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DOTTORATO DI RICERCA IN

"TERAPIE AVANZATE IN CHIRURGIA
E RIABILITAZIONE
DEL PAVIMENTO PELVICO FEMMINILE"

XX CICLO DEL CORSO DI DOTTORATO

" A prospective, randomized, controlled study comparing Gynemesh, a synthetic mesh, and Pelvicol, a biological mesh, in the surgical treatment of recurrent cystocele"

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Introduction

Surgery for pelvic floor disorders in women is widespread. It has been estimated that about 11% percent of the female population will undergo surgery for prolapse during their lifetime, with approximately 30% of patients being re-operated within 4 years of the original surgery (2).

Many risk factors for POP recurrence have been suggested: inappropriate choice of procedure or suture materials, lack of surgical expertise, chronically increased intra-abdominal pressure and, above all, low tissue quality (3). Histological studies on patients with recurrent prolapse indicate systemic collagen deficiency and increased amount of weaker type 3 collagen (4) combined with a decrease in type 1 collagen in the pubocervical fascia (5) and cervix (6). Increased collagen breakdown due to higher collagenase activity has also been noted (7). Given the limitations of traditional surgery, the use of prosthetic materials has been suggested to reinforce or replace defective native tissue. Several types of meshes have been used for pelvic floor reconstruction and have become particularly popular in cystocele repair, which is where most recurrences occur. Among synthetic meshes, Mersilene? (Ethicon Inc, Sommerville, NJ) and especially Polypropylene (Prolene? , Ethicon Inc, Sommerville, NJ) have been widely used in recent years. Those are considered ideal synthetic meshes: Type-1, as classified by Amid (8), namely macroporous and monofilament meshes. These qualities have been associated with a reduction in the risk of bacterial harboring and graft infection, which may cause extrusion or erosion of the prosthetic material through the vaginal wall. Nevertheless, complications have been described also with type 1 synthetic materials. These include erosions, infection, pain syndromes and dyspareunia (9).

In order to reduce the incidence of such complications, grafts of biologic origin have been developed as an alternative. Potential advantages of these materials include in-vivo tissue modelling, histological similarity between graft and native tissue and a reduced

erosion rate. A disadvantage of biologic grafts could be low durability of tissue support, which may not last enough for optimal collagen ingrowth (10). Based on previous knowledge, we hypothesized the occurrence of a possible lower complication rate for cystocele repair using Pelvicol® (CR Bard, Murray, NJ), a porcine dermis graft, as compared to Gynemesh PS® (Ethicon Inc, Sommerville, NJ), a soft polypropylene mesh.

Several retrospective and non-randomized studies are available in the medical literature which evaluate the use of different implant types in vaginal POP repair, but very few randomized trials have been published on the subject. In this prospective, randomized study on patients with recurrent cystocele, we evaluated the incidence of vaginal mesh erosion with Pelvicol® and Gynemesh PS® as a primary outcome. As secondary outcome measures, we evaluated the impact of surgery on quality of life and sexuality and we assessed anatomical results.

Materials and methods

Women with recurrent, symptomatic stage 2 or greater anterior vaginal wall prolapse (point Ba $\geq$ -1) planning to undergo secondary pelvic reconstructive surgery were enrolled in our study.

All patients underwent pre-operative gynecological work-up, which included:

- History

- Pelvic examination (the severity of POP was assessed in all patients, by the Pelvic Organ Prolapse Quantification (POP-Q) staging system). (11)

- Conventional urodynamic studies (uroflowmetry, filling cystometry, pressure/flow studies) with and without prolapse reduction with vaginal packing to diagnose occult stress urinary incontinence

- Validated questionnaires including:

1. Prolapse Quality of Life Questionnaire (P-QoL) (12)

2. A short form of Pelvic Organ Prolapse/Urinary Incontinence Sexual questionnaire (PISQ-12) (13)

Methods, definitions and units conform to the standards recommended by the International Continence Society (14).

Patients needing a concomitant anti-incontinence procedure and patients with diabetes mellitus or collagen disease were excluded from our study.

All patients underwent Tension-free Cystocele Repair (TCR) (15) and Levator Myorrhaphy (LM). Concomitant hysterectomy was performed on 26 patients (27.6%) in the Pelvicol® group and 13 patients (13.5%) in the Gynemesh PS® group.

For TCR, patients were randomly assigned either to cystocele repair using Gynemesh PS®, or to the same procedure using Pelvicol®. Randomization was done using a computer-generated list.

