Univerzita Karlova
1. lékařská fakulta

Doktorský studijní program v biomedicíně
Studijní obor: Experimentální chirurgie

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Stanovení indikace k užití cizorodých materiálů v rekonstrukčních operacích pánevního dna

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

Disertační práce

Školitel: as. MUDr. Kamil Švabík, PhD

Praha 2018

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Identifikační záznam:

El Haddad, Rachid. 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]. Praha, 2018, 66 s., 5 příl. Disertační práce (PhD.). Univerzita Karlova, 1. lékařská fakulta, Gynekologicko-porodnická Klinika. Školitel: as. MUDr Kamil Švabík, PhD.

PODĚKOVÁNÍ

Rád bych poděkoval všem svým učitelům a školiteli za pomoc při realizaci projektu:

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Table of contents

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). When using mesh, the recurrence rate decreases to 7% (Fatton B. et al., 2007). In 2010 approximately 300,000 women underwent surgical procedures in the United States to repair pelvic organ prolapse and approximately one out of three pelvic organ prolapse surgeries used mesh, and three out of four procedures were done transvaginally (FDA safety communication, 2011). The anterior vaginal wall is the most common site of prolapse where surgery might disturb the delicate erectile reflex and sexual response (Tunuguntla HS., Gousse AE., 2006) leading to sexual function's deterioration. Current evidence of pelvic floor surgery's impact on sexual function is conflicting (Thakar R., 2009). Only few studies reported with validated questionnaires on sexual function and quality of life after transvaginal mesh repair with a discrepancy in reported outcomes (Nieminen K. et al, 2008) (Lowenstein L. et al, 2010) (Sentilhes L. et al, 2008) (Altman D. et al, 2009) (Su T.H. et al, 2009) (Milani A.L. et al, 2011) (Gauruder-Burmester et al, 2009). Recent 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). However, mesh insertion may by associated with significant and serious adverse events. To justify the use of mesh and 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 symptoms of prolapse are significantly associated with avulsion injury in patients

after hysterectomy (Model A.N. et al., 2010) (Dallenbach P. et al., 2007). 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.

1.1 Female pelvic floor anatomy:

Increased knowledge of the anatomy of the pelvic floor has led to a better understanding of the pathophysiology of the pelvic organ prolapse. Moreover, pelvic surgery requires a perfect knowledge of pelvic anatomy to avoid complications especially injuries to viscera, blood vessels and nerves.

1.2 The Bony pelvis:

Variations in the orientation and shape of the bony pelvis have been associated with the development of pelvic organ prolapse (Barber MD., 2005). Specifically, a loss of lumbar lordosis and a pelvic inlet that is less vertically oriented is more common in women who develop genital prolapse than in those who do not. A less vertical orientation of the pelvic inlet is thought to result in an alteration of the intra-abdominal vector forces that are normally directed anteriorly to the pubic symphysis such that a greater proportion is directed toward the pelvic viscera and their connective tissue and muscular supports. Similarly, women with a wide transverse pelvic inlet appear to be at increased risk of developing pelvic organ prolapse. Variations in the shape and orientation of the bony pelvis are also an important factor that influences maternal soft-tissue damage and nerve injury during parturition (Barber MD., 2005).

1.3 The Connective tissue support and Delancey's vaginal three levels (DeLancey JOL., 1992):

- The level I support:

The uterosacral/cardinal ligament complex originates at the cervix and upper vagina and inserts at the pelvic sidewall and sacrum. It suspends the uterus and upper vagina in its normal orientation. It serves to maintain vaginal length and

keep the vaginal axis nearly horizontal in a standing woman so that it can be supported by the levator plate.

Loss of level I support contributes to prolapse of the uterus and/or vaginal apex.

- The level II support:

The anterior vagina is suspended laterally to the arcus tendineus fasciae pelvis, or white line, which is a thickened condensation of fascia overlying the iliococcygeus muscle. The arcus tendineus fascia pelvis originates on the ischial spine and inserts on the inferior aspect of the pubic symphysis. The anterior paravaginal attachment suspends the mid-portion of the anterior vaginal wall, creating the anterior lateral vaginal sulci.

Detachment of these lateral supports can lead to paravaginal defects and prolapse of the anterior vaginal wall (Barber MD., 2005).

The posterior vaginal wall is attached laterally to the pelvic sidewall and fuses with the aponeurosis of the levator ani muscle from the perineal body along a line referred to as the arcus tendinous rectovaginalis. In the proximal vagina, the lateral supports for the anterior and posterior vaginal wall are identical. This arrangement accounts for the H-shape or box-like configuration of the distal vagina when viewed in cross-section and the flattened-tube configuration seen in the upper vagina.

- Level III support:

It is provided by the perineal membrane, the muscles of the deep perineal space, and the perineal body. These structures support and maintain the normal anatomical position of the urethra and the distal third of the vagina, which is perpendicular to the floor in a standing woman. At level III, the vagina fuses with the urethra anteriorly and with the perineal body posteriorly.

Disruption of level III support anteriorly can result in urethral hypermobility and stress incontinence, and disruption posteriorly may result in distal rectoceles and/or perineal descent (Barber MD., 2005).

1.4 Muscular support of the pelvic floor:

The pelvic floor, particularly the levator ani muscle, has a critical role in supporting the pelvic visceral organs and play an integral role in urinary, defecatory, and sexual function.

The levator ani and the coccygeus muscles form the muscular floor of the pelvis. **The coccygeus muscle** extends from the ischial spine to the coccyx and the lower sacrum, forms the posterior part of the pelvic diaphragm.
The connective tissue covering the levator ani muscle on both superior and inferior surfaces is called superior and inferior fascia of the levator ani. The levator ani and the coccygeus muscles form with their associated fascia **the pelvic diaphragm**.

The Levator Ani Muscle:

The levator ani muscle has a major role in supporting the pelvic organs.

It is subdivided into 3 parts according to their attachments:

- The puboviscerallis arises from the posterior inferior pubic rami and anterior portion of the arcus tendinous of the levator ani on either side attaching to the walls of the pelvic organs and perineal body. It is further subdivided into: the puboperineus inserting into the perineal body, the pubovaginalis inserting onto the vaginal wall, and the puboanalis inserting into the intersphincteric groove of the anal canal muscle.

  The arcus tendinous of the levator ani is a dense connective tissue structure, that runs from the pubic ramus to the ischial spine and courses along the surface of the obturator internus muscle. It is a linear thickening of the fascial covering of the obturator internus muscle.
- The puborectalis muscle is located lateral to the pubovisceral muscle, originates on the pubic bone and forms a sling around and behind the rectum, cephalad to the external anal sphincter, resulting in the anorectal angle and supporting the closure of the urogenital hiatus. The urogenital hiatus is the space between the levator ani musculature through which the urethra, vagina, and rectum pass.

- The iliococcygeus muscle originates from the arcus tendineous levator ani and inserts in the midline onto the anococcygeal raphe and coccyx. It forms a flat horizontal shelf called the levator plate, on which the pelvic organs rest, which spans the potential gap from one pelvic sidewall to the other. When the body is in standing position, the levator plate is horizontal and support the rectum and the upper two third of the vagina.

