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PARAVAGINAL DEFECTS–SYMPTOMS, DIAGNOSIS, AND EVALUATION OF TREATMENT

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by

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Abstract

Pelvic organ prolapse (POP) is common in parous women with a 19% lifetime risk of undergoing at least one POP operation. The anterior vaginal wall (AVW) is the vaginal compartment with the highest risk of descent and with the highest risk of recurrence after surgery. This reflects the complex system of muscles, fasciae, and ligaments supporting the AVW, and maybe ignored anatomical defects not repaired during surgery, or defects not possible to repair. The paravaginal defect (PVD), defined as the detachment of the pubocervical fascia from arcus tendinous fascia pelvis (ATFP) has been suggested as an important contributor to prolapse, especially the AVW.

Observations during surgery and cadaver dissections have shown the PVD to be a common observation in women with POP and an isolated observation independent of defects in the pubococcygeus (PC) muscle. Due to inconsistency in diagnosing the PVD by gynecological examination, several authors have suggested the use of magnetic resonance imaging (MRI) and ultrasound (US) as a diagnostic supplement. Neither MRI nor US are able to visualize the pubocervical fascia or the ATFP. In nulliparous women, the vagina will look H shaped in the axial plane, and missing H configuration seen on MRI or US has been suggested as an indirect observation of PVD. Only two studies have evaluated the correlation between PVD found by clinical examination and missing H configuration by imaging, and they have conflicting results. Also, defects in the PC muscles have been observed together with altered vaginal shape.

Gynecological examination and MRI have been found reliable in objectively categorizing grade of POP, but to measure and quantify the subjective symptoms and quality-of-life-related to POP, there is a need for a Danish validated questionnaire.

In study I, we reviewed the literature on PVD, focusing on the anatomy, the clinical findings, and imaging by MRI and US. We concluded that no studies clearly demonstrated a relationship between missing H configuration and PVD, and most studies did not correlate missing H with defects in the PC muscle.

In study II, we translated the internationally approved questionnaire ICIQ-VS. Two-hundred-forty-four (244) women filled in the questionnaire, and we found it to be well-comprehended and to have excellent validity, reliability, and responsivity.

In study III, we enrolled 50 women with presumed PVD and 10 nulliparous. They were evaluated regarding vaginal H shape and levator ani muscle defects on MRI and endoanal US (EAUS)/endovaginal US (EVUS), together with two rounds of gynecological examination to test interrater reliability of the clinical examination. We found no muscle defects and no clinical PVD in any of the nulliparous, but one had missing H configuration. In the women with PVD, a moderate correlation was found between the two clinical examinations. We found no association between PVD found at clinical examination and missing H configuration. MRI and EAUS did not agree on the description of vaginal shape, probably due to poor US images. There was a substantial agreement between MRI and EVUS on levator ani muscle defects, and we found a large correlation between severity of muscle defect and missing H configuration on MRI. We concluded, therefore, that missing H was not a sign of detachment of the pubocervical fascia from ATFP, but rather a sign of severe PC muscle defects, and that MRI and EVUS were equal in grading the muscle defect.

In study IV, we examined 46 women who underwent PVD repair alone or together with concomitant POP surgery. Before and six months after the operation, gynecological examination (POP-Q), ICIQ-VS questionnaire, and MRI were used for evaluation of grade of prolapse, subjective symptoms, sexual matters, quality of life, vaginal H configuration, and PC muscle defects. We demonstrated that operation significantly reduces AVW descent and subjective bother of prolapse together with increased quality of life six months after operation. PC muscle defect occurred in 67%, and 46% had missing H configuration. Vaginal H shape did not change after surgery in any of the women. AVW prolapse recurred in 39%, and only MRI variables (PC muscle defect, missing H configuration, and bladder base descent) were significantly related to risk of recurrence. We concluded that missing H was a sign of severe PC muscle defect and not of PVD and that evaluation of muscle defects before surgery could help the surgeon to inform the woman of her risk of recurrence. Major muscle defects observed before operation could also help the surgeon in the decision about mode of surgery (native tissue repair versus mesh implant, and absorbable sutures versus non-absorbable sutures).

Dansk resume

Utero-vaginal prolaps er en hyppig tilstand hos kvinder, der har født børn. Risikoen for på et tidspunkt i livet at skulle gennemgå mindst én operation for prolaps er ca 19%. Vaginas forvæg er den hyppigste anatomiske struktur, hvor nedsynkning forekommer og også det sted, hvor der oftest kommer recidiv efter prolapsoperation. Vaginas forvæg støttes af et komplekst sammenspil af muskler, fascier og ligamenter, og det har været foreslået, at den høje recidivfrekvens efter operation for prolaps i forvæggen kunne tilskrives oversete defekter, der ikke blev opereret eller defekter, der ikke kunne repareres. Den paravaginale defekt (PVD), der defineres som en afrivning af den pubocervikale fascie fra arcus tendineous fascia pelvis (ATFP), har været nævnt som en vigtig bidrager til udviklingen af prolaps, specielt i forvæggen. PVD har vist sig at være en hyppig observation under operation for prolaps og i kadaver-studier. PVD har i de tilfælde vist sig at være en isoleret observation uafhængig af, om der er defekter i den pubococcygeale (PC) muskel eller ej. Brugen af gynækologisk undersøgelse til at stille diagnosen PVD har vist sig at være usikker. Derfor har flere forskere foreslået brug af magnetisk resonans (MR) skanning eller ultralyd (UL) til at supplere diagnosen. Den pubocervikale fascie og ATFP kan ikke visualiseres på hverken MR eller UL. Hos kvinder, der ikke har født børn, har vagina en form som et H, set i det aksiale plan, og manglende H konfiguration set ved MR og UL, har derfor været foreslået som en indirekte observation af PVD. To studier har evalueret sammenhængen mellem det kliniske fund af PVD og manglende H konfiguration set ved MR/UL, men med modsatrettede konklusioner.
Defekter i PC musklen har ligeledes været observeret sammen med ændret vaginalt udseende i det aksiale plan.

Kvantificering af graden af prolaps ved hjælp af gynækologisk undersøgelse og MR har vist sig meget valide, men for at kunne måle på de subjektive symptomer hos den enkelte kvinde, er det nødvendigt med et dansk valideret spørgeskema.

Studie I omhandler en gennemgang af den eksisterende litteratur om PVD med specielt fokus på beskrivelse af anatomien, den gynækologiske undersøgelse og MR/UL. Vi konkluderer, at ingen studier viser en klar sammenhæng mellem PVD og manglende H konfiguration, og at de fleste studier ikke evaluerer sammenhængen mellem manglende H konfiguration og PC muskel defekt.

I studie II oversatte vi et internationalt anerkendt engelsk spørgeskema (ICIQ-VS). 244 kvinder blev inkluderet, og resultaterne viste et spørgeskema uden misforståelser og med høj validitet, pålidelighed og responsivitet.

I studie III inkluderede vi 50 kvinder med formodet PVD og 10 nullipara kvinder. De blev alle vurderet med MR af bækkenbunden og endoanal/endovaginal UL i forhold til H konfiguration og levator ani muskeldefekt ligesom der blev foretaget to runder af gynækologiske undersøgelser for at vurdere intra-observatør varians. Vi fandt ikke muskel defekter eller klinisk PVD hos nullipara-kvinderne, men en enkelt havde manglende H konfiguration. I gruppen af kvinder med formodet PVD fandt vi en moderat overensstemmelse i at stille diagnosen PVD mellem to runder af gynækologisk undersøgelse. Vi fandt ingen korrelation mellem klinisk fund af PVD og manglende H konfiguration, ligesom vi ej heller fandt enighed i, om H konfiguration var til stede ved sammenligning af endoanal UL og MR. Dette formentlig på grund af dårlig kvalitet af UL billederne. Der var stor enighed i forhold til levator ani muskeldefekt ved sammenligning af MR og endovaginal UL, og vi fandt en god korrelation mellem muskel defekt og manglende H ved MR. Vi konkluderer derfor, at manglende H konfiguration ikke er et udtryk for PVD, men i stedet et udtryk for svær PC muskeldefekt. MR og endovaginal UL var ligeværdige i forhold til diagnostik af de muskulære defekter.

I studie IV undersøgte vi 46 kvinder med formodet PVD før og seks måneder efter operation for paravaginal defekt alene eller kombineret med anden prolaps operation. Gynækologisk undersøgelse (POP-Q), ICIQ-VS spørgeskemaet og MR af bækkenbunden blev brugt til at evaluere graden af prolaps, subjektive symptomer, seksuelle problemer, livskvalitet, vaginal H konfiguration og PC muskel defekt. Vi finder, at operation signifikant reducerer graden af prolaps og subjektive symptomer, ligesom livskvaliteten blev signifikant øget seks måneder efter operationen. Før operationen havde 67% PC muskel defekt og 46% havde manglende H konfiguration. Den vaginale H konfiguration blev ikke ændret hos nogle af kvinderne seks måneder efter operationen. Recidiv af forvægs-prolaps blev fundet hos 39% og kun MR fund (PC muskel defekt, manglende H konfiguration og graden af blære nedsynkning) forud for operationen var signifikant korreleret til risiko for recidiv ved follow-up. Vi konkluderer således, at manglende H konfiguration var et tegn på svær PC muskel defekt og ikke PVD og at vurdering af muskel defekt forud for operation for prolaps kan hjælpe klinikeren til at informere den enkelte kvinde om hendes risiko for recidiv. Store PC muskel defekter observeret forud for operationen kunne også hjælpe operatøren til at ændre operations teknik til for eksempel at bruge ikke-resorberbare suturer eller mesh.

Table of content

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Abbreviations

ATFP	Arcus tendineus fascia pelvis
AVW	Anterior vaginal wall
BMI	Body mass index
C sections	Cesarean sections
CI	confidence interval
EAUS	Endoanal ultrasound
EVUS	Endovaginal ultrasound
ICC	Intraclass Correlation coefficient
ICIQ-UI-SF	International Consultation on Incontinence Questionnaire – Urinary Incontinence-Short Form
ICIQ-VS	International Consultation on Incontinence Questionnaire – Vaginal Symptoms questionnaire
MRI	Magnetic resonance imaging
PC muscle	Pubococcygeus muscle
PCL	Pubococcygeal line
PGI-I	Patient global impression of improvement scale
POP	Pelvic organ prolapse
POP-Q	Pelvic organ prolapse quantification system
PV muscle	Puboviscerali muscle
PVD	Paravaginal defect
QoL	Quality of life score
SMS	Sexual matter score
US	Ultrasound
VSS	Vaginal symptom score

Thesis details

This PhD thesis is based on the following scientific papers:

Paper I. Arenholt LTS, Pedersen BG, Glavind K, Glavind-Kristensen M, DeLancey JOL. Paravaginal defect: anatomy, clinical findings, and imaging. Int Urogynecol J. 2017 May;28(5):661-673.

Paper II. Arenholt LTS, Glavind-Kristensen M, Bøggild H, Glavind K. Translation and validation of the International Consultation on Incontinence Questionnaire Vaginal Symptoms (ICIQ-VS): the Danish version. Int Urogynecol J. 2018 Jan 10, [Epub ahead of print]

Paper III. Arenholt LTS, Glavind-Kristensen M, Pedersen PG. Diagnosing a paravaginal defect—A comparison of gynecological examination, 3-D endoanal ultrasound, and pelvic MRI. In preparation.

Paper IV. Arenholt LTS, Pedersen BG, Glavind K, Greisen S, Bek KM, Glavind-Kristensen M. Prospective evaluation of paravaginal defect repair—a six-month post-operative follow-up with MRI, clinical examination and questionnaires. Submitted. Int Urogynecol J.

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1. Background

1.1 Pelvic organ prolapse

Pregnancy and vaginal delivery, among others, have been shown to be major contributors to the development of defects in the support of the pelvic organs with the risk of pelvic organ prolapse (POP). POP is very common and can be observed in 40-60% of parous women when performing a gynecological examination [1] According to the distance from the hymenal ring, POP can be graded from 0 to 4, where 0 is no descent, and 4 is total prolapse [2]. Not all women need treatment for their POP since subjective symptoms of prolapse and bother mainly occur when the prolapse is beneath the hymenal ring [3,4]. The subjective symptoms reported are the feeling of a bulge coming down inside or outside the vagina, dragging sensation, urinary difficulties, and sexual problems among others, leading to reduced quality of life and, for some women, depressive symptoms [3-7]. Quantification of the objective prolapse seen during gynecological examination is reproducible and standardized, and to measure subjective symptoms in the women, there is a need for validated and robust questionnaires in the language spoken by the women [8-11]. Besides the individual bother experienced by the women, POP also presents a substantial economic burden on society [12]. For Danish women, the lifetime risk of undergoing POP surgery is 18.7%, and due to the aging of the population, the number of surgeries will increase in the future [13].