Gynemesh PS® is a knitted, monofilament, large pore polypropylene, non-absorbable mesh. It is made up of reduced diameter fibers knitted into a unique, patented design with 50% more flexibility than standard Prolene mesh. Gynemesh PS® was designed specifically for pelvic floor surgery and its advantage lies in its softness, suppleness and lightness.

The Pelvicol® implant is derived from porcine dermis and has been used throughout the human body. Cellular skin components are removed, leaving the architecture of dermal collagen and elastin fibers intact. Mature collagen is stabilized by diisocyanate cross-linking, which makes the implant resistant to breakdown by naturally occurring collagenases. Pelvicol® has been demonstrated to be safe: non-cytotoxic, non-allergenic and non-mutagenic action of the implant has been noted.

Both Gynemesh PS® and Pelvicol® implants were trimmed and shaped as required for the surgical technique adopted.

Surgical technique

TCR: A midline incision is carried out on the anterior vaginal wall and the pubocervical fascia is dissected as for anterior colporraphy. The sheet of mesh is trimmed to a rounded shape, with two lateral wings. The central, rounded part of the mesh is positioned under the urinary bladder in a tension-free fashion, while the arms are inserted deep into the periurethral tissue on both sides towards the pubic bone (figure 1). A single fixating monocryl 2/0 suture is performed at the base of one wing of the mesh, at the periurethral level.

LM: A midline incision is carried out on the posterior vaginal wall, the pubocervical fascia is dissected as for posterior colporraphy and laterally to the ischio-rectal fossa, until the puborectalis sheath is visualized. Using a single vicryl-2 suture, the right apex of the vaginal cuff is attached to the ipsilateral levator sheath. This procedure is then repeated on the left side using the same suture. The two ends of the suture are tied bringing together the upper parts of the two puborectalis sheath.

Assuming a 2-sided hypothesis test with a 5% type 1 error and 80% power, 90 patients in each group would be required to detect an absolute difference of 15% in reduction of complications. We sought to enrol 200 women in this clinical trial in order to allow for a 10% drop out rate.

All patients provided their informed consent to participate in our study. The study was approved by the Ethical Committee of our Institution.

All patients were operated on by 3 different surgeons. The senior author (MC) was the primary surgeon in 140 of the cases and first assistant in 27 cases.

Post-operative work-up was performed at 6 months, at 1 year and then annually. Each visit included a pelvic examination and questionnaires. Conventional urodynamic studies were performed yearly.

We defined as cure any prolapse of degree $\leq$ 1 involving point Ba according to the POP-Q system.

Descriptive statistics were mean ± standard deviation for parametric continuous variables (after confirmation of normal distribution with histograms, Q-Q plots and Skewness-Kurtosis test), median (minimum-maximum) for non-parametric continuous variables and frequencies for categorical variables. The Chi-square test was used to compare categorical variables between pre- and post-operative periods, the paired t-test for continuous parametric variables, and the Mann-Whitney test for continuous non-parametric variables.We considered $p<0.05$ to be statistically significant.

No financial assistance was received from any company in the design or execution of this study.

Results

From September 2003 until November 2005, a total of 200 patients with symptomatic recurrent anterior vaginal wall prolapse were enrolled. Of those, 190 patients were found to be eligible for our study: 96 were randomized to Gynemesh PS® and 94 were randomized to Pelvicol®.

No significant difference was found between groups in demographic data (table 1), degree of POP, clinical or urodynamic findings.

60 patients in the Gynemesh PS® group and 54 patients in the Pelvicol® group had previously undergone hysterectomy.

Preoperative prolapse stage is shown in table 2.

There were no intra-operative complications in either group. The hospital stay was 4-10 days in the Gynemesh PS® group (mean 4.5) and 4-12 days in the Pelvicol® group (mean 4.9), with p =0.19. Resumption of spontaneous voiding occurred after 3-7 days (mean 3.7) in the Gynemesh PS® group and after 3-6 days (mean 3.4) in the Pelvicol® group (p=0.34).

All patients completed the 2-year follow-up.

Anterior vaginal wall recurrence was observed in 27 patients in the Gynemesh PS® group (28.1%): in 26 patients the recurrence was stage 2 while one patient had stage 3 recurrent prolapse. 41 patients in the Pelvicol® group (43.6%) showed recurrent cystocele, stage 2 in 39 patients and stage 3 in the two remaining patients. The difference in anatomical outcome did not reach statistical significance (p=0.06). None of the patients with recurrence was symptomatic enough to require re-operation for prolapse.

Nine women (six in the Gynemesh PS® group and three in the Pelvicol® group) had a stage 2 posterior vaginal wall recurrence. In six patients a stage 2 recurrent prolapse at the upper vaginal segment was observed, all in the Pelvicol® group.