1.5 Innervation of the pelvic floor muscles:

The pudendal nerve innervates the striated urethral and anal sphincters as well as the deep and superficial perineal muscles and provides sensory innervation to the external genitalia. This nerve follows a complex course that originates from S2–S4 n) and travels behind the sacrospinous ligament just medial to the ischial spine, exiting the pelvis through the greater sciatic foramen. It then enters the ischiorectal fossa through the lesser sciatic foramen and travels through the pudendal canal (Alcock's canal) on the medial aspect of the obturator internus muscles before separating into several terminal branches that terminate within the muscles and skin of the perineum (Barber MD., 2005).

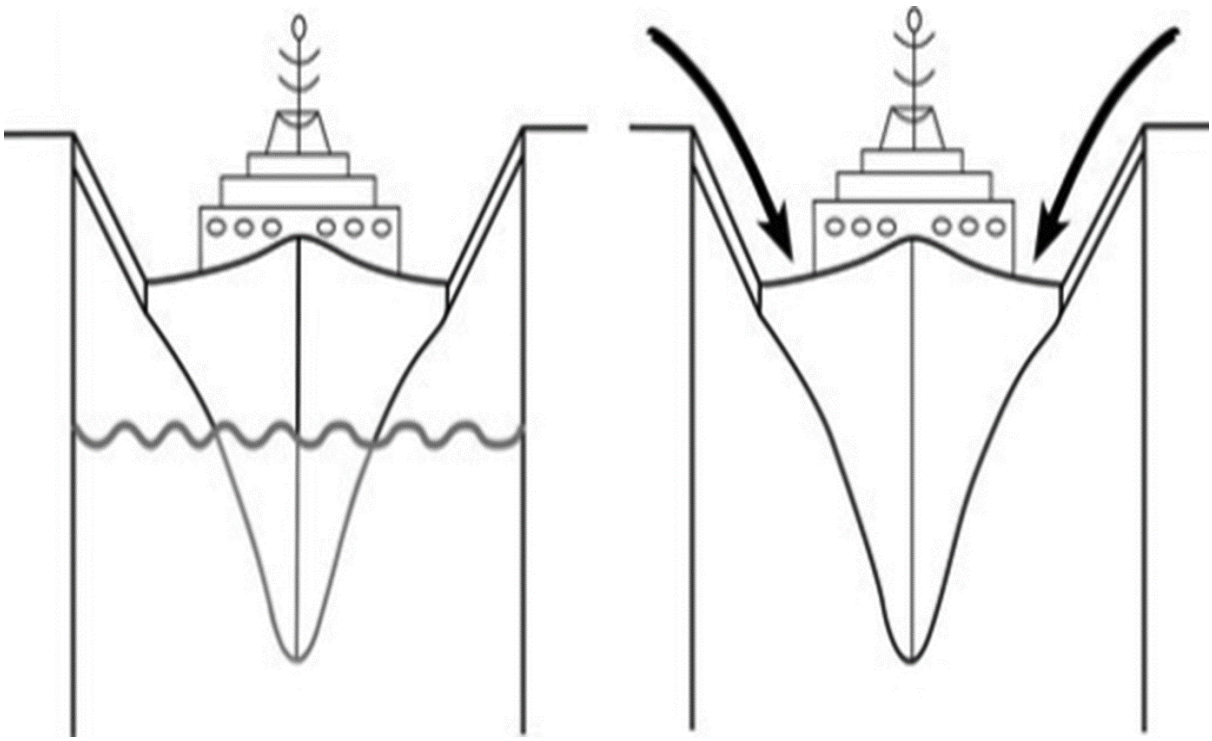
The levator ani muscle is innervated solely by a nerve traveling on the superior (intrapelvic) surface of the muscles without contribution of the pudendal nerve. This nerve, referred to as the levator ani nerve, originates from S3, S4, and/or S5 and innervates both the coccygeus and the levator ani muscle complex (Barber MD. et al., 2002). After exiting the sacral foramina, it travels 2 to 3 cm medial to the ischial spine and arcus tendineus levator ani across the coccygeus, iliococcygeus, pubococcygeus, and puborectalis. Occasionally, a separate nerve comes directly from S5 to innervate the puborectalis muscle independently. Given its location, the levator ani nerve is susceptible to injury through parturition and pelvic surgery. Specifically, the fixation points used in the sacrospinous ligament fixation and the iliococcygeus vaginal vault suspensions are in close proximity to the course of the levator ani nerve (Barber MD., 2005).

1.6 Interactions between muscular and connective tissue supports

Normal pelvic organ support and function depends on dynamic interaction between the pelvic floor musculature and the endopelvic fascia. In a standing woman, the endopelvic fascia suspends the upper vagina, the bladder, and the rectum over the levator plate while the pelvic floor muscles close the urogenital hiatus and provide a stable platform on which the pelvic viscera rests. Intra-abdominal and gravitational forces are applied perpendicular to the vagina and pelvic floor while the pelvic floor musculature counters those forces with its constant tone by closing. With proper tone of the pelvic floor muscles, stress on the connective tissue attachments is minimized. Furthermore, in times of acute stress, such as a cough or a sneeze, there is a reflex contraction of the pelvic floor musculature, countering and further stabilizing the viscera. The genital hiatus also responds by narrowing to maintain level III support. With pelvic floor weakness, such as neuropathic injury or mechanical muscular damage, there is loss of the horizontal orientation of the levator plate, the urogenital hiatus opens, and the pelvic floor assumes a more bowl-like configuration. The endopelvic fascia then becomes the primary mechanism of support. Over time, this stress can overcome the endopelvic fascial attachments and result in loss of the normal anatomic position through breaks, stretching, or attenuation of these connective tissue supports. This can result in changes in the vector forces applied to the viscera and may lead to pelvic organ prolapse (Barber MD., 2005).

As long as the levator ani muscles function to properly maintain closure of the genital hiatus, the ligaments and fascial structures supporting the pelvic organs are under minimal tension. The support of the uterus has been likened to a ship in its berth floating on the water attached by ropes on either side to a dock. The “Boat in Dry Dock” concept is a schematic representation of pelvic support that illustrates pelvic organ prolapse as a multifactorial problem. Under optimal conditions (left image), the pelvic organs (boat) are supported by the levator ani muscle (water) and stabilized by the ligaments (cables). Damage or weakness of the levator ani muscle is represented by absence of the water (right image), leaving the ligaments (cables) to support the entire weight of the pelvic organs (boat). The ligaments (cables) may be able to support the organs (boat) initially, but in the presence of external forces (black arrows), the ligaments (cables) will

eventually become insufficient allowing the pelvic organs (boat) to prolapse (fall down. (Paramore, R.H, 1918)



(Lammers K. et al., 2013) A pictorial overview of pubovisceral muscle avulsions on pelvic floor magnetic resonance imaging.

