Univerzita Karlova

1. lékařská fakulta

Autoreferát disertační práce

UNIVERZITA KARLOVA
1. lékařská fakulta

Stanovení indikace k u užití cizorodých materiálů v rekonstrukčních operacích pánevního dna

To determine the indication for the use of synthetic materials in pelvic floor reconstructive surgery

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Disertační práce bude nejméně pět pracovních dnů před konáním obhajoby zveřejněna k nahlížení veřejnosti v tištěné podobě na Oddělení pro vědeckou činnost a zahraniční styky Děkanátu 1. lékařské fakulty.

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Abstract

Introduction: Pelvic organ prolapse is a major health problem affecting 50% of parous women over the age of 50. The lifetime risk for pelvic floor surgery for prolapse is likely to be between 10 and 20% and a large number of patients require repeat surgery for recurrence. Cochrane review showed that mesh use at the time of anterior repair reduce the risk of recurrence. In our first study we prospectively evaluate the impact of mesh insertion during anterior repair on sexual function and quality of life. Mesh insertion may be associated with significant and in some cases serious adverse events. To justify its use, it seems necessary to identify women at high risk of prolapse recurrence. There is evidence indicating that levator ani avulsion injury is closely associated with prolapse recurrence. The aim of our second and main study was to demonstrate in a prospective randomized way that levator avulsion may be used to identify patients at high risk for failed native tissue prolapse surgery.

Methods: The first study prospectively evaluated with validated questionnaires the impact of mesh insertion on quality of life and sexual function. The second study is a single-center, prospective, randomized interventional trial of two standard surgical procedures for post-hysterectomy vaginal vault prolapse in women with levator ani avulsion injury: Prolift total and unilateral sacrospinous vaginal fixation with native tissue vaginal repair. The primary outcome was anatomical failure based on clinical and ultrasound assessment.

Results: Significant decrease of quality of life questionnaires scores and significant increase of PISQ-12 scores occurred after anterior repair with mesh insertion. The incidence of de novo dyspareunia after mesh repair was 4%. In the second study, at one-year follow-up we found one anatomical failure on clinical examination in the Prolift group (3%), and 22 failures in the native tissue vaginal repair group (65%), (Chi-Square: $p<0.001$).

Conclusions: Mesh insertion during reconstructive surgery do not deteriorate sexual function. Despite this finding, because of mesh-related complications, mesh should be use in indicated situations as in women at high risk of recurrence. At one-year follow-up, native tissue repair as vaginal sacrospinous fixation in patients with prolapse and avulsion levator injury has a high anatomical failure rate as 65% compared to 3% failure rate for procedure using synthetic mesh. This is the first study to demonstrate in a prospective and randomized way that ultrasound diagnosis of levator avulsion Injury identifies patients at high risk of prolapse recurrence after native tissue reconstructive surgery. To decrease recurrence risk, levator avulsion injury may be an indication for the use of synthetic materials in pelvic floor reconstructive surgery.

KEY WORDS: Pelvic organ prolapse, mesh, ultrasound assessment, levator ani avulsion, sexual function, quality of life

Abstrakt

Úvod: Výhřez pánevných orgánů je hlavním zdravotním problémem, který postihuje 50% žen ve věku nad 50 let. Celoživotní riziko podstoupení operaci pro sestup pánevních orgánů je mezi 10 a 20% a velký počet pacientek vyžaduje opakovanou operaci pro recidivu. Cochranové studie ukázalzy že použití syntetických sítěk v době rekonstrukčních operací snižuje riziko recidivy. V naši první studii jsme prospektivně zhodnotili dopad užití sítěk na sexuální funkce a kvalitu života. Použití sítěk může být někdy spojeno s významnými a v některých případech s vážnými nežádoucími následky. Pro zdůvodnění jejích použití je nutné identifikovat ženy s vysokým rizikem recidivy prolapsu. Existují důkazy, které naznačují, že avulzní poranění levatoru je úzce spojeno s recidivou prolapsu. Cílem naše druhé a hlavní studie bylo prokázat prospektivně a randomizovaně, že avulzní poranění levatoru může být použit k identifikaci pacientek s vysokým rizikem recidivy prolapsu.

Metodika: První studie prospektivně zhodnotila s validnými dotazníky kvality života vliv sítěk na kvalitu života a sexuální funkce. Druhá studie byla prospektivní a randomizovaná intervenční studie srovnávající dvou standardních chirurgických postupů: Prolift Total a klasická operace dle Amreicha-Richtera v řešení prolapsu poševního pahýlu u žen po hysterektomii a s avulzí levatoru. Primárním cílem bylo hodnotit anatomické selhání na základě klinického a ultrazvukového vyšetření.