1.2 Anterior vaginal wall prolapse

Three compartments have been described as anatomical sites of prolapse—the anterior vaginal wall (AVW), the uterus or vaginal vault (apical prolapse), and the posterior vaginal wall. One of the sites alone or combined with one or both of the others can be involved in the development of POP. Prolapse of the AVW is almost twice as likely to occur compared to prolapse in the other two compartments [14]. In Denmark, the majority of surgeries performed for prolapse are native tissue repairs, and studies have found surgeries in the AVW to be the ones with the highest recurrence rates. Recurrence rates in the range of 40% (both subjective and objective recurrence) have been reported for AVW, whereas recurrence in the other two compartments happens more rarely [1,15-16]. This may reflect the complexity that resolves the development of prolapse in the AVW compared to the other compartments. As suggested by some authors, overlooked anatomical defects that are

not repaired during surgery could be the reason for the high recurrence rate after AVW repair [17].

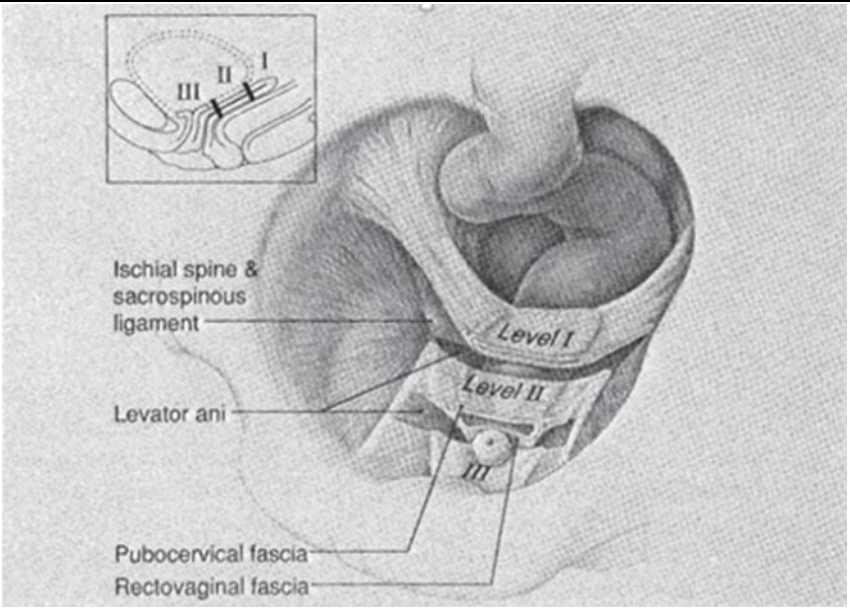

Figure 1. *Illustration of the three levels of vaginal support. DeLancey JO (1992) Anatomic aspects of vaginal eversion after hysterectomy. Am J Obstet Gynecol 166(6 Pt 1):1717-24 [18]*

1.3 Support of the anterior vaginal wall

The support of the AVW is complex and multifactorial. It is well recognized that, according to the supportive anatomical structures found by cadaver dissection, the vagina can be divided into three levels [18] (figure 1). The upper 2-3 cm of the vagina closest to the uterus is level I. This level is supported by the vaginal attachment to the cervix and indirectly thereby supported by the cardinal and uterosacral ligaments, which hold the uterus and cervix. The vaginal level III is the caudal 2-3 cm of the vagina located above the hymeneal ring. The perineal membrane and the levator ani are responsible for the support in this level [19]. Level II is located in between, and in this level, the vagina is supported by the fascial attachment of the pubocervical fascia to the arcus tendineus fascia pelvis (ATFP).

1.3.1 Fascial support

The ATFP is a condensation of connective tissue stretching from an area 2-3 cm lateral to the pubic bone to the ischial spine. At the ischial spine, the ATFP merges with the arcus tendineus levator ani [20-27]. Stretched between the ATFP on each side is the pubocervical fascia that serves as a hammock underneath the bladder and prevents the bladder and vagina from descending [18,28] (figure 2, illustration A).

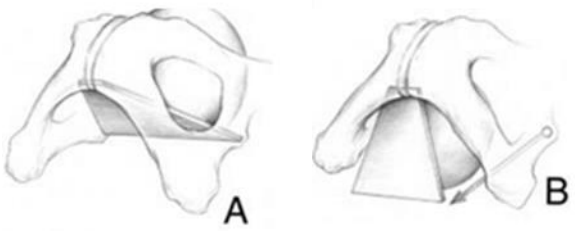

***Figure 2**. Position of AVW in normal women (A) and women with bilateral PVD (B). Illustration A. The pubocervical fascia is stretched out underneath the bladder. Illustration B: The pubocervical fascia is detached bilaterally from ATFP causing the fascia and bladder to descend. DeLancey JO (2002) Fascial and muscular abnormalities in women with urethral hypermobility and anterior vaginal wall prolapse. Am J Obstet Gynecol.187(1):93-8. ©DeLancey. [21]*

1.3.2. Apical support

In women with no prolapse, the apical part of the vagina is located above the ATFP when evaluated by MRI, and this supports the DeLancey theory of the cardinal and uterosacral ligaments being responsible for the support of the vaginal level I. [18,28-29]. Several studies have found a strong correlation between advanced AVW prolapse and apical descent [30-32]

1.3.3. Muscular support

The levator ani muscle complex has shown to be one of the most important structures for support of the AVW [33-34]. The u-shaped muscle complex consists of several subdivisions, and the naming of subdivisions has been characterized by differences and discrepancy throughout the literature [35]. For example, the terms pubococcygeus (PC) muscle and pubovisceralis (PV) muscle have been used for the same muscle subgroup. For this thesis, we have chosen to use the terms pubococcygeus muscle (PC muscle), together with the two other muscle subgroups; iliococcygeus muscle and puborectalis muscle. The PC muscle can further subdivided into the puboperineal, the pubovaginal, and the puboanal muscles [36].

The PC muscle is located underneath the ATFP and inserts laterally in the arcus tendineus levator ani. In the area just caudal to the ATFP, the muscle and the vagina are attached by collagen and smooth muscle fibers [37]. Contraction in an intact levator muscle produces a high-pressure zone in the lower part of the vagina that creates an opposite force to the downward movements of the pelvic organs. Due to this, the forces put on the fascial supportive structures are minimized [38].

1.4 Defects in the supportive structures

Development of AVW prolapse is related to defects in the supportive structures mentioned above. Often, both muscular and fascial defects are seen, and that makes treatment of the prolapse more complex. Pregnancy, vaginal birth, and aging among others predispose to developing defects or stretching in the supportive tissue of the pelvic floor [39].

1.4.1. The paravaginal defect

The detachment of the pubocervical fascia from the ATFP, called a paravaginal defect (PVD), is a common observation during POP surgery, where the space of Retzius can be opened and the defect directly observed. In a study from 2002, right sided and left sided PVD were directly observed in 89 and 87% respectively of women undergoing surgery for cystourethrocele and incontinence [21]. As a result of the detachment of the pubocervical fascia from the pelvic sidewall, a descent of the lateral vaginal wall and the bladder will occur (figure 2, illustration B). In the literature, this has been named a lateral AVW prolapse. Thinning or stretching of the pubocervical fascia in the midline is said to be involved in the medial AVW prolapse whereas defect or stretching of the uterosacral and cardinal ligaments is said to be involved in the level I AVW/apical prolapse [40] (figure 3).

For several decades, it has been discussed whether the PVD was of relevance for the development of AVW prolapse [18,21,41-44]. MRI studies have found a significant descent of the paravaginal area in women with AVW prolapse compared to women with no prolapse demonstrating that the lateral vaginal attachment was important in the normal pelvic support [45]. This study also demonstrated a strong correlation between the paravaginal and apical descent in vaginal levels I and II.

1.4.2. Levator ani defect

In a study of direct observations of PVD during surgery, only half of the women with PVD had a defect in the levator ani muscle, leading to the conclusion that PVD can occur independently of levator ani defects even if they have a close anatomic relationship [21].

The risk of levator ani defect after the first vaginal delivery is as high as 20% evaluated by MRI [46]. Major defects (especially in the pubococcygeus muscle of the levator ani) and the risk of developing POP are closely associated, and the risk of developing POP is twice as high if a levator ani defect is present compared to no defect [47]. This correlation is especially true for AVW and apical prolapse. The risk of recurrence after surgery is also higher if a defect in the levator ani muscle is present [48-50]. Both MRI and endovaginal 3D US has been found reliable in detecting levator defects [51-52]

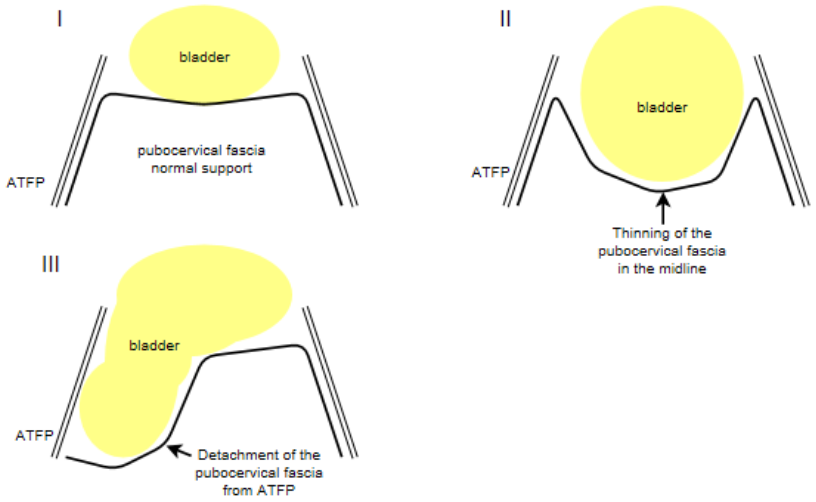

Figure 3. *Illustration of normal support and different fascial defects leading to prolapse of the AVW.*
I. Normal support of the bladder. The pubocervical fascia is attached to ATFP and functioning as a hammock underneath the bladder. II. A midline thinning of the pubocervical fascia resulting in a midline cystocele. III. A paravaginal defect leading to a lateral cystocele. Notice how the right side of the fascia is disconnected to ATFP. ATFP: arcus tendineus fascia pelvis, AVW: anterior vaginal wall.

1.5 Diagnosing the paravaginal defect

Aiming at site-specific repair, the knowledge of which supportive structures are damaged is crucial before or during surgery for AVW prolapse. With the focus on PVD, always opening the space of Retzius during surgery to evaluate if a defect is

there or not it is not beneficial due to risk of bleeding and perforation. Clinicians and researchers have therefore aimed at diagnosing the PVD before surgery.

1.5.1. Gynecological examination

A method described by Richardson et al. and Shull has been used to identify PVD by gynecological examination [42,53] The woman is placed in a supine position. Initially, the AVW is examined at rest. By applying an open sponge forceps to each vaginal corner, the connection between the pubocervical fascia and the ATFP can be imitated. The woman is then asked to do maximal straining. If no AVW prolapse occurs, the prolapse is said to be due to a PVD. If a prolapse descends in between the two branches of the forceps, a midline defect is said to be present. The observation of preserved rugal folds has also been considered to be a sign of PVD since a midline defect in the pubocervical fascia would smooth out the folds. This method has been tested in women undergoing vaginal surgery for AVW prolapse in whom clinical and surgical findings of PVD were compared [54-55]. The studies concluded that the gynecological examination of PVD was inconsistent—one study found 50% specificity and 94% sensitivity whereas the other study found 80% specificity and 24% sensitivity. This inconsistency was also demonstrated in another study in which interrater and intrarater reliability of classifying an AVW prolapse as either midline, apical, right, or left paravaginal was measured [56]. Kappa values at 0.15 and 0.36 for right and left PVD respectively were demonstrated.

1.5.2. Imaging

Due to the development of US and MRI techniques, it is possible to evaluate the location of various anatomical supportive structures in women with prolapse in order to describe presumed PVD. It is well known that the shape of the vagina in the axial plane is different in the three vaginal levels in nulliparous women. This variation reflects the different supportive mechanisms in the three levels. In level II, the vagina will appear H shaped due to the pubocervical attachment to the ATFP [21,57-65]. It has been suggested that a PVD will alter the axial image of vagina so that the H will be “sagging” on the side of defect in the axial image if evaluated by MRI and US (figure 4). In women with prolapse, missing H configuration has been found on MRI and US in 37-84% of the cases, whereas missing H configuration was found in 4-32% of women with no prolapse [58-59,61,65]. In nulliparous women without prolapse, missing H configuration was never observed [60]. One study from 2015 with the aim of detecting missing H configuration by translabial US observes, surprisingly enough, missing H configuration in 32.2% of nulliparous women at 37.2 weeks gestational age [62]. The interrater reliability of the observation of missing H configuration has been tested with kappa values at 0.63 for translabial US and 0.64 for MRI [62,64].

1.5.3. Gynecological examination and imaging

Two studies correlated the findings of PVD at gynecological examination with the findings of missing H on MRI and US. One study calculated 100% agreement between observation of PVD by gynecological examination and finding of missing H on MRI, but only two women with PVD were enrolled in the study and blinding of the observer was not described [63]. The study by Dietz found a weak but significant correlation between observations during clinical examination and translabial US at straining but not at rest [61].