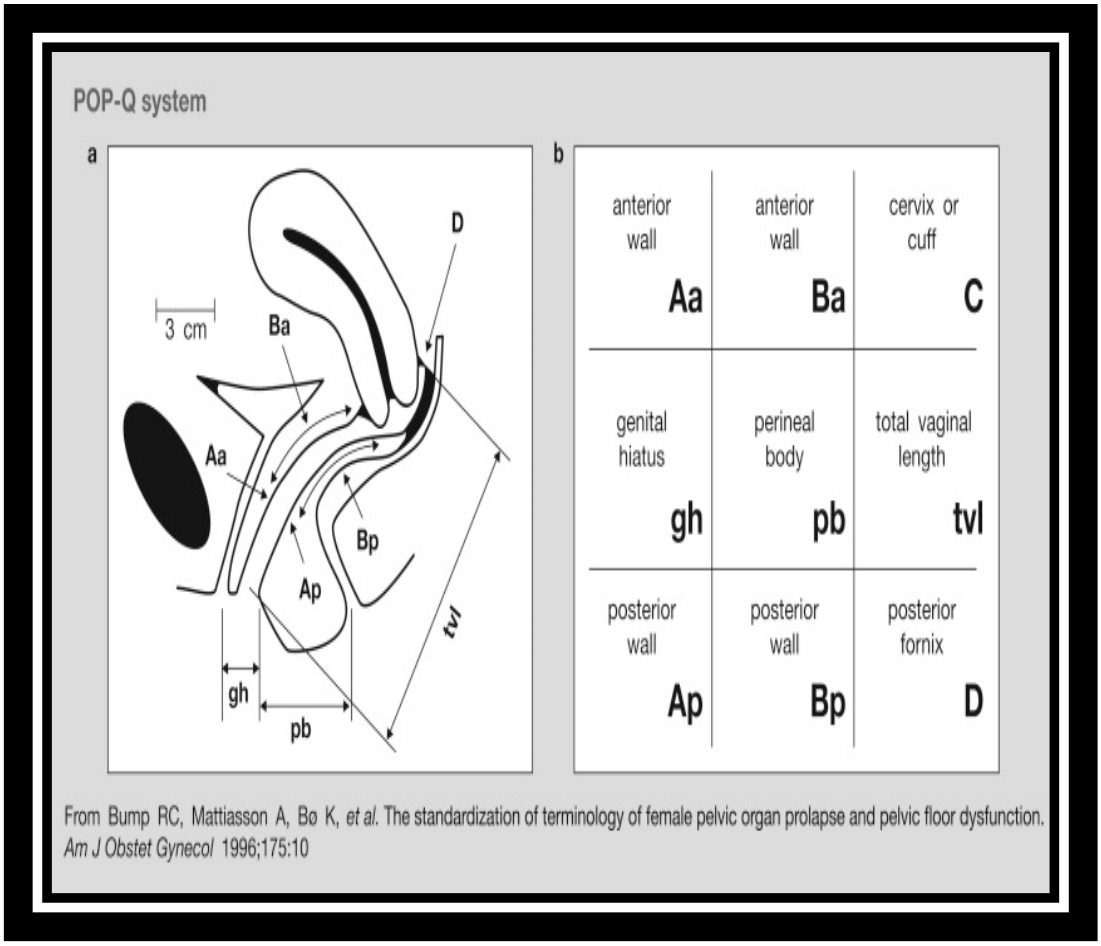
1.7 Pelvic organ prolapse:

Pelvic organ prolapse is a major health problem affecting 50% of parous women over 50 years of age (Subak L.L. et al, 2001). It is a highly heterogeneous condition. The etiology is likely to be multifactorial. It negatively impacts the quality of life by causing pelvic discomfort and interfering with sexual, urinary and defecatory function, as well as other daily activities.

1.7.1 The Pelvic Organ Prolapse Quantification System

It was introduced in 1996 (Bump R.C. et al, 1996). All examinations for pelvic organ prolapse should be performed with the woman's bladder empty, and if possible an empty rectum. A full bladder or rectum will restrict the degree of descent of the prolapse because the woman will not perform a maximal Valsalva. The choice of the woman's position during examination, supine, standing or

lithotomy is that which can best demonstrate POP in that patient and which the woman can confirm as the maximal extent she has perceived.



The hymen is the fixed point of reference used throughout the POP-Q system of quantitative prolapse description.

For measurement centimeters are used. Above or proximal to the hymen we use negative number; below or distal to the hymen we use positive number with the plane of the hymen being defined as zero.

To describe the prolapse we measure the anatomic position of 6 defined points.

- On the anterior Vaginal Wall:

Point Aa: a point located in the midline of the anterior vaginal wall 3 cm proximal to the external urethral meatus. By definition, the range of position of Point Aa relative to the hymen is −3 to +3 cm. In a patient with a history of Burch

colposuspension a point Aa at -3 cm do not eliminate the possibility of cystocele in case of point Ba prolapse.

Point Ba: a point that represents the most distal position of any part of the upper anterior vaginal wall from the vaginal cuff or anterior vaginal fornix to Point Aa. By definition Point Ba is at −3cm in the absence of prolapse and would have a positive value equal to the position of the cuff (Point C) in women with total uterine prolapse or post-hysterectomy vaginal eversion.

- On the superior Vagina:

Point C: a point that represents either the most distal edge of the cervix or the leading edge of the vaginal cuff after total hysterectomy.

Point D: a point that represents the location of the posterior fornix in a woman who still has a cervix. It is included as a point of measurement to differentiate suspensory failure of the uterosacral-cardinal ligament “complex” from cervical elongation. When the location of Point C is significantly more positive than the location of Point D, this is indicative of cervical elongation which may be symmetrical or eccentric. Point D is omitted in the absence of the cervix.

- On the posterior Vaginal Wall:

Point Ap: a point located in the midline of the posterior vaginal wall three 3 cm proximal to the hymen. By definition the range of position of Point Ap relative to the hymen is−3 to +3 cm.

Point Bp: a point that represents the most distal position of any part of the upper posterior vaginal wall from the vaginal cuff or posterior vaginal fornix to Point Ap. By definition Point Bp is at −3 cm in the absence of prolapse and would have a positive value equal to the position of the cuff in a woman with total post-hysterectomy vaginal eversion.

- Other Landmarks and Measurements.

The genital hiatus GH: it is measured from the middle of the external urethral meatus to the posterior margin of the hymen.

The total vaginal length TVL: it is the length of the vagina (cm) from the posterior fornix to the hymen when Point C or D is reduced to its full normal position.

The perineal body PB: it is measured from the posterior margin of the hymen to the mid-anal opening.

1.7.2 The Pelvic Organ Prolapse Quantification System staging:

Stage 0: No prolapse is demonstrated.