Výsledky: Významné snížení skóre dotazníků kvality života a významné zvýšení skóre PISQ-12 dotazníků se vyskytlo 6 měsíců po operaci cystokély s užitím sítky. Výskyt de novo dyspareunie byl 4%. Ve druhé studii jsme u jednoletého hodnocení, zjistili jedno anatomické selhání při klinickém vyšetření u skupiny Prolift (3%) a 22 selhání ve skupině klasické sakrospinální kolpopexe (65%) (Chi-Square: $p < 0{,}001$).

Závěr: Použití sítěk během rekonstrukčních operací pánevního dna nezhoršuje sexuální život po operaci. Ale, vzhledem k možným komplikacím souvisejícím s použití sítěk, síťky by měly byt použití jen v indikovaných situacích, jako u žen s vysokým rizikem recidivy. Vaginální sakrospinální kolpopexe u pacientek se symptomatickým sestupem po předchozí hysterektomii a s avulzí levatoru má vysoké 65% výskyt recidivy ve srovnání s 3% u operace s Proliftem jeden rok od výkonu. Jedná se o první studii, která demonstruje prospektivně a randomizovaně že avulzní poranění levatoru identifikuje pacientky s vysokým rizikem recidivy prolapsu. Ke snížení riziko recidivy, avulzní poranění levatoru může být indikací k použití syntetických materiálů v rekonstrukční operacich pánevního dna.

KLÍČOVA SLOVÁ: Výhřez pánevních orgánů, syntetické sítky, ultrazvuk, avulze levatoru, sexuální funkce, kvalita života

1. Introduction

Pelvic organ prolapse is a major health problem affecting 50% of parous women over 50 years of age (Subak L.L. et al, 2001). Surgical repairs using autologous tissues are associated with anatomic prolapse recurrence rates of 30 to 50% (Shull B.L. et al., 1994). The Cochrane review showed that mesh use at the time of anterior repair reduce the risk of recurrent anterior vaginal wall prolapse (Maher CM. et al., 2011). But there is some concern about sexual function after this surgery because mesh insertion might disturb the delicate erectile reflex of the anterior vaginal wall and deteriorate the sexual response (Tunuguntla HS., Gousse AE., 2006). Mesh insertion may by also associated with mesh-related complications and sometimes with significant and serious adverse events. To justify the use of synthetic materials and these related potential complications, it seems necessary to identify patients at high risk of prolapse recurrence (Dietz H.P., 2012) There is evidence indicating that levator ani avulsion injury is closely associated with prolapse. Avulsion is a detachment of the pubovisceralis muscle from its insertion on the inferior pubic ramus, and this is clearly associated with vaginal childbirth (Dietz H.P., Lanzarone V. , 2005) (Kearney R. et al., 2006). This leads overtime to enlargement of the levator hiatus ('ballooning') (Dietz H.P. et al., 2008). Women with levator avulsion defects are about twice as likely to show pelvic organ prolapse of stage II or higher than those without such defects. The association seems strongest for cystocele (RR 2.3, 95% CI 2.0–2.7) and uterine prolapse (RR 4.0, 95% CI 2.5–6.5) (Dietz H.P., Simpson J.M., 2008). The relative risk of recurrence after anterior colporrhaphy in patients with levator avulsion injury is 3-4 times higher than in those without (Dietz H.P. et al., 2010) (Weemhoff M. et al. , 2012). Hence, it seems that levator avulsion may be used to identify patients at high risk for failed prolapse surgery (Haylen B.T. et al, 2010) (Rogers R.G.et al., 2003), where the use of synthetic materials to reinforce pelvic floor reconstructive surgery may be indicated.

2. Objectives and research hypothesis

There is evidence for mesh use at the time of anterior repair of pelvic organ prolapse because it reduces the risk of recurrence. However, mesh insertion can be associated with unique mesh-related complications and sometimes with significant and serious adverse events worsening quality of life. Therefore, we hypothesis that synthetic reinforcement during pelvic floor surgery should be used only in selected group of patients at high risk of recurrence.

Our hypothesis:

1. Mesh insertion during anterior repair in the hand of experienced urogynecologist do not deteriorate sexual function and quality of life.
2. The ultrasound 3D/4D assessment of levator ani muscle avulsion injury identifies patients at high risk of prolapse recurrence after classical pelvic organ prolapse surgeries.
3. Levator ani muscle avulsion is a selection criterion for the use of synthetic materials during reconstructive surgery to decrease the prolapse recurrence.

