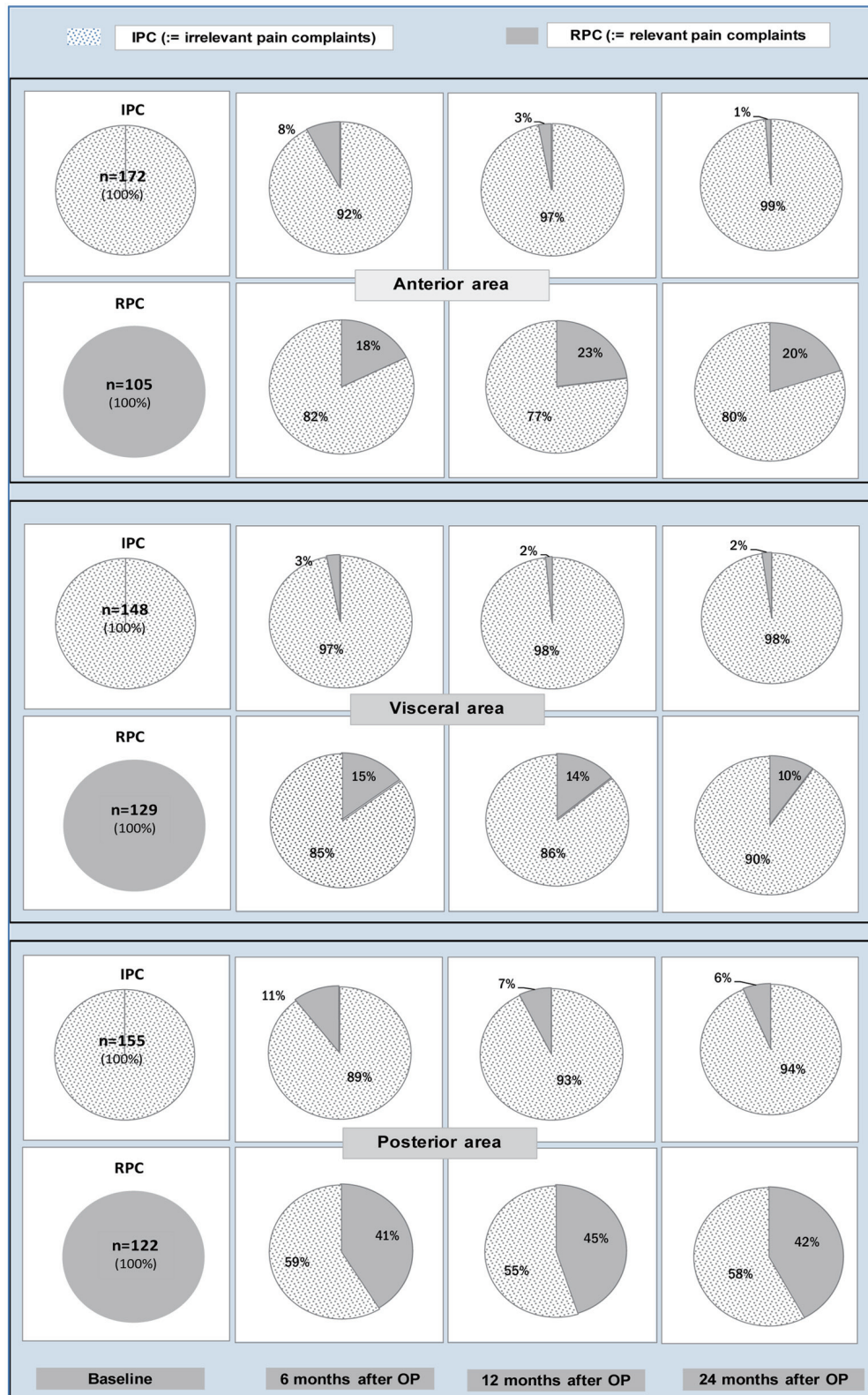


Figure 1. Proportions of patients who showed preoperatively the IPC state (bottom row of pies) or the RPC state (lower row of pies) for each pain complaint area and who stayed on the same or passed over to the other state 6, 12 or 24 months after surgery. Obviously, patients suffering from anterior or visceral pain at baseline showed better results 6, 12 or 24 months after surgery than patients suffering from posterior pain. IPC: irrelevant pain complaint; RPC: relevant pain complaint.