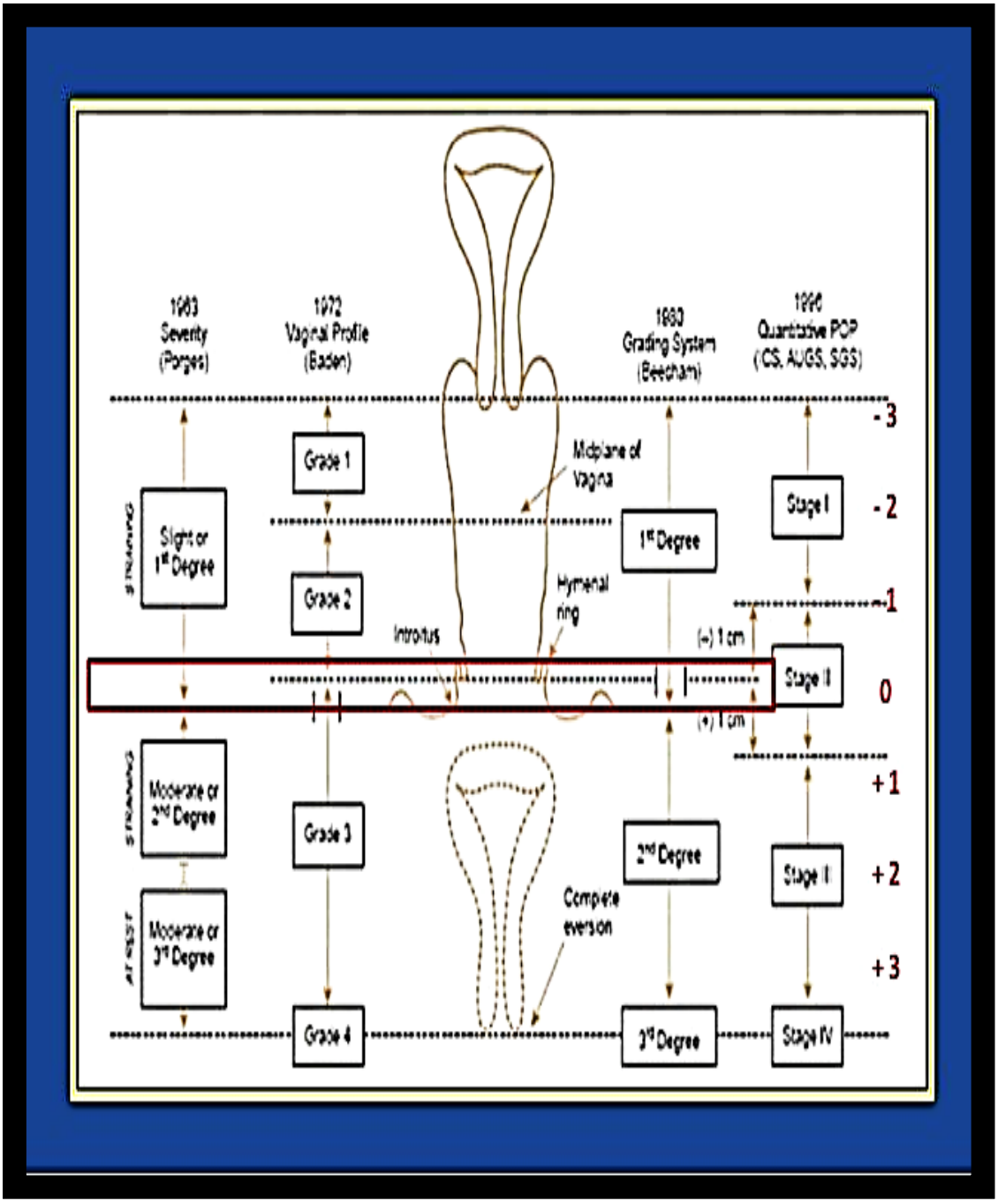
Stage I: Most distal portion of the prolapse is more than 1 cm above the level of the hymen.

Stage II: The most distal portion of the prolapse is situated between 1 cm above the hymen and 1 cm below the hymen.

Stage III: The most distal portion of the prolapse is more than 1 cm beyond the plane of the hymen but everted at least 2cm less than the total vaginal length.

Stage IV: Complete eversion or eversion at least within 2 cm of the total length of the lower genital tract is demonstrated.

Diverse classification systems for pelvic organ prolapse quantification:



1.8 Surgical mesh:

Surgical mesh has been used since the 1950s to repair abdominal hernias with greater anatomic durability. In the 1970s, in an attempt to decrease recurrence rate after traditional pelvic organ surgery, gynecologists began using surgical mesh products indicated for hernia in abdominal repair (open sacrocolpopexy). Finally, in the 1990s, they began using surgical mesh transvaginally for surgical treatment of stress urinary incontinence and pelvic organ prolapse. In 1996, the Food and Drug Administration cleared the first surgical mesh product specifically for use in stress urinary incontinence, and in 2002 the first surgical mesh product specifically for use in pelvic organ prolapse. The most commonly described permanent synthetic mesh in both the gynecologic and urologic literature is type I macroporous monofilament polypropylene, which possesses the mechanical properties of durability, elasticity, and resistance (Cosson M. et al., 2003) in addition to the in vivo characteristics of good tissue integration with minimal inflammatory response (Boulanger L. et al., 2006).

Over the next few years, surgical mesh products for transvaginal pelvic organ prolapse repair became incorporated into “kits” that included tools to aid the insertion of the mesh (FDA safety communication, 2011). The Food and Drug Administration release a safety communication in 2011 that transvaginal mesh was not routinely found to be more effective than native tissue repair and may expose patients to greater risk. Although the FDA communication was written to promote understanding of the risks associated with transvaginal mesh and encourage informed decision-making by patients and healthcare providers, it resulted in a great deal of confusion, controversy, and concern regarding the role of transvaginal mesh. The American College of Obstetricians and Gynecologists and the American Urogynecologic Society responded by releasing a committee opinion (Committee on Gynecologic Practice Committee opinion, no. 513, 2011) in December 2011, which provided background information on the use of transvaginal mesh for pelvic organ prolapse and offered practice recommendations, including restricting use to high-risk patients, device-specific training to experienced reconstructive pelvic surgeons, adequate informed

consent, and the need for continued surveillance of existing products as well as rigorous comparative trials between mesh and native tissue repairs. This opinion did not change in February 13, 2018 (https://www.augs.org/update-on-vaginal-mesh-for-prolapse-and-incontinence). In early 2012, the FDA ordered manufacturers of transvaginal mesh to conduct post market surveillance studies to better understand the long-term safety and effectiveness of mesh.

the American Urogynecologic Society initiated the national Pelvic Floor Disorders Registry. This registry collects information from healthcare providers and patients about composite subjective and anatomic outcomes and adverse events of pelvic organ prolapse treatments.

In April 2014, the FDA proposed rules to reclassify vaginal mesh (US Food and Drug Administration, 5/1/2014) from a class II (low-risk to moderate-risk) to a class III (high-risk) device. This reclassification excludes mesh used for either stress urinary incontinence or transabdominal pelvic organ prolapse repair such as sacralcolpopexy. Manufacturers must also obtain premarket approval for their devices, which requires new mesh products to undergo rigorous testing compared with native tissue repairs prior to release.