3. Study 1 (El Haddad R. et al, 2013)

3.1 Aim and methods

We undertook a prospective study on the safety and efficacy of two mesh implantation techniques for anterior vaginal wall prolapse repair. The aim of our present study was to evaluate the impact of mesh insertion on sexual activity, sexual function and quality of life.

Women with symptomatic stage II or greater prolapse of the anterior compartment and with no symptomatic prolapse of other compartments that might require surgical repair, referred to our tertiary urogynecological unit between September 2007 and May 2009 were recruited to join this prospective observational study. They were assessed with a standardized interview that included questions about symptoms of urinary incontinence, pelvic organ prolapse (POP) and sexual function and examined before, 3 and 6 months after surgery. All patients had urodynamic examination, pelvic floor ultrasound and pelvic assessment according to the International Continence Society POP- Quantification system (Haylen B.T. et al, 2010). Sexual function was assessed by inviting the patients to complete the validated condition-specific short form of the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12) (Rogers R.G.et al., 2003) before and six months after surgery. Validated QoL questionnaires (Barber M.D. et al, 2001) (Barber M.D. et al, 2006): POP distress inventory (POPDI), urinary distress inventory (UDI), POP impact questionnaire (POPIQ), and urinary impact questionnaire (UIQ) were completed pre- and 6 months post-operatively. To explore the incidence of dyspareunia and de novo dyspareunia, we analyzed the results of the PISQ-12 question 5: do you feel pain during intercourse? The possible answers are: always, usually, sometimes, seldom or never. Dyspareunia was defined as responses: sometimes, usually or always. 69 women were eligible to join this study. They were divided according to a protocol into two groups: the mesh group: treated with AR augmented by individualized mesh (Gynemesh®, Gynecare PS, Ethicon, Sommerville, NJ, USA) without lateral fixation (Mesh; n=33) and the Prolift group: treated with a Prolift anterior® (Prolift anterior™, Gynecare, Ethicon, Sommerville, NJ, USA) (Prolift; n=36). All patients received intra-operatively one prophylactic dose of antibiotics and vaginal packing was left for 24 hours. Concomitant continence procedures were not allowed. All patients attended the first control within 3 months postoperatively. Those with persistent or de novo symptoms of stress urinary incontinence (SUI) were booked to urodynamic exams and after confirming of urodynamic USI a continence procedure was performed 7-9 months post-operatively.

All data were processed and analyzed in statistical computing environment R, version 2.9.1. Continuous data were summarized as mean with standard deviation (SD) and as median or quartile range (QR). For comparison of two groups F-test was used. Wilcoxon and Kruskal-Wallis tests were used when the assumption of normality was not met. Tests were performed at 5% level of significance. To detect a 10% difference in the PISQ-12 scores between patients with POP before and after AR and to achieve a power of 90 % a minimum sample size of 32 patients was needed. The local ethics committee NR/9216-3 approved this study and all participated patients gave a written informed consent.

3.2 Results

69 women participated in this study. All women were Caucasians. Demographic data showed no statistically significant differences between the groups. The mean age was 60.7 (SD 10,2), mean parity 2.0 (SD 0.5) and mean BMI 27.8 (SD 3.7). 64 women (93%) were postmenopausal. 34 (49%) had previous hysterectomy and 15 (22%) had previous vaginal repair. Before surgery 37 women (53%) were sexually active and 32 (47%) were not. The majority of sexually inactive women were no longer interested in sexual intercourse and only 4 women were inactive for partner related reasons (two for not having a partner and two for erection disability of the partner).

All sexually active women resume their sexual activity postoperatively.

The majority of non-sexually active women remained sexually inactive (31 of 32).

Two women didn't complete the PISQ-12 questionnaires preoperatively and QoL questionnaires of 4 women were missed or incomplete. 35 complete PISQ-12 questionnaires and 65 POPDI, UDI, POPIQ and UIQ of the same patients pre- and post-operatively were available for analysis. Pre-operative PISQ-12 and QoL parameters were not significantly different between groups.

Tab.1 demonstrates a statistically significant improvement of PISQ-12.