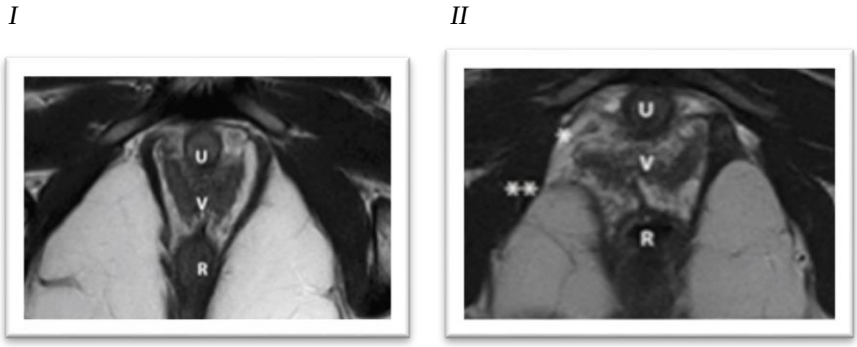

Figure 4. *MRI image of normal and missing H configuration in axial resting image. Image I: intact H configuration and normal PC muscle. Image II: missing H configuration on the right side (*) and PC muscle defect on the right side (**).U: urethra, V: vagina, R: rectum, PC: pubococcygeus muscle*

1.5.4. PVD and levator ani defect

Only a few studies evaluate the relationship between the observation of missing H on imaging with defects in the levator ani muscle, but the correlation between these two observations is very strong [62,64]. In the study by Huebner et al. missing H configuration was only seen when a levator defect was present, whereas a great deal of the women had levator defect but normal H configuration. They concluded that since levator damage could be present with intact H configuration, the missing H configuration was a sign of fascial defect. They did not consider the degree of levator defect. Cassadö-Garriga et al. evaluated the H configuration and levator ani by translabial US and found missing H associated with AVW prolapse even when controlling for levator defects.

1.6. Paravaginal defect repair

Due to the poor outcome after conventional anterior colporrhaphy and the knowledge regarding the PVD, surgeons throughout the years have tried different surgical procedures to repair this defect [66-70]. The scope of the surgery was to reconnect the pubocervical fascia with the ATFP, and abdominal, vaginal, and laparoscopic methods have been described. The objective recurrence rate was 1-31%, and the subjective recurrence rate 0-46%. Comparison of these surgical outcomes is difficult since the definition of recurrence and time to follow-up varies among the studies. Suture material, concomitant surgery, and the use of mesh and grafts also vary. To minimize the recurrence after surgery for AVW prolapse, targeting surgical repair to the specific site of defect is essential.

1.7. Aims of the study

In this thesis, we focus on the diagnosis of the PVD by gynecological examination, MRI, and US and the efficacy six months after PVD repair. To evaluate subjective symptoms in women with prolapse, we also aimed at translating and validating a questionnaire regarding vaginal symptoms, sexual matters, and quality of life.

Aims:

1. To translate and validate the questionnaire "The International Consultation on Incontinence Questionnaire—Vaginal Symptoms" (ICIQ-VS) so this questionnaire can be used in the evaluation of women with presumed PVD before and after surgery
2. To calculate the interrater reliability on detection of PVD by gynecological examination and to compare these observations with observations of vaginal H configuration on MRI and endoanal ultrasound (EAUS). We also wish to correlate the findings of missing H configuration with the severity of defect in the pubococcygeus muscle of the levator ani by MRI.
3. To describe the clinical and subjective observations together with MRI descriptions of the pelvis at rest and straining in women undergoing surgery for PVD. Furthermore, to correlate these findings to outcomes six months after surgery and to calculate a recurrence rate.

2. Material and methods

Approval for the studies was obtained from the local ethics committee (N-20150001) and the Danish Data Protection Agency (2008-58-0028). All the women signed a written consent before enrollment.

2.1. Study 1

The ICIQ-VS is a validated English questionnaire designed to evaluate vaginal symptoms, sexual matters, and quality of life in women with prolapse [71]. The questionnaire consists of 14 items; the first nine items are on vaginal symptoms leading to a Vaginal Symptom Score (VSS) (range 0-53). Items 10-13 are on sexual matters leading to a sexual matter score (SMS) (range 0-58), and the last item reflects quality of life (QoL) (range 0-10). If no symptoms and no bother, a score of 0 will be obtained. Items one to nine, 11, and 12 involve questions on frequency and bother of a specific symptom.

2.1.1. Study participants

Initially, eight randomly chosen women (six with prolapse and two without) and three medical professionals with knowledge in diagnosing and treating women with prolapse, were included in the pre-test of the translation of the Danish questionnaire.
One-hundred women with and 100 women without POP were planned to be enrolled in the main study of validity and reliability of the Danish version of the ICIQ-VS. The number of study participants was chosen based on other translations and validations of the ICIQ-VS questionnaire [72-75]. Inclusion criteria were women aged ≥18 and capable of reading and understanding Danish. Women included in the +POP (with prolapse) group had to have POP grade 2 or more whereas women in the –POP (no prolapse) group had grade 0-1 prolapse. The sensitivity of the questionnaire was planned to be tested in 50 women scheduled for POP surgery.

2.1.2. Study design

The recommendation by Guillemin F et al., together with the International Consultation of Incontinence Modular Questionnaire Validation Protocol, have been the guidelines for the translation process, the study design, and the statistics used [76-77].
The original English questionnaire was initially translated from English into Danish by three gynecologists with excellent English skills and one bilingual doctor with no gynecological knowledge. The group agreed on a consensus translation based on the four individual translations, resulting in one Danish version. Eight women were asked to complete the questionnaire, and afterward individual semi-structured interviews

were made to ensure no misunderstandings. No change to the questionnaire was necessary. Three medical professionals reviewed the questionnaire and found it fulfilling and clear and no changes were made. To ensure the original concept of the questionnaire, a bilingual gynecologist, not familiar with the original English questionnaire, conducted a back translation of the Danish questionnaire into English. The International Continence Society questionnaire group reviewed and accepted this version of the questionnaire.

The 200 women for the main study were consecutively included at the outpatient clinic at Aalborg University Hospital and North Denmark Regional Hospital, Hjørring, from February 2015 to January 2016. The women were referred to the hospital due to prolapse or other gynecological problems. After consenting to participate, a gynecological examination and POP-Q measurements were performed to evaluate the grade of prolapse if any. Before leaving the clinic, a paper version of the ICIQ-UI was completed by the women (time point t1) together with a questionnaire on baseline data (age, height, weight, number of deliveries and cesarean sections). Two to three weeks later, another paper version of the ICIQ-VS was sent to the women and the completed questionnaires (time point t2) were returned to the clinic by regular mail. We chose the timeframe of two to three weeks because prolapse symptoms probably would not change during that short period, and yet the duration was long enough for the women not to recall the answers from t1. Intervention for prolapse symptoms could not be performed during the two to three weeks.
For the sensitivity analysis of the questionnaire, 50 women scheduled for POP surgery completed the questionnaire on the day of surgery (t3) and three months after (t4). We chose this long period so that any pain or discomfort related to the surgery would be gone. At t4, the women also completed the Patient Global Impression of Improvement (PGI-I) to evaluate satisfaction with the surgery [78].

2.1.3. Statistical analyses

The following analyses were performed:

Reliability

1. Stability over time evaluated by Intraclass Correlation Coefficient (ICC). Values of ICC between 0.75 and 1.0 were excellent and between 0.6 and 0.74 good.
   Median values of VSS, SMS, and QoL at time points t1 and t2 were compared and tested by Wilcoxon matched-pairs signed rank test.
2. Internal consistency measured within the two combined scores (VSS and SMS) by Cronbach's α. Values above 0.7 were accepted.

Validity

3. Content validity measured by the level of missing data.
4. Construct validity measured by comparing median scores from women with and without POP at t1 and tested by Mann-Whitney U test.
5. Criterion validity measured by comparing degree of prolapse with questionnaire scores and tested by Jonckheere-Terpstra trend test.

   Spearman's rho correlation coefficient was used to test if the mean difference before and after surgery and PGI-I were correlated.

Responsiveness

6. Sensitivity to change was tested by comparing mean scores before and after surgery (t3 and t4) using Wilcoxon matched-pairs signed rank test.

Only women with POP were included in analysis one and six, whereas the total population (with and without POP) at time point t1 were included in the remaining analyses

P value at 0.05 was set to be the level of significance if no other value is mentioned in the list above.

2.2. Studies 2 and 3

2.2.1. Study participants

PVD cohort

At the urogynecological outpatient clinic at Aarhus University Hospital, Denmark, 50 consecutive women with presumed PVD were planned for enrollment for the two studies. Inclusion criteria were age above 18, ability to understand oral/written information, ability to sign the consent, clinical signs of PVD observed at the gynecological examination, and a planned PVD repair. Exclusion criteria were presence of metal implants in the body that contraindicates MRI scan, severe claustrophobia, and abdominal circumference larger than 180 cm.

Nulliparous cohort

Ten nulliparous women were recruited as a healthy control group. Posters at the hospital and an online advertisement at "Sundhed.dk" served as the recruitment method. Inclusion criteria were age above 18, ability to understand oral and written information. Exclusion criteria were as mentioned above supplemented with were

prior surgery in the pelvic floor or uterus together with births after gestational week 22.
The women were enrolled during the period March 2015 until January 2017.
The nulliparous women came into the study at time point t2 as illustrated in figure 5.

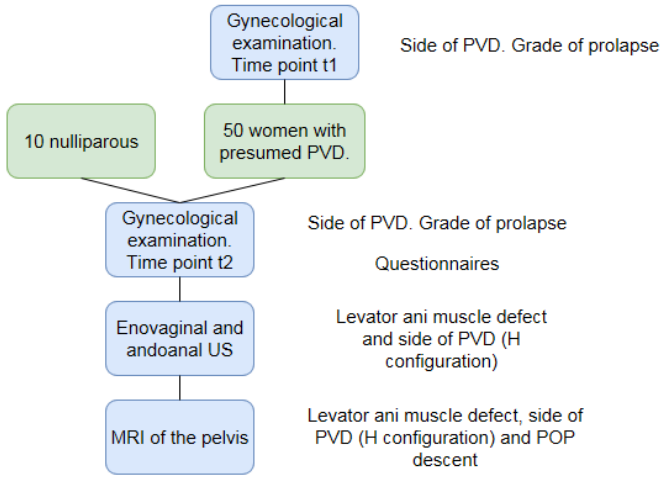

Figure 5. *Study design for the two cohorts. The 10 nulliparous women did not have gynecological examination at time point t1, but only at time point t2, together with an US examination. US: ultrasound, PVD: paravaginal defect, MRI magnetic resonance imaging, POP: pelvic organ prolapse*

2.2.2. Study design

2.2.2.1. Gynecological examination (time point t1)

In the outpatient clinic, the PVD diagnosis and the decision on whether to perform PVD repair were based on a gynecological examination performed by one of the doctors in the clinic (time point t1). For more than seven years, four doctors have performed vaginal PVD repair, and they are experienced in diagnosing PVD. Lateral descent and side of defect were noted during the gynecological examination together with the grading of the prolapse in all three compartments (anterior and posterior vaginal wall and cervix/apex) using Baden-Walker classification [79]. The women were then scheduled for vaginal PVD repair and asked if they were interested in enrollment in the PhD study. If interested, they were booked a few weeks later for an MRI scan together with a second gynecological examination (time point t2) and US examination.

2.2.2.2. Gynecological examination (time point t2)

The examinations at time point t2 were performed by investigator LTSA or MGK. Dorsal lithotomy position was used for both the gynecological and the US examination. By depressing the posterior vaginal wall with a speculum, the AVW could be observed. During straining, the two lateral sides of the AVW were described as descending or not, and the diagnosis was tested according to the method described by Shull (details in the background chapter) [53]. A PVD was said to be present if lateral descent was observed and the prolapse disappeared when lifted with forceps, and it was classified as "right-sided", "left-sided" or "bilateral". Presence of rugal folds or not was also noted. A POP-Q measurement was performed, and the three compartments were evaluated for prolapse or not [80]. The PVD diagnosis found by the first examination was known by the examiner at time point t2, but she was blinded to the side of the presumed PVD.

2.2.2.3. Questionnaires

To evaluate subjective symptoms and bother of prolapse and incontinence, the women were asked to complete the two questionnaires ICIQ-VS and ICIQ-UI-SF [81] The ICIQ-VS is described above. The ICIQ-UI-SF is a questionnaire that is not psychometrically validated in Danish but is used in evaluation of all patients who undergo urogynecological surgery in Denmark. The questionnaire is composed of three questions on frequency, amount, and bother of urinary incontinence producing a score between 0 and 21, where 0 represent no symptoms. A fourth question, not calculated into the total score, involves type of incontinence. Well knowing that the study is on POP, we included the incontinence questionnaire because many women with POP also complain of urinary incontinence.