Surgical mesh materials can be divided into four general categories:

a- non-absorbable synthetic (polypropylene)

b- absorbable synthetic (polylactic-co-glycolic acid, monocryl)

c- biologic (e.g., acellular collagen derived from bovine or porcine sources)

d- composite (i.e., a combination of any of the previous three categories)

-Biological implants:

- Autologous from the woman’s own tissue as rectus fascia or fascia lata
- Allografts as implants from post-mortem tissue bank from dermis or fascia lata
- Xenografts from porcine dermis /Pelvicol, small intestinal mucosa or bovine pericardium.

The advantage of these materials is the low exposure rate but one of the disadvantages is the similar risk rate for recurrence as after native tissue repair.

-Synthetic mesh materials can be divided according to porosity (Amid P.K., 1997) Pore size influences resistance against infection and cellular infiltration, as well as the flexibility of the mesh. In macroporous monofilament implants - typ I- the pore size exceeds 75 µm allowing the penetration of macrophages, fibroblasts, collagen fibers and angiogenesis.

Amid's classification according to porosity (Amid P.K., 1997)

Typ I	Macroporous monofilament The pore size exceeds 75 µm	Gynemesh Prolift Elevate Nuvia Uphold
Typ II	Microporous implants The pore size is less the 10 µm	Gore-Tex
Typ III	Multifilament Fibers / macro- and microporous The pore size is less the 10 µm	Vypro II (El Haddad R. et al, 2009) IVS
Typ IV	Submicroscopic pores	Silastic

The organism response to implant insertion was described by Williams (Williams D.F., 1973)

- Minimum response with a thin layer of fibrosis around the implant
- Chemical response with a severe and chronic inflammatory reaction around the implant

- Somatic reaction with an inflammatory reaction to the material and the presence of giant cells.
- Tissue necrosis

A weight-based classification of prosthetic materials was put forward by Earle and Mark in 2008: heavyweight (>90 g/m2), medium weight (50–90 g/m2), lightweight (50-35) and ultra-lightweight (<35 g/m2) (Earle D.B., Mark L.A., 2008)

Earl and Mark's classification according to implant weight (Earle D.B., Mark L.A., 2008)

Heavyweight >90 g/m2	Mediumweight 50-90 g/m2	Light 50-35 g/m2 and Ultra-lightweight <35 g/m2
Mersilene Marlex	Parietex Intepro (Apogee/Perigee)	Prolift 42 g/m2 Intepro Lite 25.2 g/m2 Prolift+M after insertion 31 g/m2 Surgimesh Prolase Xlight 28 g/m2 Elevate 25.2 g/m2 Uphold LITE 25 g/m2 Alyte 17.67 g/m2

The occurrence rates for complications of Transvaginal synthetic mesh for pelvic organ prolapse include mesh erosion/exposure (5–19%), pelvic pain (0–10%), de-novo dyspareunia (8–28%), and reoperation (3–22%) (Committee on Gynecologic Practice Committee opinion, no. 513, 2011)

Weight and Structural textile properties of a mesh play a role in its biocompatibility. On animal models the vagina's mechanical properties were significantly more deteriorated with a mediumweight mesh than with a lightweight mesh (Feola A. et al, 2013)

Sacrocolpopexy using mesh, completed abdominally via open incision, laparoscopically or robotically, has long been considered the gold standard repair for vaginal vault prolapse. In 2004 Nygaard reported, in a review of abdominal sacrocolpopexy, the range of mesh extrusion between 1 and 20 % (Nygaard I.E. et al, 2004). However, in recent studies, with the utilization of type I polypropylene mesh, the extrusion rate decreased and ranged between 0.7 and 2.3 % (Stepanian A.A. et al., 2008). Moore and Lukban found a 46 % reduction in rate of mesh exposure in patient receiving lighter type I polypropylene transvaginal mesh (Moore R.D., Lukban J.C., 2012)

The transvaginal synthetic materials used currently for pelvic organ prolapse reconstructive surgery are 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 was 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).

The largest population-based study of 110,329 women undergoing pelvic organ prolapse repair between 2005-2011 in the state of California provides evidence against the hypotheses that mesh itself is independently responsible for mesh-related repeated surgery. Rather, it provides evidence that patient selection plays the most important role and vigilant use of mesh in anterior and anterior-apical compartment repairs optimizes outcomes. This occurs when the known anatomic durability of mesh is balanced against the risks of mesh specific complications. As such, use in specific cases with careful patient selection may be justified. Further research is warranted to better understand which patients specifically are at higher risk of native tissue repair failure and might benefit the most from mesh augmentation (Dallas K.B. et al., 2018).

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

We undertook a prospective interventional 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.

3.2 Methods

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). The Prolift procedure was performed as described by Fatton et al. (Fatton b. et al., 2007). For mesh insertion without lateral fixation a full thickness midline vertical incision was made 3 cm proximally to the urethral meatus toward the cervix or the vaginal cuff. The blunt dissection of the paravesical space continued laterally toward the arcus tendineus fascia pelvis bilaterally. The bladder was also dissected off of the cervix or vaginal vault. Intra-operatively a butterfly shape mesh was cut and inserted in a way to completely cover the cystocele and to lie flat, without folding and in a tension-free manner. Laterally the mesh edges (winds) were inserted toward the ATFP. To prevent peri and early postoperative slipping, the mesh was attached by two 2-0 Vicryl Rapid (Ethicon, Somerville, NJ, USA) sutures at the level of the bladder neck and by two sutures at the level of the vaginal cuff or the cervix. The vaginal wall was closed by 2-0 Monocryl (Ethicon, Somerville, NJ, USA) in a running non-locked fashion. 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.

3.3 Statistical methods

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.

3.4 Results

69 women participated in this study. All women were Caucasians. Demographic data showed no statistically significant differences between the groups (Tab. 1). 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. 2 demonstrates a statistically significant improvement of PISQ-12. 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) (Tab. 3). 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. The Table 4 and Table 5 show the significant decrease of UIQ, POPIQ, UDI and POPDI scores that indicate an improvement of QoL after surgery.

Tab. 1 Demographic data

	Prolift		Mesh		ANOVA F-test p-value
	N	Mean (SD)	N	mean (SD)	
Age [years]	36	60.4 (10.6)	33	61.2 (8.4)	0.7284
Weight [kg]	36	163.3 (5.9)	33	165.3 (6.4)	0.2915
Height [cm]	36	76.2 (11.0)	33	73.9 (11.7)	0.1666
BMI [kg/m^2]	36	28.6 (3.8)	33	27.0 (3.5)	0.0945
	Prolift		Mesh		Kruskal-Wallis test p-value
		median (QR)		median (QR)	
Parity [number]	36	2.0 (1.0)	33	2.0 (0.0)	0.6274
Gravidity [number]	36	3.0 (2.0)	33	3.0 (2.0)	0.7309

Prolift - women treated with the Prolift anterior procedure

Mesh - women treated with anterior colporrhaphy augmented by individualized mesh

Tab. 2 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**

Tab. 3 Dyspareunia and de novo dyspareunia according to answers of the 5th question of PISQ-12: Do you feel pain during intercourse?