Tab. 1 Impact of different techniques of anterior repair on sexual function

	Prolift			Mesh			
	N	PISQ Median	QR	*N*	PISQ Median	QR	p Kruskal-Wallis
Before surgery	19	33.0	4.0	16	35.0	8.25	0.6363
After surgery	19	36.0	5.0	16	36.0	6.0	0.7422
Change from baseline	19	1.0	6.0	16	1.0	5.25	0.6945
p Wilcoxon	**0.03321***						

*** statistically significant**

Before surgery, the incidence of dyspareunia among women with cystocele was 25% (9 of 35): 4 women reported dyspareunia usually or always and 5 experienced pain during intercourse only sometimes. After surgery 10 women (29%) reported dyspareunia: one patient with de novo dyspareunia felt pain during intercourse sometimes as other 6 and 3 patients reported dyspareunia usually. Worsening occurred in 31%, while improvement or no impact on frequency of pain occurred in 69% of women.

The incidence of de novo dyspareunia was 4% (1 out 26 women with no dyspareunia before surgery)

There were no surgical or post-operative complications requiring reoperation. The overall incidence of mesh exposure was 11.5% (8/69): four exposures in the group of non-sexually active women and 4 in the sexually active women. Their PISQ 12 scores were 26, 31, 29, 23 before surgery and 40, 32, 28 and 27 respectively after surgery. The frequency of pain decreased in the first patient from usually to seldom. The second women had no dyspareunia before and after surgery. The frequency of pain increased from seldom to sometimes for the third patient. The fourth patient felt usually pain during intercourse before and after surgery.
Mesh exposure occurred five times in the Prolift group (5/36) and three times in the mesh group (3/33), with p=0.3083. All exposures were asymptomatic 2 or 3 Aa T2 S1.

There was a significant decrease of UIQ, POPIQ, UDI and POPDI scores that indicate an improvement of QoL after surgery.

3.3 Discussion

Sexual dysfunction, de novo dyspareunia and mesh exposure after transvaginal mesh surgery represent the main concern for every surgeon. Studies, which reported about these problematic issues, are few in number and often with conflicting results (Moore R.D. et al, 2010).

In our study, the statistically significant increase of PISQ 12 score and decrease in quality of life questionnaires scores indicate an improvement in sexual function and in quality of life. These results are consistent with previous studies (Gauruder-Burmester et al, 2009) (Moore R.D. et al, 2010) (Hoda M.R. et al , 2011) and suggest that mesh insertion by itself should not have a priori a negative effect on sexual function.

In addition, all sexually active women resume their sexual activity postoperatively and despite quality of life improvement, the majority of sexually inactive women remain sexually inactive. We can conclude that sexual activity is not changed by surgery. These conclusions are similar with previously published statement of Gauruder-Burmester et al. (Gauruder-Burmester et al, 2009) that sexual dysfunction is not related to urogynecological surgery and vaginal mesh repair does not interfere with a healthy sexual life.

Women in our study were in the majority postmenopausal, and the baseline dyspareunia was 25%. Dyspareunia is commonly reported in late menopause (Dennerstein L. et al, 2003) and in women with pelvic floor disorders (Silva W.A. et al, 2006) (Handa V.L. et al, 2007) (Lowman J.K. et al, 2008). Only few data are available on de novo dyspareunia and this severe complication may occur after cystocele repair with or without mesh insertion. Weber et al. (Weber A.M. et al, 2000) found a 19% de novo dyspareunia rate after anterior colporrhaphy.

In our study the rate of de novo dyspareunia after mesh insertion was 4% that is lower than the 17% reported by Lowman et al. (Lowman J.K. et al, 2008) after Prolift procedures. This may be due to the large experience of the surgeons involved in this study.

The incidence of mesh exposure in this study was 11.5 % and is similar reported by Jacquetin et al. (Jacquetin B. et al , 2010) and Maher et al. in the cochrane review on surgical management of POP in women (Maher C.M. et al., 2011). All exposures were asymptomatic. Mesh exposure is a specific complication for mesh use, and we can suggest that asymptomatic does not necessary impair sexual function. Negative impact on sexual function and quality of life might be mostly caused by severe complications as mesh mal-insertion, mesh protrusion to adjacent organs and fistulas. All these mesh-related complications may require additional surgery.

In accordance with the FDA safety communication in July 2011 (FDA safety communication, 2011) , the use of mesh should be indicated in specific situations and patients should be fully aware of these complications prior to giving consent.

There is a concern that further mesh shrinkage might cause dyspareunia, but Dietz et al. (Dietz H.P. et al, 2011) concluded after analyzing ultrasound volumes of 40 women followed-up for an average of 18 months, starting 3 months after Perigee mesh implantation, that there was no evidence of mesh shrinkage. Svabik et al. (Svabik K. et al, 2011) found that intraoperative folding seems to be responsible for a large part of the difference between preoperative (in vitro) and postoperative measurements of mesh dimensions.