2.2.2.4. Magnetic resonance imaging

MRI was applied to this study as a gold-standard examination due to its high-resolution soft-tissue images and knowledge on excellent reproducibility [64,82-83]. With the woman in a supine position, a MRI of the pelvis was performed at 1.5 or 3 T platforms. Pelvic phased array or cardiac coil was used. We used no enema, contrast, or bowel filling during the scans.

The following scans were performed at rest: T2 weighted images in the sagittal plane of the entire pelvis was obtained followed by axial images of the pelvis angulated perpendicular to the anal sphincter. Images were obtained from the subcutaneous part of the external sphincter muscle to the promontory. Coronal T2 weighted images angulated parallel to the anal sphincter were obtained from the entire pelvis. The slice thickness of the images was 4 mm, and the field of view was 240.

T2 weighted images during maximum straining were obtained in the sagittal plane. To ensure that enough strain was put on the organs to demonstrate a POP, the acquisition was repeated three to four times.
The interpretations of the images were performed by a senior radiologist experienced in interpreting MRIs of the pelvis and blinded to information on the gynecological examination, ultrasound, and study group belonging (nulliparous or PVD).

Levator ani defects
In the axial and coronal images at rest, the three levator ani subdivisions (pubococcygeus (PC), iliococcygeus, and puborectalis) were individually evaluated regarding grade of defect as validated by other research groups [51,83]. Each side of the muscles were scored from 0-3 as illustrated in table 1 and added together resulting in a combined muscle score between 0 and 6. No defect of the muscle was said to be present if the combined score was 0, mild if the score was between 1 and 3 and major if the score was ≥4 or a unilateral score of 3 was obtained.

Extent of muscle defect	Muscle score
No defect of the muscle	0
Defect less than 50%	1
Defect more than 50%	2
Muscle totally absent	3

***Table 1**. Scoring system for defects in the levator ani subdivisions (pubococcygeus, iliococcygeus, and puborectalis muscle)*

Descent of the AVW and the cervix
To assess the degree of POP, mid-sagittal images at maximum straining were analyzed (dynamic MRI). During the gynecological examination (POP-Q), the hymeneal ring was used as the reference line. The hymeneal ring was not visible at MRI, and another reference line had to be applied to the images. We chose to use a line from the lower border of the symphysis pubis to the articulation between the os sacrum and the coccyx bone called the pubococcygeal line (PCL) (figure 7). Measurements using this line are reliable; it is the line most often used in the literature and the one recommended by a European Radiologic Pelvic Floor Working Group [84-85]. The quantification of the prolapse grade measured by MRI using the PCL correlates well with POP-Q measurements (especially for the AVW) and the subjective sensation of a bulge coming down in the vagina [86-88]. We chose to focus on the descent of the AVW and the cervix even though descent of the posterior vaginal wall and perineum can be measured as well. The descent of the AVW and the anterior cervical lip was measured in centimeters (cm) from the PCL as shown in figure 6. Above the line, distance was given a negative value whereas below the line a positive value was noted.

The POP was graded as follows; mild: 1.1-3 cm below the PCL, moderate: 3.1-6 cm below, and severe: more than 6 cm below the PCL [84,89].

H-configuration

In the axial MRI images at rest, the vaginal level 2 was identified and H shape of the vagina was described to be present or not, and side of the presumed defect was noted (figure 4). If both sides of the "H" were missing, both "right-sided" and "left-sided" defect were said to be present.

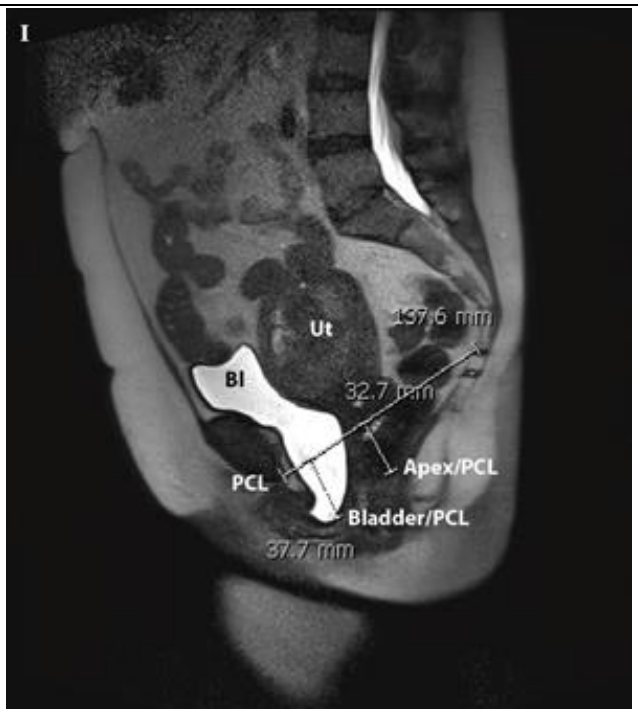

***Figure 6**. MRI during straining. Mid-sagittal image. The PCL runs from os pubis to the articulation between os sacrum and os coccyges. Bladder/PCL is the distance between the PCL and the lowest part of the bladder base. Apex/PCL is the distance between the PCL and the anterior part of the cervical tip. Bl: bladder, Ut: uterus, PCL: pubococcygeal line. [PhD paper IV]*

2.2.2.5. Ultrasound

3-D ultrasound examination was performed with the woman in dorsal lithotomy position with the BK Medical Flex Focus 500 and Pro Focus 2202 US machines and the 3-D endocavity 8838 probe (9-12 MHz). No contrast in either vagina, bladder, or

rectum was used. Before examination, the woman was asked to empty the bladder. The examinations were performed by LTSA and MGK. Both endovaginal (EVUS) and endoanal (EAUS) 3-D US scans were performed. Initially, with the purpose to evaluate levator ani, the probe was inserted into the vagina in a position following the normal curve of the vagina. Focus was laid on keeping the probe in the midline and without pushing the muscles and surrounding structures. A 3-D US cube was obtained at rest, and the images were evaluated for quality. The posterior border of the symphysis pubis had to be in the image. Often, more images had to be acquired due to artifacts. No scoring of the muscle was made at this point but performed later on the computer.

The shape of the vagina (H configuration) was evaluated by doing endoanal ultrasound at rest and maximum straining. No one has ever evaluated the vaginal shape by EAUS, and we hypothesized that an image of the AVW could be obtained by this method, without manipulating the vaginal shape. We also thought that by straining during the recording of the 3-D image a clearer image of the vaginal shape could be obtained. In the axis of the anal canal, the probe was inserted 6-10 cm into rectum. The probe was held in the mid-sagittal plane, and the starting position of the scan was evaluated so that the entire length of the vagina (from the cervix to the urethral meatus) was in the image. The posterior border of the symphysis pubis was sought to be represented in the image as well. At rest and maximum straining, a 3-D cube was obtained. Often, several images had to be acquired due to image artifacts, the woman not being able to hold the strain or movement during the recording of the cube.

Blinded to the results of the gynecological examinations, the MRI scans, and the study group belonging (nulliparous or PVD), LTSA evaluated the 3-D cubes using the software system BK viewer version 7.0.0.519.

Levator ani defects

The EVUS images at rest were evaluated regarding levator ani defects. The same muscle scoring system as described in the MRI section was used (each muscle scores between 0 and 3) (table 1). The levator muscle was evaluated for defects in the axial image at the level where the pubococcygeus muscles and puborectalis muscle were attached to the pubic bone (figure 7) [90-91].

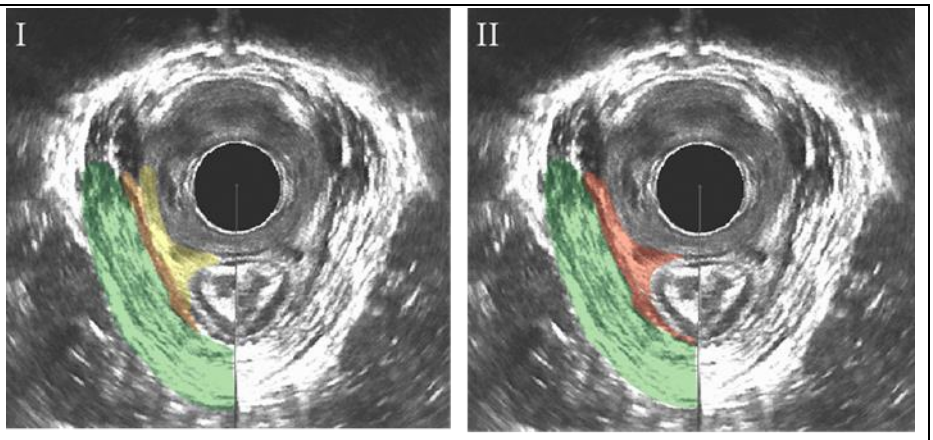

***Figure 7**. Endovaginal ultrasound images of the levator ani subdivisions.*
Image I illustrates the levator subdivision terms used in part of the existing literature. Green: puborectalis, orange: pubovisceralis, yellow: puboanalis.
Image II illustrates terms used in our study. Green: puborectalis, red: pubovisceralis

Different terms for the subdivisions of the levator ani muscle have been used in the studies published on EVUS and levator ani defects compared to the terms used in the MRI studies and in the definition of the muscle by Terminologia Anatomica [47,90-92] (table 2). In some MRI studies, the term pubovisceralis muscle has been used synonymously with what is named pubococcygeus by Terminologia Anatomica, with agreement on the muscle sub-subdivision into puboperinealis, pubovaginalis and puboanalis. With reference to the standard nomenclature and the recommendations from a recent work, we have chosen to use the term pubococcygeus (PC) muscle [92-93].

Terminologia Anatomica	**MRI**	**EVUS**
Pubococcygeus *-puboperinealis* *-pubovaginalis* *-puboanalis*	Pubovisceralis *-puboperinealis* *-pubovaginalis* *-puboanalis*	Puboanalis *-puboanalis* *-puboperinealis*
Iliococcygeus	Iliococcygeus	Pubovisceralis *-iliococcygeus* *-pubococcygeus*
Puborectalis	Puborectalis	Puborectalis

***Table 2.** Naming of the levator ani subdivisions suggested by Terminologia anatomica and other MRI/EVUS studies [35,51-52,91-92]*

Describing the levator ani muscle defects by EVUS has been validated in the literature, using the terms: puboanalis (consists of puboperinealis and puboanalis), pubovisceralis (consist of iliococcygeus and pubococcygeus) and puborectalis (see figure 7 and table 2 for details). Opposite the MRI studies and Terminologia Anatomica, the pubovisceralis muscle was defined as a composition of iliococcygeus and pubococcygeus making comparison of MRI and US very difficult.

We often found it almost impossible to differentiate between the puboanalis and pubovisceralis defined by EVUS, especially when a muscle defect was present. Due to this, and to compare our EVUS results with the results from the MRI scans, we decided to combine the muscle subgroups found by EVUS as illustrated in table 3 and figure 7. The puboanalis and pubovisceralis defined by EVUS were scored together as one muscle group called pubovisceralis that was comparable to the pubococcygeus muscle seen on MRI.

MRI (our study)	***EAUS (our study)***
Pubococcygeus (PC) ***-puboperinealis*** ***-pubovaginalis*** ***-puboanalis***	***Pubovisceralis (PV)*** ***-puboperinealis*** ***-pubovaginalis*** ***-puboanalis*** ***-iliococcygeus***
Iliococcygeus	
Puborectalis	***Puborectalis***

Table 3. *Naming of levator ani subdivisions in our study. Note that iliococcygeus on US could not be scored as individual muscle, and is included in the pubovisceralis muscle.*

H configuration

Images at rest and maximum straining were evaluated regarding H configuration. The US cube was rotated in order to evaluate the sagittal images. The entire vaginal length was measured and the middle part (vaginal level 2) was marked. By rotating the cube, the axial image of the vagina in level 2 could be evaluated. Figure 8 illustrates the preserved and missing H configuration. If the vaginal H was intact no defect was said to present and if one or both sides of the H were missing “right” and/or “left” defect were noted.