	PROLIFT (n = 19)			MESH (n = 16)		
DYSPAREUNIA	BEFORE	AFTER	DE NOVO	BEFORE	AFTER	DE NOVO
ALWAYS	1	0	0	1	0	0
USUALLY	1	2	0	1	1	0
SOMETIMES	5	5	**1**	0	2	**0**
SELDOM	6	6	2	5	3	3
NEVER	6	6	0	9	10	0

Tab. 4 Impact of surgery on Urinary distress inventory (UDI) and Pelvic Organ Prolapse Distress Inventory (POPDI)

Scores		Before surgery	After surgery	Change from baseline	Wilcoxon test p-value
	N	median (QR)	median (QR)	median	
UDI Obstructive Discomfort	65	15 (15)	4 (12)	-12	**0.0000***
UDI Irritation	65	13(15)	8 (13)	-8	**0.0000***
UDI stress	65	8 (25)	4 (13)	-6	**0.0052***
UDI total	65	43 (48)	18 (31)	-21	**0.0000***
POPDI general subscale	65	18 (21)	4 (11)	-14	**0.0000***
POPDI anterior subscale	65	17 (25)	4 (8)	-15	**0.0000***
POPDI total	65	45 (50)	14 (33)	-32	**0.0000***

*** statistically significant**

3.5 Discussion

Mesh repairs are increasingly used. 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. 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 recent 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. 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 and to the used surgical technique where always an appropriate hydro-dissection was done, a full thickness small incision of the vaginal wall, a sufficient lateral dissection that the mesh or the Prolift lied flat and in a tension free manner, no trimming of the vaginal wall, a monofilament suturing material and a perioperative antibiotic prophylaxis. Our study had several limitations: The lack of a control group (traditionally operated, non-operated, pessary only), the short-term follow-up of 6 months, the small number of sexually active women as only 53% of women were sexually active and no interviews of the sexual partners of our patients. The evaluation of sexual activity 6 months after surgery may be short-term but all sexually active women resume their sexual activity within 6 to 10 weeks postoperatively. 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. (Švabík K. et al, 2010) (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. Despite these limitations the strength of this 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.

Acknowledgement:

This work was supported by the Grant Agency of the Ministry of Health of the Czech Republic (grant NT 12147-4)

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

4.1 Aim

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 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)

4.2 Methods

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.

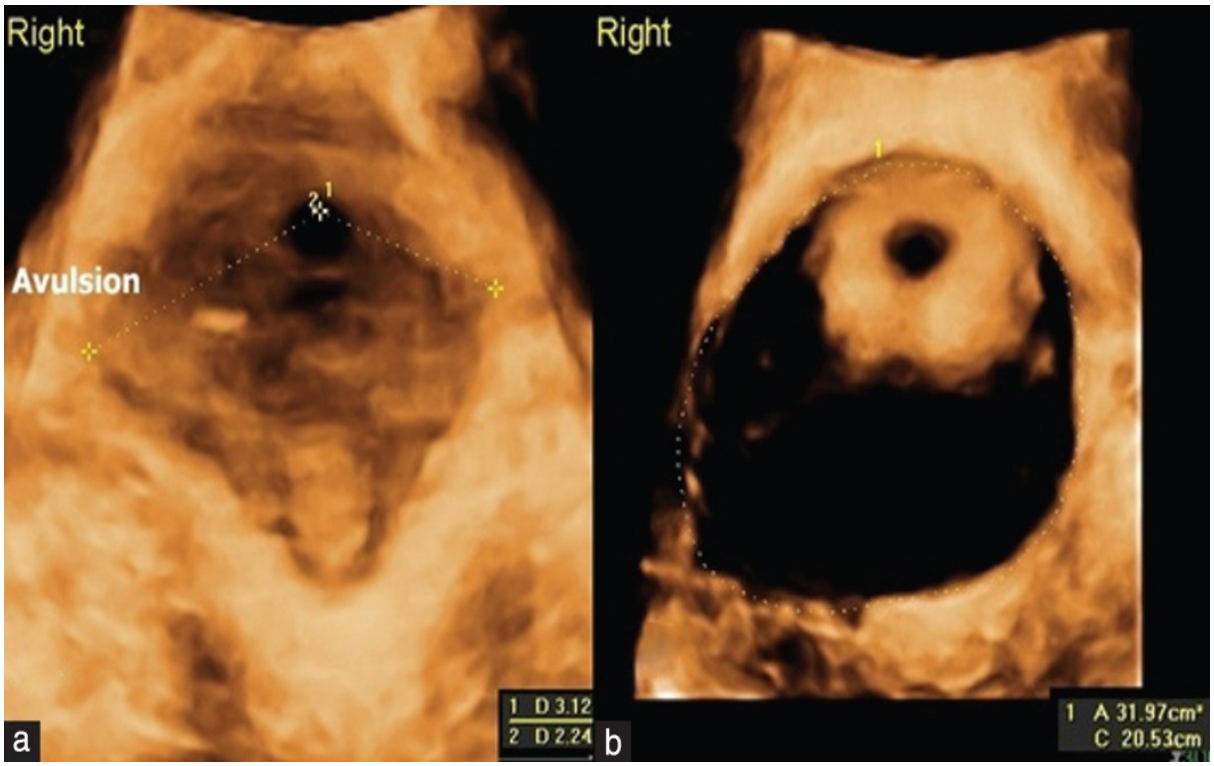
At the time of enrolment (usually 2–3months prior to surgery), to fulfill the main inclusion criterion, preoperative levator assessment and avulsion diagnosis was performed. Patients were examined clinically and by translabial 3D/4D ultrasound by one of two physicians (K.S. and J.M.), both experienced 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). After hydrodissection, a midline anterior colpotomy with fascia dissection was performed, and the bladder was dissected laterally to the pelvic side wall. The posterior vaginal wall was dissected between apex and perineum, and sacrospinous ligaments were verified. The Prolift guides were inserted (two pairs through obturator membrane and one pair through sacrospinous ligament via ischiorectalis fossa). The mesh was inserted, spread anteriorly from the bladder neck, and sutured to the vaginal apex using (Jacquetin B. et al , 2010) Vicryl plus 2.0 (Ethicon, Sommerville, NJ, USA). Posteriorly, the mesh was attached to the introitus. The vaginal wall was sutured with running Monocryl 2.0 suture (Ethicon). The last step of the procedure involved stretching the mesh and removing the guides. There was no fascial plication in the Prolift group.

Figure 1 Ultrasound images (axial plane) in a patient with right-sided levator ani avulsion injury: (a) during contraction, showing uretrhra-gap measurement (calipers) (b) during Valsalva, showing hiatal area measurement (dotted line) and moderate ballooning.



Dissection for the SSF procedure was performed in a similar manner but without dissection of fascia. 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 to 10 mm 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).

4.3 Statistical methods

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.

4.4 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 (Figure1) 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 (Diagram1). 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 (see Table 1).

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.