The strength of our study is being prospective and reports with condition specific validated questionnaires on the impact of transvaginal mesh insertion on sexual function, quality of life and on pain during intercourse.

In conclusion the results of our study suggest no deterioration in sexual function, a significant improvement of quality of life and a low incidence of de novo dyspareunia six months after anterior repair with mesh insertion.

4.Study 2 (Svabik K. et al., 2014)

4.1 Aim and methods

Our aim was to compare, with a one-year follow-up, the efficacy of two standard surgical procedures for vaginal vault prolapse – Total Prolift and sacrospinous fixation with native tissue vaginal repair (SSF) - for patients with post-hysterectomy prolapse. We limited this trial to patients who had been diagnosed with levator avulsion in order to maximize its robustness and indicate the potential benefit of mesh use. We considered that it is potentially unethical to offer mesh to all patients with post- hysterectomy prolapse due to concerns about mesh complications, and since there is some evidence that reduction in recurrence due to mesh may be limited largely to patients with levator avulsion (Wong V. et al. , 2011)

This was a single-center, prospective, randomized controlled trial of two standard surgical procedures for post-hysterectomy vaginal vault prolapse: Total Prolift (Total Prolift ™, Gynecare, Ethicon, Sommerville, NJ, USA) and sacrospinous vaginal colpopexy (the Amreich-Richter procedure) with native tissue vaginal repair (anterior and posterior vaginal repair) – SSF (Kaum H., 2003). Both procedures are designed to treat vault prolapse vaginally – one

with mesh implantation and the other with vaginal repairs and apical fixation to the sacrospinous ligament, usually on the right (Maher C.F. et al., 2004) (Hefni M.A., 2006) (Jacquetin B. et al, 2010).

All patients attended our urogynecological unit (Ob/Gyn Department of General University Hospital in Prague) during the period from 2008 to 2011. Eligible for inclusion were: post-hysterectomy patients with at least two compartments prolapse (with affected apical/vault compartment, stage II or higher on the Pelvic Organ Prolapse Quantification system) (Bump R.C. et al, 1996), suffering from symptoms of prolapse, requesting pelvic floor reconstructive surgery, and diagnosed with a complete unilateral or bilateral avulsion injury.

Excluded were: patients with prolapse and uterus in place, those without levator ani avulsion and those not requesting pelvic floor surgery.

Patients underwent identical pre- and postoperative assessment procedures, including POP-Q examination, 4D ultrasonography with acquisition of volume datasets at rest, during pelvic floor muscle contraction (PFMC), and on maximum Valsalva maneuver, which were archived on a server, and validated questionnaires. The study was approved by the local ethics committee (as part of national grant application NT 12147-4) and all subjects gave written informed consent to participate.

At the time of enrolment (usually 2–3months prior to surgery), to fulfill the main inclusion criterion, preoperative levator assessment and avulsion diagnosis was performed.

Patients were examined clinically and by translabial 3D/4D ultrasound by one of two physicians (K.S. and J.M.), both experienced in pelvic floor ultrasound examination, using a Voluson 730 Expert/E8 system (GE Medical Systems, Zipf, Austria) equipped with an 8–4-MHz curved array volume transducer. The POP-Q classification for prolapse was used, and diagnosis of avulsion injury was performed by palpation and confirmed by 3D tomographic ultrasound imaging during maximum PFMC, using the levator–urethra gap measurement in three axial slices (one at the plane of minimal hiatal dimensions and two parallel slices, with 2.5-mm slice intervals, above this reference plane) (Dietz H.P., Shek K.L. , 2009) (Dietz H.P. et al., 2011) (Dietz H.P., Shek K.L. , 2008).

In addition, volume datasets were acquired with the patient in a supine position and with empty bladder, at rest, on maximum Valsalva maneuver and during PFMC, for later offline analysis using the proprietary software GE Kretz 4D View v. 9.0 (GE Medical Systems). This analysis included measurement of levator ani hiatal dimensions on Valsalva maneuver in the axial plane of minimal hiatal dimensions (Dietz H.P., Simpson J.M., 2008). All offline analyses were performed by one of two doctors (R.E. and P.H.), who were semi-blinded: they were not aware of the POP-Q score or the surgical procedure, but in most cases postoperatively, the implants were visible on ultrasound.

The randomization process was carried out the night before surgery by computer and emailed from a remote center after sending the hospitalization the numbers of the patients. Both procedures were performed by experienced surgeons (K.S. or J.M., both of whom are familiar with both procedures), with the patient under general anesthesia.