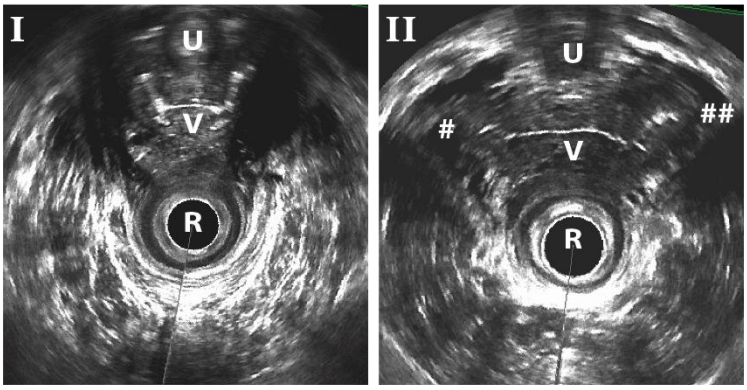

Figure 8. *EAUS images at rest of intact and unilateral (right side) missing H configuration. Images constructed from a 3-D cube. Image III illustrated intact H configuration. Image IV illustrated bilateral missing H configuration (# right sided defect, ## left sided defect). U: urethra, V: vagina, R: rectum. [PhD paper III]*

2.2.2.6. PVD repair

The 50 women with diagnosed PVD were scheduled for a vaginal PVD repair. The surgeon performing the operation was not aware of the US and MRI findings together with results of the second gynecological examination at time point t2. Whether to perform the PVD repair together with the decision of the side of repair was based only on the gynecological examination at time point t1 and the perioperative examination, and the surgeon could choose only to do a unilateral repair if it was assumed that a bilateral repair would overstretch the pubocervical fascia.

Local anesthesia with infiltration in the AVW (20ml of Carbocaine® 5 mg/ml with adrenaline 5 μg/ml or 40ml of Lidocaine® 2.5 mg/ml with adrenaline 5 μg/ml) together with bilateral pudendal block (7ml of Marcaine® 5 mg/ml) was routinely used. If necessary, intravenous light sedation and pain relief were given (Alfentanile®, Propofol® or Fentanyl ®). Prophylactic antibiotics were not routinely given. The vaginal mucosa was opened in the midline of the AVW from 2 cm from the external urethral orifice to the cervix. By blunt dissection, the ATFP was reached and with the Capio™ Suture Capturing Device (Boston Scientific, Marlborough, MA, USA) three polydioxanone 0 sutures were placed in the ATFP approximately 1.0, 2.0, and 3.0 cm from the ischial spine. In case of an apical defect, a suture was placed in the sacrospinous ligament 1.5 cm medial to the ischial spine. The pubocervical fascia was duplicated with a continuous suture polydioxanone 3-0 suture. The three sutures from ATFP were attached to the lateral part of the pubocervical fascia whereas the

suture from the sacrospinous ligament was attached to the cardinal ligament. Vaginal mucosa was trimmed and closed with a running polyglactin 3-0 suture. In case of prolapse in the posterior vaginal wall, posterior repair was performed corresponding to the anterior repair. Perineal repair was performed by isolation of the bulbocavernous muscles in each side and assembling of the muscles with two polyglactin 2-0 sutures. A cystoscopy was performed at the end of the operation to ensure normal function of the ureters. Postoperatively, the vagina was packed for three hours, and in this period, the patient had an indwelling bladder catheter. When the patient had spontaneous voiding (residual urine < 150 ml) and felt well, she was discharged from hospital.

2.2.2.7. Six months follow-up

Follow-up was planned six months after the operation, and gynecological examination, questionnaires, EAUS, EVUS, and MRI were repeated. The questionnaire PGI-I was additionally filled in by the women [78]. The English validated questionnaire measures satisfaction after surgery.

2.2.2.8. Definition of recurrence

Recurrence of prolapse was defined according to the gynecological examination (POP-Q) and subjective symptoms felt by the woman [94]. The subjective symptoms were defined from question 5a and 6a in the questionnaire ICIQ-VS (5a: Are you aware of a lump or bulge coming down in your vagina?, 6a: Do you feel a lump or bulge come out of your vagina, so that you can feel it on the outside or see it on the outside?). If the woman answered "sometimes," "most of the time," or "all the time" to one or both of the questions, symptoms were said to be present. Recurrence was defined as illustrated in figure 9.

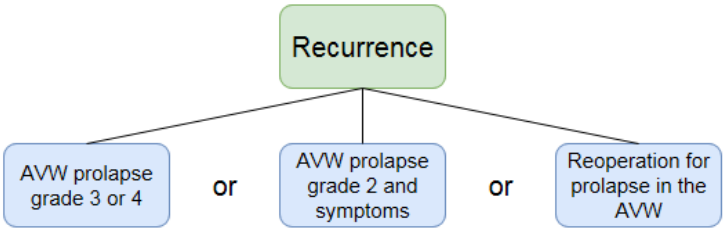

Figure 9. *Definition of recurrence after surgery evaluated by POP-Q and the questionnaire ICIQ-VS (questions 5a and 6a).*

2.2.3. Statistics used

For statistical analyses, IBM SPSS statistics 22.0 (SPSS, Chicago, IL, USA) was used. Agreement on the PVD diagnosis evaluated by gynecological examination at first visit (t1), US and MRI were tested on the 50 women with presumed PVD. On each side of the vagina it was evaluated if PVD was present or not. If two modalities agreed on the diagnosis (either both agreed on PVD or both agreed on no PVD), the pair was said to be concordant. If there was no agreement between the two modalities, the pair was said to be discordant. Agreement was measured by Cohen's kappa. Agreement was poor with values between 0.01 and 0.2, fair between 0.21-0.4, moderate between 0.41-0.6, substantial between 0.61-0.8, and excellent when above 0.8.

Intraclass correlation coefficient (two-way-random, absolute agreement, single type) was used to test agreement between total PV/PC muscle scores by MRI and EVUS. The same interpretation of values as for Cohen's kappa mentioned above.

Correlation between missing H configuration and grade of PC muscle defect was tested using Cramer's V. Correlation between the side of missing H and the side of PC defect was tested using phi correlation. Values above 0.5 showed strong association.

To compare the results before and after surgery and the women with and without recurrence, parametric and non-parametric tests were used. The level of significance was set to be 0.05.

3. Results

3.1. Study 1

Ninety-four women with grade 2 prolapse or more, 98 women with grade 0-1, and 52 women scheduled for POP surgery accepted enrollment in this study. Baseline data are shown in table 4.

The median time between t1 and t2, and t3 and t4 were 23 days (range 9-51) and 94 days (range 80-116) respectively. Retest was completed by 89 (95%) in the group of women with POP and by 46 (88%) of the women undergoing surgery.

	+ POP	-POP	Surgery
Total number	94	98	52
Median age (range)	64 (25-86)	43 (18-82)	61.5 (40-81)
Median BMI (range)	27.0 (20-41.5)	25.1 (18.1-47.3)	26.1 (20.0-38.0)
Median births (range)	2 (0-5)	2 (0-7)	2 (1-6)
Median C sections (range)	0 (0-1)	0 (0-4)	0 (0-1)
Grade 0 POP N (%)	0	52 (53.1%)	NA
Grade 1 POP N (%)	0	46 (46.9%)	NA
Grade 2 POP N (%)	71 (75.5%)	0	NA
Grade 3 POP N (%)	23(24.5%)	0	NA

Table 4. *Baseline data for the women with (+POP) and without (-POP) prolapse at time point t1 together with data on women enrolled at surgery (t3). Grade of POP evaluated from POP-Q. Data on grade of POP is not available (NA) for the surgery group. POP: pelvic organ prolapse. BMI: body mass index (kg/m²), C sections: cesarean sections.*

3.1.1. Reliability

Stability over time

For all three domains (VSS, SMS, and QoL), there was no statistical difference between median scores at t1 and t2, and ICC for single items ranged from good to excellent. Figure 10 illustrates the mean values of the three scores.

Internal consistency

Evaluating the correlation between the individual items in the VSS and SMS score showed Cronbach's alpha at 0.79 for VSS and 0.84 for SMS.

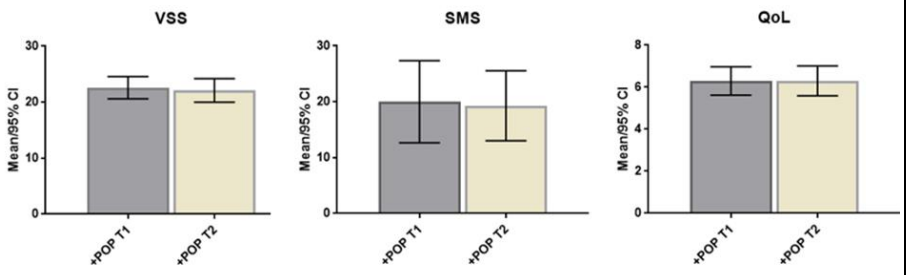

Figure 10. *Mean value (including 95% confidence interval (CI)) for VSS, SMS, and QoL for women with prolapse (+POP) at time t1 and t2. VSS: vaginal symptom score, SMS: sexual matter score, QoL: quality of life score, POP: pelvic organ prolapse [PhD paper II]*

3.1.2. Validity

Content validity

For every item in the questionnaire, missing data were evaluated and ranged between 0 and 1%. A whole page was skipped in two questionnaires, and two different women missed another two questions.

Construct validity

The median scores of the three domains (VSS, SMS, and QoL) between women with and without POP were compared, and we found a significant difference ($p<0.001$ for all domains) Mean values of the three scores are displayed in figure 11.

Criterion validity

We evaluated if increasing grade of prolapse was associated with higher questionnaire scores and found a significant correlation by Jonckheer-Terpstra trend test ($p<0.001$). In the study group of women undergoing surgery for POP, 46 women did a retest three months after the operation together with the questionnaire PGI-I. According to the PGI-I, five women felt the same as before surgery, five a little better, nine much better and 27 felt very much better compared to before surgery. The satisfaction measured by PGI-I correlated strongly with SMS (Spearman's rho -0.73 (p value 0.001)),

weakly with VSS (Spearman's rho -0.27 (p 0.03), but very weak with QoL (Spearman's rho -0.007 (p value 0.48)).

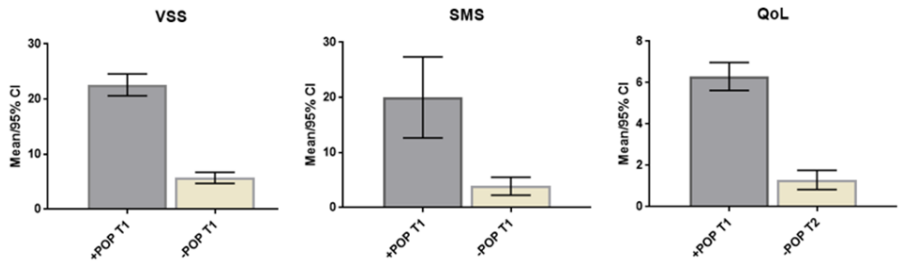

Figure 11. *Mean value (95% CI) for VSS, SMS, and QoL for women with (+POP) and without (-POP) prolapse at time T1. VSS: vaginal symptom score, SMS: sexual matter score, QoL: quality of life score, POP: pelvic organ prolapse [PhD paper II].*

3.1.3. Responsiveness

Sensitive to change

POP surgery (t3) was performed in 52 women whereas 46 responded to the retest three months after the operation (t4). Evaluating the three domains individually showed significant reduction in median values for VSS and QoL (p values <0.001) but not for SMS (p-value 0.059). Mean values are displayed in figure 12.

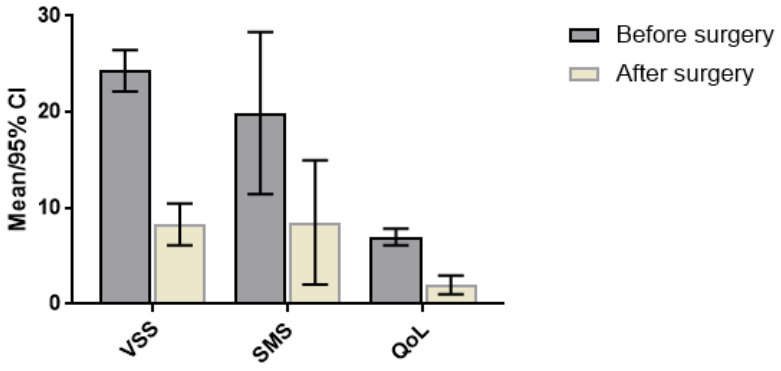

Figure 12*. Sensitivity to change. Mean value (including 95% confidence interval (CI)) for VSS, SMS, and QoL for women with pelvic organ prolapse before and three months after surgery. VSS: vaginal symptom score, SMS: sexual matter score, QoL: quality of life score [PhD paper II]*

3.2. Studies 2 and 3

Inclusion of 50 women with presumed PVD and 10 nulliparous women was achieved. Baseline characteristics are listed in table 5.

		PVD		Controls	P value
	N		N		
Age (years) ***Median(range)***	50	40.0 (27-67)	10	34.5 (30-53)	0.244*
BMI (kg/m²) ***Mean (95%CI)***	50	24.8 (23.8-25.8)	10	24.8 (19.8-29.9)	0.969**
Births ***Median(range)***	50	2 (1-4)	10	0	0.000*
Cesarean sections ***Median(range)***	50	0 (0-2)	10	0	0.202*
Smokers ***N(%)***	50	7 (14%)	10	2 (20%)	0.637***
Prior POP surgery ***N(%)***	50	8 (16%)	10	0	0.330***

Table 5. *Baseline characteristics of women with PVD and nulliparous (controls). PVD: paravaginal defect, BMI: body mass index, POP: pelvic organ prolapse, CI: confidence interval [PhD paper III].*
** Mann-Whitney-U test, ** Two-sample T-test, *** Fisher's exact test*

In the data presented below, missing data are observed. Mostly artifacts in the US images and neglect of handing out or filling in the questionnaires were the reason.