Diagram 1: Consort diagram

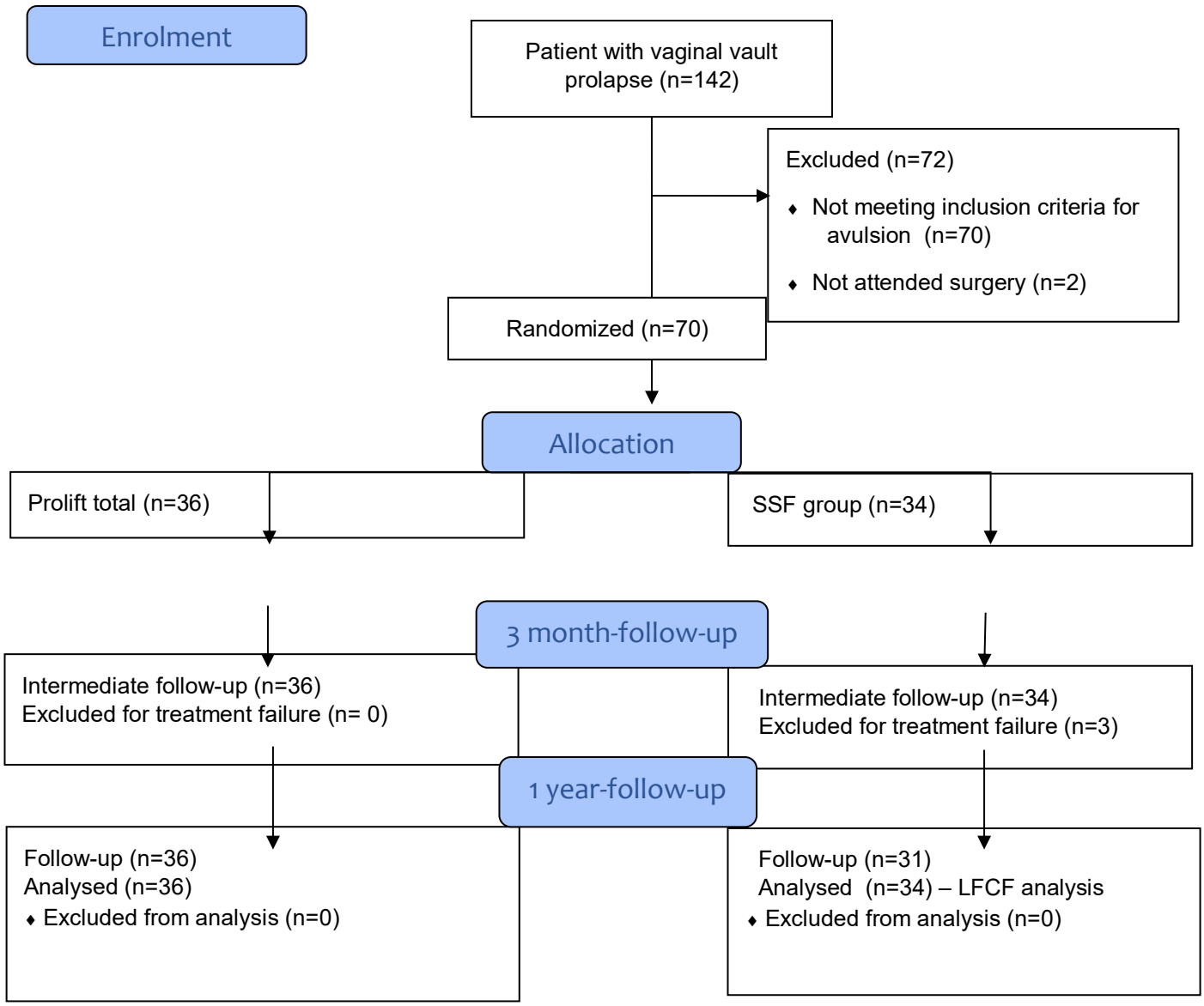


Table 1: Pre-operative demographic, clinical (POPQ) and ultrasound parameters comparison of the two interventional arms.

Table 1 Preoperative data	Prolift N=36	SSF N=34	t	P	Prolift SD	SSF SD
Age	63.4	62.5	0.404	0.687	8.614	10.858
Height (cm)	163.8	163.0	0.561	0.576	6.173	5.815
Weight (kg)	73.139	74.8	-0.688	0.494	9.894	10.602
BMI	27.2	28.2	-1.103	0.274	3.215	4.188
Parity	2.1	2.2	-0.207	0.837	0.833	0.673
Aa	1.3	0.9	1.164	0.248	1.721	1.274
Ba	4.1	3.6	0.845	0.401	2.435	2.450
C	2.1	1.5	0.690	0.492	3.897	3.863
TVL	8.1	8.0	0.396	0.693	0.919	0.797
Ap	0.4	0.7	-0.807	0.423	1.761	1.508
Bp	2.4	2.4	-0.036	0.971	2.872	2.743
GH	4.8	4.6	0.886	0.379	0.989	1.078
PB	3.6	3.9	-1.179	0.243	1.150	0.983
Hiatal Area - Valsalva (cm^2)	43.5	43.1	0.137	0.891	12.491	12.223

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 (Table 2)

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 (see Table 3). 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), see Table 4.

Table 2: Results at one year follow-up – POPQ parameters; ultrasound parameters: UVJ Valsalva – distance between the urethro-vesical junction and the inferior margin of the symphysis pubis on Valsalva; Bladder Valsalva – distance between the lowest point of the bladder and the inferior margin of the symphysis pubis on Valsalva; Hiatal Area Valsalva – area of the levator ani hiatus on Valsalva

Table 2 1 year follow-up	Prolift N=36	SSF N=34	t	P	Prolift SD	SSF SD
Aa	-2.4	-0.9	-7.019	0.000	0.649	1.158
Ba	-2.4	-0.1	-7.533	0.000	0.645	1.684
C	-6.2	-3.2	-4.618	0.000	1.298	3.568
Ap	-2.3	-1.8	-2.278	0.026	0.717	1.304
Bp	-2.3	-1.4	-2.839	0.006	0.717	1.937
GH	3.3	3.5	-0.978	0.331	0.632	0.788
PB	4.6	4.8	-1.115	0.269	0.843	0.946
TVL	7.4	7.1	0.833	0.408	1.073	1.077
Hiatal Area Valsalva (cm^2)	29.6	37.0	-2.682	0.009	7.443	14.248
UVJ Valsalva (cm)	-1.2	0.0	-6.415	0.000	0.744	0.762
Bladder Valsalva (cm)	-1.1	1.2	-10.365	0.000	0.721	1.111

Table 3: PISQ-12 score – Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire.