For the Prolift Total procedure, the Prolift Total kit was used and the mesh placed according to the recommended technique (Jacquetin B. et al, 2010).

In all cases in the SSF group we performed conventional anterior vaginal repair and posterior high levatorplasty. The anterior vaginal repair (fascial plication of the entire anterior wall starting at the level of the bladder neck) was done using Vicryl plus 2.0 stitches (Ethicon). For the posterior high levatorplasty, Vicryl plus 1.0 stitches (Ethicon) were used. The SSF procedure was performed unilaterally on the right using two permanent sutures of Nurolon 1.0 (Ethicon) inserted under visual control and attached to the vaginal apex.

Patients were followed up at 3 months and at 1 year (Toozs-Hobson P. et al., 2012). These postoperative clinical examinations were performed by a single examiner (A.M.), who had not been involved with the surgical procedures and was unaware of a patient's procedure at the start of the assessment, although in some cases group allocation became obvious due to palpable mesh, mesh erosion or visibility of an SSF suture.

The follow-up translabial ultrasound examinations were performed by a single examiner (K.S.) after the clinical examination. Anterior vaginal wall descent was assessed in the mid-sagittal plane, at maximum Valsalva maneuver. The inferior margin of the symphysis pubis was used as a reference point, with measurements presented being distances from this reference line, as previously published (Dietz H.P. et al., 2011). Two reference points of the anterior vaginal wall were defined: the bladder neck and the lowermost part of the bladder wall.

As in the preoperative examination, volume datasets were stored for later offline analysis by the same two doctors (R.E. and P.H.).

At the 3-month follow-up, in cases of urinary stress incontinence we offered patients treatment with a tension free vaginal tape-obturator (TVT-O) procedure. In the case of recurrence of prolapse and distressing symptoms which a patient desired to be resolved, we performed reoperation of prolapse (symptomatic prolapse). For evaluation in such cases we used the 'last failure carried forward' method, i.e. in cases which underwent an anti-incontinence procedure or reoperation after the 3-month follow-up, we used the data obtained at the 3-month follow-up for evaluation rather than obtaining data at the 1-year follow-up.

The primary outcome measure was anatomical failure based on clinical and ultrasound assessment. Failure was defined clinically as Ba, C or Bp at the hymen or below, and on translabial ultrasound as bladder descent to10mm or more below the lower margin of the symphysis pubis on maximum Valsalva (Dietz H.P., Lekskulchai O., 2007).

As secondary outcome measures we used a continence status assessment based on a clinical stress test performed with the bladder containing 200–300mL urine and assessed by ultrasound, and on subjective evaluation of continence, sexual function and prolapse symptoms based on validated questionnaires: ICIQ-SF (International Consultation for Incontinence Questionnaire – Short Form), PISQ-12 (Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire), POPDI, UDI (Urinary Distress Inventory) and CRADI (Colorectal Distress Inventory).

The power calculation was based on the two primary outcome measures and available data which led us to expect a failure rate of 60% in the SSF group (Dietz H.P., Simpson J.M., 2008). To detect an expected difference of 45% between the groups, with 80% power of the test and with a 5% level of significance, 30 patients were required in each group. Data were analyzed using the software STATISTICA 10 (StatSoft. Inc software, Tulsa, OK, USA). Descriptive analyses are provided. Comparisons between the groups were performed after normality testing by parametric two sample t-test or non-parametric Mann–Whitney U-test. Categorical data were analyzed by Pearson's chi-square test or the McNemar test. All tests were performed at the 5% level of significance.

4.2 Results

During the study period 592 patients underwent surgery for female pelvic organ prolapse in our unit. Of these, 142 had a post-hysterectomy vault prolapse, of whom 72 were diagnosed with an avulsion injury. These patients were offered participation in this trial, and 70 were randomized into two groups: 36 in the Prolift group and 34 in the SSF group.

There were no drop-outs during the one-year follow-up process.

There was no difference between the groups in terms of demographic parameters and pre-operative POPQ, or in ultrasound measures used as outcome measures in this trial.
There were no major complications such as heavy bleeding, bladder or bowel injury in either group.

At the 3-month follow-up 11 patients in the Prolift group and three in the SSF group were diagnosed with stress urinary incontinence and scheduled for a TVT-0 procedure. (Chi-Square - p=0.02).

Three patients in the SSF group were diagnosed with symptomatic prolapse recurrence and scheduled for repeat surgery. One patient underwent re-operation with Prolift total mesh, one patient with Prolift anterior mesh and one patient with Prolift posterior mesh.