3.2.1. Gynecological examination

Gynecological examination at time points t1 and t2 before surgery revealed that all the women in the PVD group had AVW prolapse grade 2-3. Seven (14%) women also had grade 2-3 apical prolapse, whereas another seven (14%) had posterior vaginal wall prolapse (table 6).

All women in the nulliparous group had grade 0 or 1 prolapse in all of the compartments. Mean POP-Q values are presented in table 6.

	PVD cohort		Nulliparous cohort		
	n	Mean (SD)	n	Mean (SD)	p-value
Aa	48	-0.1 (0.8)	10	-3.0 (0)	<0.001
Ba	48	0.3 (0.9)	10	-3.0 (0)	<0.001
C	48	-3.7 (2.1)	10	-6.4 (1.0)	<0.001
Gh	48	4,0 (1.0)	10	2.7 (0.9)	0.001
Pb	48	3.3 (0.9)	10	3.6 (0.5)	0.32
Tvl	48	8.7 (1.0)	10	8.9 (1.1)	0.59
Ap	48	-2.4 (0.9)	10	-3.0 (0)	<0.001
Bp	48	-2.3 (0.9)	10	-3.0 (0)	<0.001
D	48	-6.5 (1.4)	10	-6.7 (1.3)	0.71

Table 6. *Mean POP-Q values in the nine measure points. Anterior vaginal wall descent is measured by Aa and Ba, cervical descent by C, and posterior vaginal wall by Ap, Bp, and D. Reference point is the hymeneal ring. Gh: genital hiatus height, Pb: perineal body height, TvL: total length of vagina at rest. Independent T-test was used. Missing data on two women in the PVD cohort. PVD: paravaginal defect.*

PVD was found in all the women in the PVD cohort at time point t1 (figure 15). At time point t2, both cohorts were evaluated by gynecological examination, including if PVD was present or not. As illustrated in figure 13, two were said not to have a PVD at time point t2.

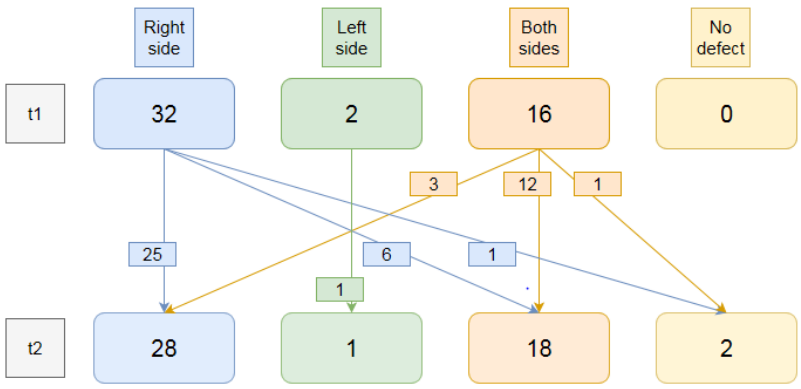

Figure 13. *Number of women with right-sided, left-sided, bilateral, or no PVD in the PVD cohort evaluated by gynecological examination at time points t1 and t2. There is no data on side of defect at time point t2 for one woman in the group of women with left-side defect at time point t1. PVD: paravaginal defect*

In 25 of the cases, we agreed on right-sided defect, one on left side, and in 12 of the cases, we agreed on bilateral PVD. This resulted in an absolute agreement of 96% for the right side with moderate kappa value (0.48, $p<0.001$) and 80 % for the left side with moderate kappa value (0.56, $p<0.001$). None of the women in the nulliparous group were said to have a PVD by gynecological examination at time point t2.

3.2.2. Agreement between gynecological examination, MRI, and US

Assuming that missing H configuration was a sign of PVD, the MRI images and EAUS images at rest and straining were evaluated for vaginal H shape and presented in table 7. One woman from the nulliparous cohort had right sided missing H at EAUS rest.

PVD cohort	**t1 (n=50)**	**t2 (n=49)**	**EAUS rest (n=46)**	**EAUS strain (n=37)**	**MRI (n=50)**
Right side	32 (64%)	28 (57%)	18 (39%)	9 (24%)	3 (6%)
Left side	2 (4%)	1 (2%)	3 (6%)	6 (16%)	2 (4%)
Bilateral	16 (32%)	18 (37%)	9 (20%)	14 (38%)	17 (34%)
No PVD	0	2 (4%)	16 (35%)	8 (22%)	28 (56%)
Nulliparous cohort	**t1**	**t2 (n=10)**	**EAUS rest (n=10)**	**EAUS strain (n=9)**	**MRI (n=10)**
Right side	-	0	1 (10%)	0	0
Left side	-	0	0	0	0
Bilateral	-	0	0	0	0
No PVD	-	10 (100%)	9 (90%)	9 (100%)	10 (100%)

Table 7. *Missing H configuration evaluated by EAUS at rest and straining together with MRI in women with PVD at gynecological examination (t1 and t2). EAUS: endoanal ultrasound, MRI: magnetic resonance imaging, PVD: paravaginal defect [PhD paper III].*

The agreement between the modalities was tested in the PVD cohort. Since the aim of our study was to evaluate MRI and US as methods to support the clinicians when diagnosing a PVD, only the results of gynecological examination at time point t1 were included. In general, the absolute agreement between gynecological examination and imaging modalities was low between 44 and 65% and with poor not statistically

significant kappa values (table 8). The agreement between MRI and US were higher, especially for the resting US images.

	Concordant -PVD	Concordant +PVD	Discordant	Absolute agreement	Kappa	P value
t1 and EAUS rest (n=46)						
Right side	1	27	18	61%	0.06	0.23
Left side	22	5	19	59%	0.06	0.69
t1 and EAUS strain (n=37)						
Right side	1	23	13	65%	0.09	0.19
Left side	11	7	19	49%	-0.003	0.99
t1 and MRI (n=50)						
Right	2	20	28	44%	0.05	0.24
Left	22	9	19	62%	0.19	0.19
EAUS rest and MRI (n=46)						
Right	14	14	18	61%	0.24	0.08
Left	27	10	9	80%	0.55	<0.001
EAUS strain and MRI (n=37)						
Right	9	11	17	54%	0.11	0.47
Left	13	10	14	62%	0.26	0.10

Table 8. *Number of concordant and discordant pairs between the three modalities. Gynecological examination (t1), EAUS (rest and strain), and MRI together with the individual kappa values. Concordant –PVD: both modalities agree on no PVD present. Concordant +PVD: both modalities agree on PVD present, discordant: the two modalities disagree on PVD being present or not [PhD paper III].*

3.2.3. Pubovisceralis/pubococcygeus muscle defect

The comparison of PV/PC muscle defect evaluated by MRI and EVUS at rest showed substantial agreement on total score with ICC at 0.69 (95% CI 0.51-0.81), p<0.001. Due to artifacts, one US image could not be interpreted. The categorized muscle defects distributed as follows.

- EVUS: no muscle defects were found in 10 (20%), mild in 24 (49%), and 15 (31%) had major defects
- MRI: no PC muscle defects were found in 17 (34%), 16 (32%) had mild, and 17 had major (35%).

3.2.4. H configuration and muscle defects

A close anatomical relationship between the insertion of the pubococcygeus muscle and the attachment between ATFP and the pubocervical fascia is observed. Therefore, we wanted to correlate findings of missing H configuration with muscle defect. Due to the missing validation of the EAUS procedure in detecting H configuration and the amount of missing data, MRI was chosen over US as the modality. Missing H configuration was seen only in the women who also had PC muscle defect (figure 14). There were statistically more women with major and minor PC muscle defect in the group of women with missing H (χ^2 test, P<0.001), and the correlation between grade of muscle defect and missing H was large (Cramer's V 0.69, p<0.001). We also tested if there were a correlation between side of muscle defect and side of missing H. Right and left side were calculated together. A large association between side of missing H and side of PC muscle defect (phi coefficient 0.63, p<0.001) was observed.

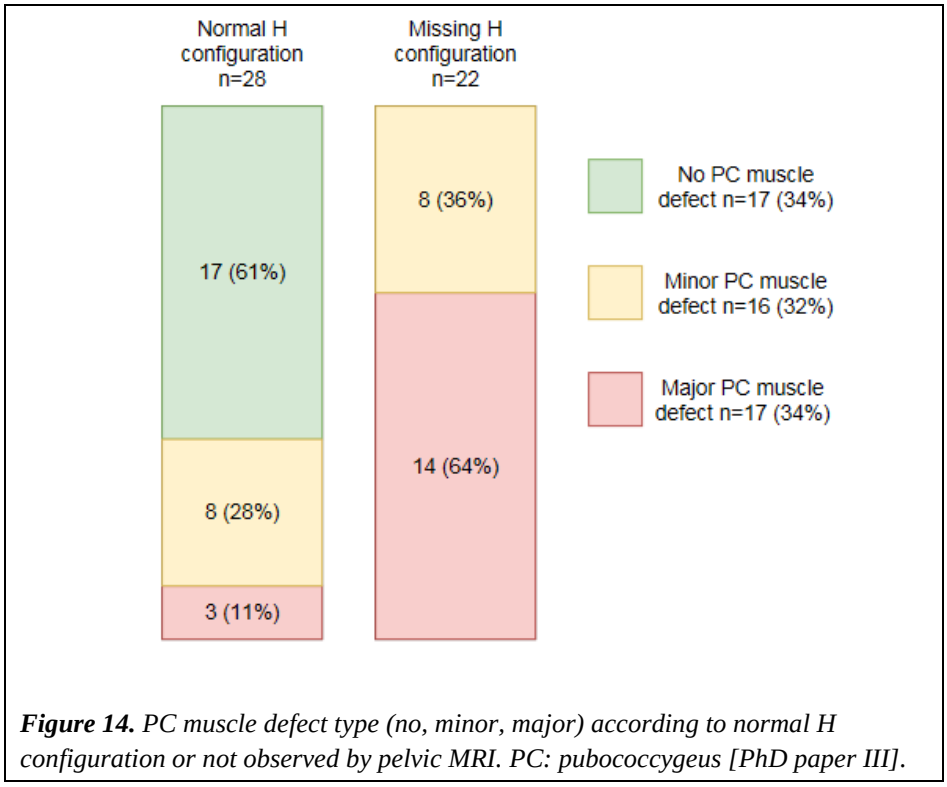

Figure 14. *PC muscle defect type (no, minor, major) according to normal H configuration or not observed by pelvic MRI. PC: pubococcygeus [PhD paper III].*

Knowing that the missing H configuration and muscle defect were closely related, we wanted to examine if the observations of lateral vaginal wall descent by gynecological examination could be an observation of not just a PVD but also a muscle defect. Table 9 shows the number of concordant and discordant pairs when gynecological examination was compared to EAUS/MRI and the findings of either missing H and/or PC muscle defect.

	Concordant -PVD	Concordant +PVD	Discordant	Absolute agreement	Kappa	P value
t1 and MRI PC muscle defect and/or missing H (n=50)						
Right	2	31	17	66%	0.13	0.065
Left	19	10	21	58%	0.14	0.309
t1 and EAUS (rest) PC muscle defect and/or missing H (n=50)						
Right	2	41	7	86%	0.32	0.002
Left	21	9	20	60%	0.15	0.279

Table 9. *Distribution of concordant and discordant pairs between gynecological examination at t1, EAUS at rest and MRI together with the individual kappa values evaluating the agreement between clinical PVD and missing H and/or PC muscle defect. Concordant +PVD: agreement between modalities on PVD present, discordant: disagreement on PVD being present or not.*

3.2.5. Evaluation of PVD repair

All of the 50 women enrolled in the study were scheduled for a PVD repair. One woman canceled her surgery; one was perioperatively evaluated not to have a PVD, and two were lost to follow-up at six months, leaving 46 women in the study group. At inclusion (t1), 29 were said to have a right-sided defect, two left-sided, and 15 bilateral.

In 20 women, PVD repair as described above was performed as a single procedure whereas 16 also had sacrospinous ligament fixation, six had perineorrhaphy, three had sacrospinous ligament fixation and perineorrhaphy, and one had posterior colporrhaphy, sacrospinous ligament fixation, plus perineorrhaphy. All the women diagnosed with right- and left-sided defect had repair on that specific side, whereas five of the women with bilateral defect only had right-sided defect repair due to fear of overstretching the pubocervical fascia.

Operations were performed using local anesthesia, but due to fear of pain, one woman had general anesthesia. Mean operating time was 52.6 minutes (95% CI 48.4-56.8), and perioperative bleeding was 53 ml (95% CI 35-71). The desired number of sutures applied between ATFP and the pubocervical fascia was three, but in two women, only two sutures were applied (due to difficulties during operation).