significantly less severe pain in all three areas preoperatively. The best cure effects after surgical POP repair were achieved in aaP patients with middle or anterior pain (> 96%), while paP patients with posterior pain noted a much lower cure effect (50%). This means that paP patients had significantly more pain than aaP patients pre- and postoperatively. Surgery in patients with pain in the posterior region was associated with limited results in both groups, especially in paP patients. How can this be explained?

Visceral and anterior pains are mainly transmitted via descended Frankenhauser ganglia. If these paired ganglia are surgically returned to a normal position, patients can appreciate improvement, if not persistence of their pain.

The second mechanical pathway described by Martius [34] is the main transmission pathway for posterior pain. This type of pain radiates primarily to the lumbosacral region and is characterized by low dragging abdominal pain or deep sacral backache.

Three mechanical changes can cause these pains: 1) Deficient suspensory ligaments. Deficient suspension of the visceral organs in the pelvic cavity due to loose ligaments can lead to serious tension on the sacral plexus, resulting in severe posterior pain in this area [8]; 2) Deficient support from the pelvic floor. The contents of the small pelvis are also supported from the base. A decline in the support of the pelvic floor followed by the unavoidable descent of pelvic organs causes tension on the suspending ligaments. This can generate pain in the lumbosacral area, primarily initiated by the deficient pelvic floor [8]; 3) Pain induced by overstretching the uterosacral ligaments (USLs). The nerve fibers in the uterosacral ligaments are parasympathetic visceral fibers. Stretching of lax ligaments via gravity may stimulate the nerve fibers within these tissues and cause pain [8].

All three possibilities lead to a stretching of either the nerve endings or muscle fibers within the USL, generating traction against the sacral plexus [8].

Because all three possibilities can be responsible for posterior pain, all damaged structures have to be repaired. Otherwise, pain remains or returns.

The posterior reconstruction performed in this study was obviously not sufficient enough to restore the suspending and supporting system sufficiently. Therefore, the cure rate of posterior pain in tP patients was only 45%. In contrast, the elevation of prolapsed Frankenhauser ganglia led to a pain cure rate of more than 84% in tP patients with visceral or anterior complaints.

POP stage

Preoperatively, no correlation was found between POP stage and pain intensity. Therefore, the expectation that patients with higher POP stages have more severe pain could not be verified. This finding could be attributed to a patient's sense of accommodation to chronic pain over time, resulting in a decreased perception of pain intensity in women with more severe POP.

However, with respect to pain cure rates, the best cure rates (> 93%) were noted in patients with pronounced POP

(S34P) suffering from visceral or anterior pain. By comparison, only limited cure rates (31.5%) were seen in S2P patients with posterior pain. These findings suggest that S34P patients stand to benefit significantly more with respect to improvement or resolution of pain symptoms from reconstructive surgery than those with smaller POP.

De novo pain

In the literature, the reported incidence of *de novo* pain after POP repair is variable [1-3]. In a study following the use of Elevate (American Medical Systems) or Prolift (Gynecare/Ethicon) kit-based POP repair systems, pelvic pain was noted in 11% of patients [1]. Kowalik et al reported only 5% *de novo* pain after POP mesh surgery [2]. The true incidence is likely underreported since 38.6% of complaints to the FDA pertained to vaginal pain and/or dyspareunia; however, a recent Cochrane review in 2013 noted only 0.5% of patients undergo mesh removal for pain [3].

In our study, surgically induced *de novo* pain was low and decreased over time from 16% at 6 months, 11% at 12 months and 7% at 24 months postoperatively, and the prevalence rate of "quite a bit" complaints was only 0-6%. This shows that patients suffering from *de novo* pain after POP reconstruction, even when mesh is used, should proceed with conservative, non-operative management rather than rush to a surgical intervention, as neo-pain often improves and can even resolve over time.