No patients in the Prolift group were diagnosed with symptomatic recurrence (Chi-Square; p=0.06).

There was minor mesh exposure at 3-month follow up in the Prolift group in three (8%) cases.

There were five (15%) patients with vaginal blood spotting due to granulation tissue in the SSF group. All cases of vaginal blood spotting were treated on an outpatient basis.

Two cases of minor mesh exposure were resected during a TVT-o procedure; the third was asymptomatic and treated conservatively. There were no additional cases of protrusion at one-year follow-up.

At the 1-yearfollow-up, there was one (3%) anatomical failure clinically, i.e. prolapse to the hymen or beyond, in the Prolift group (posterior compartment), compared with 22 (65%) failures in the SSF group (20 affecting anterior, six central and eight posterior compartment) (chi-square $P<0.001$). In two of the latter cases, the anterior compartment was not affected.

Based on POP-Q grade II prolapse criteria, there were six (17%) failures in the Prolift group and 30 (88%) failures in the SSF group (chi-square $P<0.001$).

According to ultrasound criteria for anterior compartment prolapse recurrence, there was one (3%) failure in the Prolift group compared with 21 (62%) failures in the SSF group (Chi-Square; $p<0.001$).

There were significant differences between the Prolift and SSF groups for all POPQ parameters except genital hiatus size (GH), perineal body length (PB) and total vaginal length (TVL), see Table 2. On translabial ultrasound there was a significantly smaller hiatal area and a lower degree of bladder neck and bladder descent in the Prolift group

At the one-year follow-up, using a LFCF approach, 16 patients in the Prolift group and 10 in the SSF group were rated as stress incontinent (Chi-Square; $p=0.19$).

Sexual activity was not influenced by the type of surgery. There was no difference in PISQ 12 score between groups before and after the surgery.

The postoperative POPDI score for subjective outcome was 15.3 in the Prolift group vs. 21.7 in the SSF group (Mann-Whitney-U test – $p=0.16$).

4.5 Discussion

To the best of our knowledge, this is the first prospective, randomized study of women with vaginal prolapse to adopt the 3D/4D ultrasound diagnosis of levator avulsion as an entry criterion, based on the assumption that avulsion identifies a group of patients at high risk of prolapse recurrence after reconstructive surgery.

Female pelvic organ prolapse is a highly heterogeneous condition and the etiology is likely to be multifactorial. There are a number of studies identifying predictors of recurrence, with levator ani avulsion injury being one of the main risk factors for recurrent prolapse after

classical native tissue repair (Dietz H.P. et al., 2010) (Weemhoff M. et al. , 2012) (Wong V. et al. , 2011).

This prospective randomized controlled trial confirms the previous retrospective data showing high recurrence rates after native tissue repair, especially for the anterior compartment.

The study of Dietz et al. found a recurrence rate of 79% after native tissue repair at an average follow-up interval of 4.5 years in women with levator avulsion, which is comparable to our data of 62% failure at one year, using identical assessment criteria (Dietz H.P. et al., 2010).

The comparison of our data with the results of studies assessing similar procedures without levator ani assessment reveals substantial discrepancies. In general, recurrence rates are higher after SSF than after mesh treatment, but the differences between these groups are much smaller in studies not utilizing levator ani assessment (Halaska M. et al., 2012).

A comparison of our data in the SSF group with the results of studies using the same procedure shows our observed failure rate to be much higher. Hefni and El-Toukhy (Hefni M.A., El-Toukhy T.A., 2006) reported only 10% recurrent cystoceles at a median 15-month follow-up. Maher et al. (Maher C.F. et al., 2004), in a randomized trial comparing abdominal sacral colpopexy and vaginal sacrospinous colpopexy (SSF), found at 2-year follow-up that there was no difference in objective cure rates between the groups. The cure rate in the SSF group was 9%. Such discrepancies are likely to be due to our selection of a high-risk group of patients, which apparently increased substantially the power of our study.

As regards of mesh-related complications, on the other hand, our results are comparable to data in the literature. The protrusion rate of 8.3% is similar to that reported in other trials (Feiner B., Maher C., 2010) (Jacquetin B. et al , 2010) (De Landsheere L.et al., 2012).

We observed a significantly higher reoperation rate for urinary stress incontinence in the Prolift group, which differs from previously published data (Maher C.M. et al., 2011). This is consistent with a higher prolapse recurrence rate in the SSF group, which may have resulted in a higher incidence of urethral kinking, masking stress incontinence in those with recurrent cystocele. It has been shown by Eisenberg et al. that avulsion is associated with Green type III cystocele and an increased likelihood of urethral kinking and voiding problems rather than stress incontinence (Eisenberg V.H. et al., 2010).