Discharge from the hospital within 24 hours after operation was possible for 40 women. Four women stayed 24-48 hours, and two remained at the hospital more than 48 hours. There were no perioperative complications, and only minor postoperative complications were observed. Five had urinary retention (treated with self-catheterization for less than seven days), four had vaginal wall hematoma (one needed small surgery due to continuous vaginal bleeding, one had fever and urinary retention treated with self-catheterization and antibiotics), and two had fever without known focus (sepsis was diagnosed in one but recovered after hospitalization and antibiotic treatment).

Follow-up was planned after six months with a mean time of 195 days (95% CI 184-207).

In the following, results from before and after the operation on the 46 women will be reported.

3.2.5.1. Gynecological examination

Evaluating grade of prolapse before and after the operation showed a significant reduction in the descent of the anterior vaginal wall but not in the apical and posterior compartments measured by POP-Q (table 10).

Two women did not have POP-Q measurement before operation but were evaluated by Baden Walker instead. Before operation, 41 out of 46 (89%) had grade 2, and five (11%) had grade 3 AVW prolapse. At follow-up, 26 out of 46 (57%) hade grade 2 and, one (2%) had grade 3.

	Before operation			After operation			
	N	Mean	SD	N	Mean	SD	P-value
Aa	44	-0.9	0.8	46	-1.2	1.3	<0.001
Ba	44	0.3	0.9	46	-1.1	1.3	<0.001
C	44	-3.6	2.2	46	-3.7	2.3	1.00
Gh	44	4.0	1.1	46	3.9	0.8	0.40
Pb	44	3.3	0.9	46	3.7	0.7	0.01
TvL	44	8.7	1.0	46	8.8	0.9	0.42
Ap	44	-2.4	1.0	46	-2.5	0.7	0.55
Bp	44	-2.3	1.0	46	-2.4	0.8	0.33
D	44	-6.4	1.3	46	-6.1	1.2	0.23

***Table 10**. Mean POP-Q measurements before and after operation. Aa and Ba: the anterior vaginal wall. C: the apical compartment. Ap and Bp: the posterior vaginal wall. The hymeneal ring is the reference point. Gh: genital hiatus height, Pb: perineal body height, TvL: length of vagina at rest. Paired T-test was used [PhD paper IV].*

3.2.5.2. Questionnaires

The subjective sensation of prolapse, sexual problems due to prolapse, quality of life and urinary incontinence significantly improved six months after PVD repair (table 11). This was also demonstrated by the PGI-I showing that 78% felt better than before operation.

	Before operation		After operation		
	n	Median (range)	n	Median (range)	P value
ICIQ-VS					
VSS	46	26.0 (8-47)	46	12.5 (2-36)	<0.001
SMS	29	37.0 (0-58)	36	9.0 (0-58)	<0.001
QoL	46	8.0 (2-10)	46	2.0 (0-10)	<0.001
ICIQ-UI-SF	46	10.0 (0-16)	38	2.0 (0-15)	<0.01
PGI-I			Number (%) in each category		
Very much better			6 (17%)		
Much better			16 (44%)		
Slightly better			6 (17%)		
No change			8 (22%)		
Missing data			10		

***Table 11.** ICIQ-VS and ICIQ-UI-SF median scores before and six months after PVD repair together with distribution of women in the different PGI-I categories at follow-up. ICIQ-VS: International Consultation on Incontinence Questionnaire—Vaginal Symptoms, VSS: vaginal symptom score (score 0-53), SMS: sexual matter score (score*

0-58), QoL: quality of life (score 0-10). ICIQ-UI-SF: International Consultation on Incontinence Questionnaire—Urinary Incontinence-Short Form (score 0-21), PGI-I: patient global impression of improvement [PhD paper IV].

3.2.5.3. MRI

Measuring the distance from the bladder base and the anterior cervical tip to the PCL respectively during straining served as another modality to evaluate descent in the two compartments. There was a significant reduction in descent in both compartments after surgery, but still, 11 had moderate to severe descent in the AVW, and nine had severe apical descent (table 12).

			Before PVD repair	After PVD repair	P value
AVW					
	Bladder/PCL distance (mean (95% CI))		2.7 (2.2-3.2)	2.0 (1.5-2.4)	0.001
	Anterior descent according to the PCL(n=46)				
		No decent, n	7	13	
		Mild decent, n	18	22	
		Moderate decent, n	21	10	
		Severe decent, n	0	1	
APEX					
	Cervix/PCL distance (mean (95% CI))		2.0 (1.6-2.5)	1.6 (1.2-2.1)	0.032
	Apical descent according to the PCL(n=46)				
		No decent, n	12	14	
		Mild decent, n	23	23	
		Moderate decent, n	0	0	
		Severe decent, n	11	9	

Table 12. *MRI of the pelvis during straining in 46 women operated for PVD. Comparison of distance between bladder base/cervix and the PCL before and six months after operation. Paired sample T-test was used. Underneath each measurement is the descent categorized according to severity. PVD: paravaginal defect, AVW: anterior vaginal wall, PCL: pubococcygeal line [PhD paper IV].*

PC muscle defects were evaluated in the images before operation, and 31 out of 46 (67%) had mild or major PC muscle defect. Missing H configuration was detected in 21 (46%) of the women (right side was missing in three women, left side in two and 16 had missing H configuration in both sides). The classification of having missing or normal H configuration did not change in any of the women six months after surgery.

3.2.5.4. Recurrence

Of the 46 women enrolled, 18 (39%) had recurrence six months after surgery, defined as in figure 9. Grade 2 AVW prolapse was diagnosed in 17, and one had grade 3. Eight of the women with recurrence in the AVW also had descent in other compartments. Four had apical prolapse grade 2, three had posterior vaginal wall prolapse grade 2, and one had grade 2 prolapse in both apical and posterior compartment. Of the five women with apical prolapse after operation, four also had apical prolapse before and had PVD repair together with apical suspension.

To establish if any preoperative variables were significant for the risk of recurrence, women with and without recurrence were compared (table 13). Only defects in the PC muscle, missing H configuration and MRI-descent of the bladder base were significantly different in the group of women with recurrence. There was no significant difference in distribution of defects in the iliococcygeus or puborectalis muscle between the two groups.

Relative risk of recurrence when missing H (and thereby PC muscle defect) was observed was 5.9 (95% CI 2.0-17.8, p=0.001) whereas relative risk was 4.4 (95% CI 1.1-17.0, p=0.03) when major PC muscle defect was present compared to no defect.

3.2.6 Evaluation of the 20 women with no concomitant surgery

We also evaluated the 20 women who only had PVD repair as described in the method section, to test whether the PVD repair alone significantly improves objective and subjective signs of prolapse. A significant reduction in ICIQ-VS and ICIQ-UI-SF scores were calculated together with significant reduction in AVW prolapse (Aa and Ba measured by POP-Q) but not apical descent. Missing H was observed in 10 (50%) of the women and 14 (70%) had mild or major PC muscle defects. Recurrence was observed in 7 (35%) women. In this small sample size PC muscle defect and bladder base distance to the PCL could not be demonstrated as risk factors of recurrence, but as in the large cohort (46 women), missing H was still a significant risk factor.

	No recurrence (28)	Recurrence (18)	P value
Age, median (range)	38 (27-67)	39.5 (29-56)	0.660*
Births, median (range)	2 (1-4)	2 (1-4)	0.903*
Cesarean sections, median (range)	0 (0-1)	0 (0-2)	0.271*
BMI, mean (95%CI)	24.5 (23.2-25.8)	25.2 (23.5-27.0)	0.468^
Previous POP surgery, n(%)	4 (14.3%)	3 (16.7%)	1.000#
ICIQ-VS BEFORE OPERATION			
VSS, median (range)	25 (8-47)	26 (13-47)	0.830*
SMS, median (range)	29.5 (0-58)	40 (1-47)	0.236*
QoL, median (range)	7 (2-10)	8 (3-10)	0.208*
GYNECOLOGICAL EXAMINATION BEFORE OPERATION			
AVW prolapse grade, median (range)	2 (2-3)	2 (2-3)	0.249*
Apical prolapse grade, median (range)	1 (0-2)	1 (0-3)	0.097*
OPERATION DATA			
Operation on apex as well, n(%)	13 (46.4%)	7 (38.9%)	0.615#
MRI BEFORE OPERATION			
PC muscle defect type, n(%)			
No defect	13 (46.4%)	2 (11.1%)	0.03¤
Mild defect	8 (28.6%)	6 (33.3%)	
Major defect	7 (25.0%)	10 (55.6%)	
Iliococcygeus muscle defect type, n(%)			
No defect	16 (57.1%)	9 (50%)	0.381¤
Mild defect	10 (35.7%)	9 (50%)	
Major defect	2 (7.1%)	0	
Puborectalis muscle defect type, n(%)			
No defect	26 (92.9%)	15 (83.3%)	0.365#
Mild defect	2 (7.1%)	3 (16.7%)	

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	No recurrence (28)	*Recurrence (18)*	*P value*
Missing H configuration, n(%)	*6 (21.4%)*	*15 (83.3%)*	*<0.001¤*
Bladder base/PCL distance, mean (95%CI)	*2.04 (1.37-2.71)*	*3.69 (3.04-4.35)*	*0.001^*
Apex/PCL distance, mean (95%CI)	*1.71 (1.15-2.26)*	*2.56 (1.73-3.40)*	*0.071^*

Table 13. *Preoperative variables in women with and without recurrence six months after operation, BMI: body mass index, POP: pelvic organ prolapse, VSS: vaginal symptom score, SMS: sexual matter score, QoL: quality of life, PCL: pubococcygeal line [PhD paper IV] * Mann-Whitney-U test, ^T-test, # Fisher's exact test, ¤ Chi² test*

4. Discussion

4.1. Study 1

In this study, we demonstrated a robust and well-comprehended translation of the ICIQ-VS questionnaire into Danish. No misunderstandings were detected during interviews in the pretest and we demonstrated good to excellent reliability, validity and sensitivity which were similar to other studies translating and validating the questionnaire [72-75]. Only the sensitivity for the SMS was not significant (p value 0.059) probably due to small sample-size and three months being too short a period after surgery to expect significant improvements in sexual problems (pain after surgery etc.).

The re-test response rate was high and only a few of the women had to be reminded by a telephone call to send back the questionnaire. At the time of enrollment, it was not possible to send out the questionnaire electronically, but we believe that the response rate could have been even higher if we have had that opportunity.

We choose to translate and validate the ICIQ-VS questionnaire over a large number of other urogynecological questionnaires due to the size and content. The questionnaire is short (only 14 items) and covers both frequency and bother of vaginal symptoms, sexual problems due to prolapse, and quality of life. The questionnaire is widely used in international prolapse research and has been validated in several languages [7,72-75,95-100]. By choosing a questionnaire that was short, we hoped that the response rate would be higher [101]. Not only does vaginal prolapse contribute to local vaginal symptoms but also diffuse symptoms from the lower abdomen, sexual problems, and reduced quality of life are observed [3-7]. Therefore, we selected a questionnaire with multiple approaches to measure the vaginal symptoms together with sexual matters and quality of life. When choosing the questionnaire, we had some concerns regarding three of the questions (1a: are you aware of a dragging pain in your lower abdomen? 2a: Are you aware of soreness in your vagina? and 7a: Do you feel that your vagina is too dry?). A positive answer to those questions could arise due to vaginal prolapse but also due to, for example, menopausal vaginal atrophy, constipation or menstrual cramps. This could lead to a high score in women without prolapse and thereby not make the questionnaire able to distinguish between women with and without prolapse. We observed higher scores in these three questions compared to the rest of the questions in women without prolapse, but the construct validity was good anyhow.

Even though the questionnaire was designed to measure subjective symptoms in women with prolapse, no definition on scores according to severity of prolapse was available. For example, no one has defined if a specific score was high or low and

what change in score that would be clinically meaningful. In that context, the interpretation of the scores for individual women has limited usage but could be meaningful when evaluating subjective symptoms before and after treatment or when evaluating different surgical methods.

By using a questionnaire designed by the ICS group, you have to accept their translation and validation protocol. The unification of the translation and validation process makes the comparison between studies using the questionnaire in different languages more robust. We find it very important to use a questionnaire that is widely used so that study outcomes are easily compared and interpreted when evaluating results from different research groups all over the world [7,95-100]. The increased focus on using questionnaires in prolapse research reflects the knowledge that subjective symptoms and patient satisfaction are important and should be considered whenever evaluating women with prolapse and the efficacy of any POP treatment [102-104].

In 2006, a Danish nationwide urogynecological clinical database (DUGABase) was established with the aim of monitoring the urogynecological surgeries performed in Denmark [105]. Regarding women with POP, subjective symptoms and objective measurements of POP before and three to six months after surgery are collected. Only three questions regarding POP (do you feel a lump coming out of your vagina, how often and how much does it bother you) are included in the questionnaire handed to the women. The questions are collected and cut from the ICIQ-VS (before it was translated and validated by us), and the questions are modified in a way that makes them non-comparable with the questions in the original English questionnaire. The translation of the questions used in the database questionnaire is not the same as in our validated version. We find it very important that questionnaires used in a clinical database are validated in the language spoken so that data collected from the database can be trusted and used for research. We also encourage the use of questionnaires measuring not only the feeling of a lump but also quality of life and sexual problems [102-104].