PISQ 12 score	Preoperatively (mean)	one year follow-up (mean)	Score difference (mean)
Prolift group	30.3	32.6	2.8
SSF group	33.1	35.6	3.1
Mann-Whitney U test; p =	0.614	0.194	0.274

Table 4: Distress inventory scores – POPDI - Pelvic Organ Prolapse Distress Inventory; UDI - Urinary Distress Inventory; CRADI - Colorectal Distress Inventory

Distress inventory		mean	Min	max	SD	Mann-Whitney U test
UDI –preoperatively.	Prolift	40.2	1.9	133.5	30.1	p=0.10
	SSF	53.2	7.7	130.2	32.4	
POPDI-preoperatively	Prolift	64.8	0.0	200.0	48.0	p=0.96
	SSF	60.4	0.0	151.8	35.5	
CRADI-preoperatively	Prolift	42.4	0.0	135.7	42.3	p=0.61
	SSF	46.8	0.0	150.1	43.1	
UDI-postoperatively	Prolift	22.7	0.0	105.0	23.4	p=0.66
	SSF	24.5	0.0	125.9	29.0	
POPDI-postoperatively	Prolift	15.3	0.0	95.2	19.4	p=0.16
	SSF	21.7	0.0	114.3	28.5	
CRADI-postoperatively	Prolift	15.5	0.0	54.7	16.7	p=0.09
	SSF	31.6	0.0	189.1	45.5	

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 69%. 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 (Švabík K. et al, 2015). 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.

Acknowledgement:

This work was supported by the Grant Agency of the Ministry of Health of the Czech Republic (grant NT 12147-4) and by Charles University in Prague (UNCE 204024)

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.Annexes

Annex 1: Related publications

Annex 2: Publications related to thesis with impact factor

Annex 3: Publications related to thesis without impact factor

Annex 4: Publications non-related to thesis with impact factor

Annex 5: Publications non-related to thesis without impact factor

Annex 2: Publications related to thesis with impact factor

1- **El Haddad R.**, Svabik k., Masata J., koleska T., Hubka p., Martan A.(2013). Women's Quality of life and sexual function after transvaginal anterior repair with mesh insertion. Eur J Obstet Gynecol Reprod Biol, 167(1):110-3. **IF: 1.843**

2- Svabik K., Martan A., Mašata, J**., El Haddad, R.** et al (2014). Comparison of vaginal mesh repair with sacrospinous vaginal colpopexy in the management of vaginal vault prolapse after hysterectomy in patients with levator ani avulsion: a randomized controlled trial. Ulrasound in Obstetrics and Gynecology. 43(4):365-371 **IF : 3.557**

3- Svabik K., Martan A., Mašata, J**., El Haddad, R.** et al et al. (2011). Ultrasound appearances after mesh implantation- evidence of mesh contraction or folding? Int Urogynecol J Pelvic Floor Dysfunc, 22 (5): 529-33.1. **IF: 1.832**

Annex 3: Publications related to thesis without impact factor

1- **El Haddad, R**., Martan, A., Mašata, J., Švabík, K., Koleška, T. (2009). Dlouhodobé léčebné výsledky vysoké zadní plastiky s plikací levátorů s použitím síťky Vypro II. Čes.Gynek., 74 (4), s.282-285

2- Švabík K**., El Haddad R.**, Mašata J., Hubka P., Martan A. (2015) Korelace subjektivního a objektivního hodnocení operace vaginálního prolapsu– sekundární analýza výsledků randomizované kontrolované studie pacientek s defektem pánevního dna a operovaných vaginální síťkou nebo závěsem na sakrospinosní ligamentum. Čes.Gynek., 80, (5), s.351-354

3- Švabík, K., Martan, A., Mašata, J., **El Haddad, R.**, Pavlikova, M. (2010) Změny délky implantované síťky po rekonstrukčním výkonu přední stěny poševní. Čes. Gynek.,75 (2), s.132-135

Annex 4: Publications non-related to thesis with impact factor

1- Martan, A., Švabík, K., Mašata, J., Koleška, T., **El Haddad, R.** et al. (2009) Correlation between changes in ultrasound measurementes and clinical curative effect of tension-free vaginal tape-SECUR procedure. Int Urogynecol J., 20(5),533-9 **IF: 2.412**

2- Martan, A., Švabík, K., Mašata, J., Koleška, T., **El Haddad, R.** et al. (2009) Initial experience with a short, tension-free vaginal tape (the tension-free vaginal secur system). European J of Obstet and Gynecol. 143 (2), s. 121-125

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3- Mašata, J., Švabík, K., Zvara, K., Drahorádová, P., **El Haddad, R.** et al. (2012) Randomized trial of a comparison of the efficacy of TVT-O and single-incision tape TVT SECUR systems in the treatment of stress urinary incontinent women-2-year follow-up. Int Urogynecol J. 23(10):1403-12 **IF: 2.169**

4- Hubka, P., Nanka, O., Martan, A., Svabik, K., **El Haddad, R.**, Masata J. (2013) Fixation of the Ajust minisling based upon cadaveric study. Int Urogynecol J. 24(12):2119-23 **IF: 2.169**

Annex 5: Publications non-related to thesis without impact factor

1- El Haddad, R. et al. (2003) Trombóza vnitřní jugulární žíly u pacientky s ovariálním hyperstimulačním syndromem. Česk. Gynekol. 68 (2), s. 114-117

2- Hájek, Z., Vráblík, J., El Haddad, R. et al. (2002) Fetální EKG – ST analýza v diagnóze fetální hypoxie. Česk. Gynekol., 67 (1), s. 16-19

3- Hájek, Z., Srp, B., El Haddad, R. et al. (2005) Analýzy současných diagnostických metod intrapartální hypoxie plodu. Česk. Gynekol. 70 (1), s. 22-26

4- Hájek, Z., Srp, B., Zvárová, J., Liška, K., El Haddad, R. et al. (2006) Intrapartální fetální monitoring, senzitivita a specificita metod: Česk. Gynekol. 71 (4), s. 263-267

5- Martan, A., Mašata, J., Švabík, K., El Haddad, R. et al. (2008) TVT-S-systém: léčebné výsledky této operační metody stresové inkontinence. Praktická Gynekol. 12 (1), s. 52

6- Martan, A., Švabík, K., Mašata, J., Koleška, T., El Haddad, R. et al. (2008) Řešení stresové inkontinence moči u žen operační metodou TVT-S- vztah mezi léčebným efektem operační metody a změnami hodnot ultrazvukových parametrů. Česk. Gynekol. 73 (5), s. 271-277

7- Martan, A., Švabík, K., Mašata, J., Koleška, T., El Haddad, R., Pavlíková, M. (2009) Řešení přetrvávající stresové inkontinence moči u žen po neúspěšné operaci TVT-Secur. Česk. Gynekol., 74 (1), s.3-7

8- Martan, A., Švabík, K., Mašata, J., El Haddad, R., Pavlikova, M. (2010) Vztah stresové inkontinence moči či urgence k defektu předního kompartmentu před jeho operačním řešením a po něm, Česk. Gynekol., 75 (2), s.118-125

9- Martan, A., Mašata, J., Švabík, K., El Haddad, R., Hubka, P. (2011) Změny léčebného efektu transuretrální aplikace polyakrylamid hydrogelu (Bulkamidu) při léčbě ženské stresové inkontinence moči v závislosti na čase od operace. Česk. Gynekol., 76 (6), s. 476-481