Mesh erosions through the vaginal mucosa were encountered in 6 patients in the Gynemesh PS® group (6.3%), while no cases of erosion were observed in the Pelvicol® group (p=0.02). All cases of erosions were detected at the 6- month follow-up visit. No other post-operative complications were detected in either group.

As regards symptoms, we observed in both groups a statistically significant reduction in voiding LUTS, in symptoms associated with pelvic organ prolapse and in post-micturition symptoms (table 3).

A comparison of pre- and post-operative urodynamic parameters showed no statistically significant changes in the Gynemesh PS® group, while a significant decrease in detrusor pressure at maximum flow was observed in the Pelvicol® group following surgery (table 4).

In the Gynemesh PS® group, analysis of quality of life questionnaires revealed significant improvement in the following domains: prolapse impact, social limitations, emotions and severity measures. Patients in the Pelvicol® group reported a positive change in all domains, with the exclusion of physical limitations.

As regards sexuality, pre- and post-operative PISQ-12 scores revealed no change in the Gynemesh PS® group (p=0.31) and a statistically significant improvement in the Pelvicol® group (p=0.03).

Discussion

The use of graft material in recurrent POP surgery has been adopted in clinical practice in the attempt to improve surgical outcome. Although an advantage has been suggested to graft augmentation (16,17), this must be balanced against potential mesh related complications such as erosion and dyspareunia. Following surgery with Marlex? mesh, the erosion rate has been reported 1.4%-25% (18, 19), whereas the rate of erosion associated with Prolene® mesh placement has been reported 8%-13% (20, 21). There is some evidence that lower-weight polypropylene meshes may be associated with a decreased erosion rate (22). In this prospective, randomized study, comparing Gynemesh PS® and Pelvicol® grafts for the treatment of recurrent cystocele, vaginal mesh erosion was observed only in the Gynemesh PS® group. The occurrence of this complication in 6.3% of Gynemesh PS® patients is comparable to that reported by previous studies (16,17). The presence of concomitant vaginal hysterectomy in four out of six cases of erosion in our sample seems to confirm that hysterectomy might increase the risk of such complication, as reported by some authors (23).

We hypothesized that Pelvicol® biologic grafts would be less likely to cause erosion, due to potentially better tissue remodeling resulting from histological similarity between graft and native tissue at the surgical site (24). Our data indicating the absence of erosions with Pelvicol®, confirm the results of some previous studies (25, 26). Our results do not concord with a recent paper by Handel et al in which extrusion of porcine dermal graft through dehiscence of the anterior vaginal epithelium occurred in 22% of patients after surgical correction of cystocele (27). The authors postulated that perioperative bleeding accumulating deep to the graft could not drain from the vagina because of the nonporous

nature of the graft, causing hematoma and eventual infection. We believe meticulous hemostasis and avoidance of extensive dissection of the anterior vaginal wall can reduce the rate of hematoma formation. Furthermore, “tension-free” positioning of the graft and avoidance of pubocervical fascia plication might better preserve blood perfusion to the vaginal skin, thus reducing the erosion rate (28).

The better impact of Pelvicol® on sexuality observed in our study could be explained by the impairment in vaginal flexibility occurring even with low-weight polypropylene meshes, which may lead to discomfort during sexual intercourse (23). Higher mesh flexibility at the level of the bladder neck might also explain the better impact of Pelvicol® on urodynamic voiding phase parameters as compared to Gynemesh PS®, which was observed in this study.

This is the first prospective, randomized trial comparing the use of synthetic and biologic grafts in a selected population of patients with postoperative cystocele recurrence. Approximately 30% of patients have been reported to require repeated surgery for prolapse within 4 years of the original procedure. Nevertheless, review of the medical literature reveals paucity of data regarding surgical outcome of recurrent POP. In this regard, this study supplies important information which may affect clinical decisions, patient counseling and informed consent.

With a follow-up of 24 months, we observed recurrent cystocele in 28.1% of Gynemesh PS® patients and in 43.6% of Pelvicol® patients. Difference between groups did not reach statistical significance (p=0.06). The cross-linked structure of Pelvicol® may result in decreased durability of tissue support, due to lower potential for collagen ingrowth, limited vascularization and encapsulation of the graft (29). This could explain the low success rate encountered in the Pelvicol® group. While judging the low anatomical success rates observed in both study groups, it should not be forgotten that the study population included only women with one or more previous surgery for POP, thus at

highly increased risk for postoperative recurrence. It should also be noted that all patients in our sample underwent LM, a variation of the High Levator Myorrhaphy described by Lemack for suspension of the vaginal apex (30). The combination of a "tension-free" technique with a "tension-based" procedure such as LM may possibly play a role in the unsatisfactory anterior vaginal wall outcome.