It is interesting that despite the highly significant difference in anatomical failure rates we were unable to show any difference in subjective outcomes using the Distress inventory questionnaire. This correlates with many previously published studies (Maher CM. et al., 2011) (Dietz H.P. et al., 2010) (Halaska M. et al., 2012) and may be due to a lack of power. A post-hoc power calculation based on questionnaire results suggests that, in order to prove the superiority of mesh surgery with questionnaire data as primary outcome measure, we would have needed 200 patients in each arm. This is very likely due to the large variability in assessment of subjective symptoms (El Haddad R. et al., 2012). This observation raises the question of which outcome measures to choose in trials of this kind. Clearly, subjective measures are important since our ultimate goal is not cosmetic improvement, but improvement

of quality of life. However, assuming that one procedure is superior in correcting an anatomical abnormality that is causing significant symptoms (as shown in our study), it may be neither ethical nor economical to require much larger trials for proof of superiority on the basis of inferior outcome measures. Requiring a trial of 400 patients rather than 60 would of course mean that a much larger number of patients would have to undergo an inferior procedure.

Several weaknesses of this trial have to be acknowledged. The Total Prolift mesh has recently been removed from the market. However, judging from published data it is likely that our conclusions may apply to other type I polypropylene meshes (Wong V. et al. , 2011). The transvaginal synthetic materials used currently for pelvic organ prolapse reconstructive surgery are Type I light or ultralightweight meshes (second generation mesh) as Uphold (Altman D. et al., 2016) and Surgimesh (De Tayrac R. et al., 2015). The second-generation mesh is very well tolerated (contraction rate of 5.1 %, exposure rate of 1.3 %, no cases of residual pain, and postoperative dyspareunia rate of 2.8 %) (De Tayrac R. et al., 2015).

Furthermore, the follow-up of the study is one year, which may be considered too short, although recent data suggests that the vast majority of prolapse recurrences are evident at the one- year mark (Hankins K. et al., 2014). We will, however, continue the follow-up in order to assess long-term outcomes and complications. We are aware that, due to palpable or visible mesh or visibility of SSF sutures, there was a lack of blinding during the assessment in some patients; this is unavoidable in trials of this kind. We tried to minimize any resulting bias by using two objective assessment methods, i.e. the POP-Q and sonographic assessment of prolapse.

5. Conclusion and recommendations

Hypothesis summary:

1- Mesh insertion during anterior repair in the hand of experienced urogynecologist do not deteriorate sexual function and quality of life.

We were able to prospectively demonstrate with validated questionnaires that mesh insertion during anterior vaginal repair do not worsen the sexual function and there is a significant improvement in quality of life and a low incidence of de novo dyspareunia 6 months after surgery. Our first hypothesis was confirmed.

2- The ultrasound 3D/4D assessment of levator ani muscle avulsion injury, identifies patients at high risk of prolapse recurrence after classical pelvic organ prolapse surgeries.

In our second prospective randomized controlled trial, we were able to demonstrate and confirm the previous retrospective data, that women with levator avulsion injury undergoing a native tissue reconstructive surgery for pelvic organ prolapse have a high 65% risk of recurrence. In other words, the ultrasound diagnosis of levator ani avulsion in women with symptomatic

prolapse advocates that they are at high risk for failed native tissue reconstructive surgery. The hypothesis was confirmed.

3- Levator ani muscle avulsion is a selection criterion for the use of synthetic materials during reconstructive surgery to decrease the prolapse recurrence.

In a selected group of patients with levator ani muscle injury i.e. at high risk (65%) of recurrence after native tissue reconstructive surgery, the use of synthetic materials decreased the risk to 3%. The third hypothesis was also confirmed.

Recommendations:

To the best of our knowledge this is the first prospective, randomized study suggesting the routine evaluation of levator avulsion injury as an entry criterion to identify patients at high risk of prolapse recurrence.

The largest population-based study of 110,329 women undergoing pelvic organ prolapse repair between 2005-2011 in the state of California provides evidence that patient selection plays the most important role to decrease mesh complications and Dallas et al asked for further research to better understand which patients specifically are at higher risk of native tissue repair failure (Dallas K.B. et al., 2018).

Our study provides the way to select patients that could benefit the most from the use of synthetic mesh reinforcement (abdominally or vaginally) where the decrease of recurrence will be balanced against possible risks of mesh specific complications.

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7.1.a. Publications related to thesis with impact factor

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