Limitations of the study

The data are derived from a study group of women who decided to undergo prolapse repair for symptomatic POP.

Comorbidities

In 1993, Petros and Ulmsten described CPPS as being caused by lax uterosacral ligaments as part of the "posterior fornix syndrome" [12], along with other pelvic symptoms such as nocturia, urgency and abnormal emptying. They reported a significant cure rate of CPPS and other posterior fornix symptoms following repair of the uterosacral ligaments and vaginal apical reconstruction [12].

In 2003, Van Os-Bossagh et al [35] reported that 43% of 60 women with CPP had serious urinary incontinence, 10% had an urge component, 25% had pure stress urinary incontinence and 8% had unclassified incontinence.

In a recently published paper, Goeschen [36] reported a 30-40% coexistence of bladder and bowel dysfunctions in patients with CPP. All symptoms improved significantly following surgical repair of the pelvic floor.

In the present study, nearly identical data regarding comorbidities were observed. This underlines the Iceberg concept of Pescatori [37], who pointed out that patients usually come for treatment with one main symptom, while other symptoms, though present, may be latent.

Pain severity changes

The illustration of pain severity changes for the six different pain types (from baseline to 24 months after surgery) shows that the most bothersome severity level “quite a bit” (94%) had the highest cure rates 24 months after repair regarding PFDI types 1, 2, 3 and 6. For PFDI types 7 and 46, the pain cure rates were less, but still 49% and 62%, respectively. Once again, pain perceived to be “visceral” or “anterior”, benefits significantly more from POP reconstructive surgery than pain perceived to be “posterior”.

Hypotheses in the introduction chapter

Reflecting upon the hypotheses in the introduction chapter regarding type-dependent pain in the total sample and the subgroups it can be summarized that POP reconstruction causes a relevant improvement in pain severity for a long time irrespective of pain type with the best results for visceral complaints.

Conclusion

The present findings provide further evidence that POP causes relevant pelvic pain in two-thirds of patients. Appropriate anterior/apical or posterior/apical POP reconstruction enables resolution of the six pain types in 75-92% of patients, with a long-lasting durability of response. The visceral complaints had the highest pain reduction rate (87%) after surgical POP repair, followed by the anterior (84%) and the posterior (45%). The surgical principle of re-establishing vaginal apical support may provide a primary surgical option for the cure of pelvic pain experienced concomitantly with prolapse. The use of alloplastic material and the restoration of the correct vaginal axis towards S2-S4 seem to be important for a durable cure. Preoperative simulated operations and the use of a diagnostic algorithm, such as that previously proposed by Petros [38-40], may be helpful. All available techniques for POP repair should be evaluated in the context of pain relief and activation so that the effects of different techniques on pain can be adequately compared. While women with relevant preoperative pain have a good chance of pain relief after mesh-supported vaginal POP-repair, women without preoperative relevant pain can develop relevant pain, which should be considered in preoperative indication for type of surgery with or without alloplastic material.

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Conflict of Interest

B. Liedl: consultant - American Medical Systems, Boston Scientific; research - American Medical Systems. K. Goeschen: none. N. Grigoryan: none. S. Sutherland: Consultant - American Medical Systems, Boston Scientific, Axonics; research - American Medical Systems, FemPulse, Pelvital. A. Yassouridis: none. M. Witczak: none. JP Roovers: consultant - American Medical Systems, Coloplast, Tepha, Promedon; research - American Medical Systems, Coloplast, Tepha.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Author Contributions

BL: project development, data collection, management data analysis and manuscript writing. KG: manuscript writing and management data analysis. NG: manuscript writing and data analysis. SES: data collection, manuscript writing and editing. AY: statistics and data analysis. MW: manuscript writing and editing. JPR: data collection and editing.

Data Availability

Dr. Yassouridis and all other authors analyzing the data got the raw data of the whole study.

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