Despite anatomical outcome, analysis of P-QoL questionnaires resulted in good subjective outcome for patients in both study groups.

The impact of surgery on vaginal anatomy, on sexual and urinary function, and on the rate of mesh erosion might be influenced by surgical approach and by associated procedures, as well as by mesh type. The technique for cystocele repair adopted in this study was TCR, described by our group in a previous report (15). As a result, the outcomes of the present study might not be predictive of the effect of the studied grafts when other surgical techniques, such as the popular trans-obturator approach, are adopted. This may limit the implications of our results for current clinical practice.

Recently, a biologic graft of porcine dermis, cross-linked but with a perforated structure, was developed and introduced in the market (Pelvisoft? , CR Bard, Cranston, R.I., USA). The addition of perforations might allow better native tissue ingrowth and graft incorporation, maybe overcoming the risk of encapsulation and possibly yielding better tissue support.

Recently, surgical kits combining a polypropylene structure with biologic lining on the vaginal side of the graft have been developed and introduced in the market (e.g., Avaulta Plus? BioSynthetic Support System, CR Bard, Covington, GA).

Those modifications, combining a trans-obturator approach with biologic grafts, may become a safe and effective option for cystocele repair, the main withdraw being the high cost of biologic graft kits currently commercially available.

Such innovations, aimed at delivering strong tissue support while yielding low erosion rates, should be the subject for future research and should be evaluated in the context of further prospective, randomized trials.

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Tab. 1 - Demographic data

	Gynemesh PS®	Pelvicol®.	P
Patients	96	94	0.18
Age	49-79 (mean 62.5 SD 8.5)	50-82 (mean 67.0 SD 8.1)	0.24
Parity	0-4 (median 2)	0-4 (median 2)	0.51
Menopause	90 (93.8%)	86 (94.7%)	0.35
BMI	20.9-43.4 (mean 25.9 SD 5.5)	18.6-39.1 (mean 24.7 SD 4.5)	0.34
N° sexually active	56 (58.3%)	48 (51.1%)	0.44

BMI : body mass index

Table 2 – POP-Q measurements at baseline

	Stage 0	Stage I	Stage II	Stage III	Stage IV
Gynemesh PS®					
Point Ba	0	0	26	60	10
Point C	16	50	9	15	6
Point Bp	20	48	16	9	3
Pelvicol					
Point Ba	0	0	27	58	9
Point C	7	38	24	20	5
Point Bp	13	45	16	19	1

Table 3 - Pre and post-op symptoms Gynemesh PS® and Pelvicol® groups

	Gynemesh PS® 96 paz			Pelvicol® 94 paz		
	Pre-op # (%)	**Post-op # (%)**	**P***	**Pre-op # (%)**	**Post-op # (%)**	**P***
Urgency	30(31.3)	12(12.5)	0.5	48(51.1)	21(22.3)	0.26
Urgency Urinary Incontinence	33(34.3)	12(12,5)	0.3	45(47.9)	20(21.3)	0.38
Voiding symptoms	57(61,29)	12(12,5)	0.001	39(44,82)	1(1.1)	0.003
Post-micturition symptoms	48(51,61)	12(12,5)	0.001	39(44,82)	1(1.1)	0.003
Symptoms associated with POP	63(67,64)	3(3.1)	0.001	57(65,51)	3(3.2)	0.004

Table 4 – pre- and post-op urodynamic parameters in the Gynemesh PS® and Pelvicol groups

	Gynemesh PS®			Pelvicol®		
	Pre-op # (%)	**Post-op # (%)**	**P***	**Pre-op # (%)**	**Post-op # (%)**	**P***
Detrusor pressure at maximum flow	2-100 cm H2O (mean 31.68 cm H2O SD 20.96)	8-57cm H2O (mean 31.75 cm H2O SD 24.62)	0.88*	2-61 cm H2O (mean 30.68 cm H2O SD 14.38)	4-54 mc H2O (mean 25.70 cm H2O SD 13.53)	0.002*
Maximum flow	2-36 ml/sec (mean 12.46 ml/sec SD 7.46)	5-25 ml/sec (mean 13.59 ml/sec SD 6.15)	0.76*	6-32 ml/sec (mean 13.48 ml/sec SD 6.27)	7-21 ml/sec (mean 13.83 ml/sec SD 4.78)	0.83*