4.2. Studies 2 and 3

These studies demonstrated poor agreement between the clinical observation of paravaginal descent and the observation of missing H by MRI and EAUS. By evaluating the grade of PC muscle defect and missing H by MRI, we found a strong correlation between the two observations and concluded that missing H was a sign of severe muscle defect rather than PVD. This was also concluded by evaluating MRI images of the women undergoing PVD repair since none of the women in the cohort

had changes in their vaginal shape (missing or normal H) after their surgery compared to before. We also evaluated whether the descent observed during gynecological examination could be a sign of either PVD (defined as missing H) and/or muscle defect, but agreement was low.

The agreement of the observation of missing H by EAUS and MRI was fair to moderate, but substantial agreement was found between EVUS and MRI regarding PC muscle defect scores. We concluded that both MRI and EVUS were useful in the evaluation of PC muscle defects, but due to the poor agreement between MRI and EAUS and difficulties in interpreting the images and poor quality, EAUS was not useful in the evaluation of missing H.

All the women in the nulliparous cohort had intact H configuration and intact PC muscle when evaluated by MRI, together with no PVD observed during gynecological examination.

By doing PVD repair alone or together with concomitant surgery, we demonstrated a small but significant reduction in descent of the AVW evaluated by clinical examination and MRI, and significant reduction in subjective symptoms of prolapse, urinary incontinence, and sexual matters together with increased quality of life six months after operation.

At six-month follow-up, a recurrence rate of 39% was observed. The risk of recurrence was significantly higher among women with missing H, major defects in the PC muscle, and women with a higher degree of bladder descent before surgery evaluated by MRI. No other preoperative parameters were able to help the clinicians in the risk assessment.

We chose to enroll 50 women with presumed PVD, diagnosed by clinicians at the outpatient clinic. This was due to the desire to evaluate modalities to help the clinicians diagnosing the PVD. We found moderate agreement between the initial diagnose of defect made by the clinicians during a gynecological examination at time point t1 and the diagnose made at time point t2. Other studies have found the method to detect PVD unreliable [54-56]. In our study, the conflicting results could be due to circumstances other than the examination itself, for example, different approaches when evaluating the women. The clinicians in the outpatient clinic at time point t1 evaluated the woman with the approach of choosing the right surgery, whereas our approach at time point t2 was toward describing the actual anatomical defects seen by gynecological examination. At the outpatient clinic, the approach was also biased by the age of the women. By the belief that prolapse in younger women developed directly due to birth-related defects (for example the PVD) and that prolapse in older women developed mainly due to stretching of the pubocervical fascia could result in

a huge bias when evaluating our cohort of young women [40,106]. Another limitation is the unblinding of the investigators from group belonging (nulliparous or PVD) when doing the second gynecological examination (t2). As a strength, we were not aware of the side of defect and the planed surgical procedure in the PVD cohort. When interpreting the US and MRI images, we were unaware of cohort belonging, the clinical examinations, surgeries performed, and results of the other imaging modality.

Women with prior POP surgery were not excluded from enrollment in the PVD cohort (table 5). In the literature, conflicting results have been found regarding risk of recurrence and prior POP surgery. We did not find any significant difference in recurrence among women with and without prior POP surgery (p=1.00) [50,106-107].

The 10 nulliparous women were enrolled as a control group to test whether the vaginal H configuration was intact in these women. To ensure blinding from cohort belonging, he images from the nulliparous cohort were interpreted together with the images from the PVD cohort. All the women had intact vaginal shape except one with missing H configuration on the right side evaluated by EAUS. Evaluating the US cube from that particular woman afterward reviled poor image quality, which could explain the interpretation of the missing H.

The PVD diagnosis established during the first gynecological examination was confirmed during surgery for all the women. A huge bias must be considered since the surgeons were the same as the ones who did the initial clinical examination at t1, and they were not blinded to the results of that examination. Furthermore, one could imagine, that a defect between the pubocervical fascia and ATFP could occur, when the paravaginal space was digitally opened during operation, leading to a false agreement between clinical examination and observation during surgery.

For the last decades, evaluation of US as a modality to describe the normal and abnormal anatomy in the pelvic area has been of much interest [47,58,60,62,108-109]. US is easily accessible and does not harm the women. Most of the examinations and interpretations are easily learned, and the reproducibility is high. The 3-D ultrasound, where a cube of the pelvic floor is stored for later interpretation, is especially of value due to the possibility of more raters evaluating the same image and due to the possibility of demonstrating the findings repeatedly.

Translabial 3-D US has been used in the attempt to describe vaginal shape and with good reliability [62]. By using translabial US, there is a risk of altering the anatomical locations when pushing the transducer against the introital area, and we wanted, therefore, to demonstrate the H configuration by EAUS. No other studies have evaluated this method. We found it difficult to obtain a good image of the AVW due to air in the rectum and the vagina, and it was difficult to demonstrate the exact

location of the midvagina in the axial images. If the axial images were interpreted cranial to the midvagina, the vaginal corners would flatten out making the shape of the vagina a straight line, which could make the interpreter think a bilateral PVD was present. The air in the rectum and the vagina could have been minimized if gel had been introduced in these anatomical locations before the scan, but we were afraid that gel in the vagina would alter the location of the AVW. If an apical descent was present, the descending cervix made the interpretation of the US image almost impossible. We also observed, that not keeping the probe in the midline, altered the image of the vaginal shape, even after modifying and tilting the image in the 3-D viewer program. This was also demonstrated by the missing agreement on H configuration between EAUS and MRI in our study. Therefore, we do not think that EAUS is useful in the detection of vaginal shape. Since translabial US has good reliability, it should be the US modality of choice for evaluation of vaginal shape, even though it too has limitations.

3-D EVUS as a modality for evaluation of defects in the PV portion of the levator ani muscle has previously been demonstrated to be beneficial like translabial US [47,110-112]. Our findings support this use of US, and we think both translabial and EVUS can be used in future evaluation of female patients and pelvic floor research. EVUS examination is the US modality of choice for most gynecologists when evaluating, for example, uterus and ovaries, and we believe, therefore, that adding the 3-D EVUS to the evaluation of women with prolapse would be preferable over translabial US.

All the women enrolled in the PVD cohort were scheduled for vaginal PVD repair. At Aarhus University Hospital, this procedure was always combined with a plication of the pubocervical fascia in the midline and, therefore, together with the fact that 57% of the women had concomitant surgery performed, it was not possible to conclude that PVD repair alone reduces objective and subjective signs of prolapse. Throughout the years, the observation of midline defect in most of the women with PVD has served as an argument for adding the midline plication to the surgical procedure of PVD repair. We think that stretching of the pubocervical fascia happens when the lateral support weakens due to PVD. Midline repair was also used in other studies on vaginal PVD repair [66,68,70,113]. In the ideal clinical set-up, the women should have had only PVD repair performed, and both paravaginal spaces would have been opened to explore if a PVD was present or not. Since most women have prolapse in more than one compartment, it would not be ethical to repair the PVD alone. To explore both paravaginal areas even if no defect were thought to be present would be problematic too, due to the risk of surgical complications. To overcome this confounder, a comparison of women undergoing PVD repair with concomitant surgery could be compared to women undergoing the concomitant surgeries but without the PVD

repair. Again, to compare these groups, they must be similar in causes (defects) of prolapse, and if PVD were observed in both groups, it would not be ethical to leave out the PVD repair in one of the groups.

In the isolated group of 20 women, who only had PVD repair (and midline plication) a significant reduction in vaginal symptoms and objective measurements of prolapse was observed, but sample size was very small.

Several groups have evaluated the recurrence after PVD repair—both vaginal, laparoscopical and abdominal repair [66-70]. In general, the recurrence rate demonstrated in our study was high compared to the other studies. We believe that one of the reasons for that was our use of resorbable sutures over non-resorbable used in the other studies. Without systematically measuring this, most of the women with recurrence in our study reported that reappearance of prolapse symptoms happened four to five months postoperatively. This is the period in which the absorbable sutures dissolved, and if major downward force was put on the structures, especially if PC muscle defect was present, the adhesion between ATFP and the pubocervical fascia could disrupt [114-115]. Native tissue repair with absorbable sutures is the method of choice for the majority of prolapse surgeries performed in Denmark. Due to the risk of erosion, pain, and dyspareunia, mesh, grafts, and non-absorbable sutures are used only when recurrence is present after multiple prolapse surgeries [114-118]. By identifying women with a high risk of recurrence before their first surgery, a different surgical approach could be considered. By using non-absorbable sutures or mesh implant, recurrence and multiple surgeries could be prevented.

Defects in the PC muscle of the levator ani have previously been described as a risk factor for prolapse recurrence after surgery, but it has never been demonstrated in an isolated group of young women with presumed PVD [48-50,107,119-122]. The iliococcygeus and puborectalis muscles were also evaluated by MRI, and we did not find a correlation between defects in those muscles and risk of recurrence. No one has ever evaluated recurrence and defects in levator ani subgroups. We also demonstrated a higher risk of recurrence if H configuration was missing, but as we concluded, the missing H was a sign of muscle defect and not an isolated risk factor (PVD). Opposite the other studies [48-49,106], we could not demonstrate grade of prolapse assessed by gynecological examination as a risk factor, but we believe this was due to the small study population and that the majority of the women had only grade 2 prolapse. On the contrary, dynamic MRI demonstrated the correlation between risk of recurrence and the extent of AVW descent measured from the PC line. Previous studies have

shown a good correlation between grade of prolapse measured on MRI and at gynecological examination [82].

Throughout the literature, the PCL was the reference line most often used when evaluating the decent of the pelvic organs by dynamic MRI [84-85]. The application of this line was found to be reliable and with high agreement with findings of prolapse by POP-Q measurement in the AVW and apical compartment but not the posterior compartment [86,88]. These were the reasons for us to use the PCL as reference line in this study. There were some limitations to using this line as a reference. The line did not correct for differences in the pelvic inclination at rest and strain as proposed by Betschart C et al., but due to the knowledge on the excellent correlation with clinical findings, we chose to use the clinically most accessible and well-proven method [123]. Another issue to address was the measurement of the descent in the midsagittal plane. By evaluating the AVW descent in the midline, descent in the lateral part of the vagina could be missed. Therefore, images in the coronal plane during straining were sampled and evaluated as well, and we did not find any women in whom the lateral edges of the vagina extended the descent in the midline. We concluded, therefore, that measuring the descent in the mid-sagittal plane was the best method to evaluate the maximal AVW descent. A recent study by Reinar CS suggests a 3-D coordinate system to evaluate the location of pelvic organs in all three planes [124]. We found this measuring system interesting but outside the scope of our study. A comparison of the lateral descent on each side in women with unilateral missing H using a 3-D model was obtained in a study by Larson K et al. in 2012 [125]. They showed that on the side of missing H the ATFP was positioned more downward than on the side of normal vaginal configuration and that the descent was more significant in the region closest to the os pubis compared to the region closest to the ischial spine. They did not evaluate the women after surgery.

It could also be discussed whether a supine position of the women when doing gynecological examination, MRI, and US was suitable for evaluation of POP. With the woman in a supine position, fewer gravity forces were put on the pelvic organs compared to a standing position. This could result in underestimating the grade of prolapse. Whether a supine position altered the position of the organs compared to standing position, has previously been tested with both MRI, gynecological examination, and US with conflicting results [126-128]. The clinical examination and US procedures used in our study to evaluate presence of PVD were not feasible in a standing position, and an MRI scan with vertical magnets was not available which is why a supine position was chosen for all three modalities. Notice must also be put on the straining when lying in the MRI scanner and the fact that the women had to hold the strain for 9 seconds for the complete dynamic acquisition. For some women,

straining while lying inside the scanner was difficult and uncomfortable, and therefore, the dynamic scan was repeated three to four times to ensure maximal straining. Before the MRI scan, the women had practiced the straining procedure during the gynecological examination and US scan, and we believe, therefore, that the strain obtained during the MRI scan was sufficient. The 3-D US cube obtained by dynamic EAUS had an even longer period during which the woman had to hold the strain. A period of 45-60 seconds was difficult for many women, and if the strain was loosened during the acquisition of the cube, image artifacts due to movement of the organs, were observed. Often, many cubes had to be obtained, and for many of the images, no interpretation could be made.

Whether a PVD is responsible for AVW prolapse must also be discussed. The paper by Larson et al. demonstrated a significant descent in the paravaginal area in women with prolapse compared to women without prolapse, concluding that the paravaginal area was involved in the development of AVW prolapse [45]. They also demonstrated only small differences in vaginal width in women with and without prolapse, leading to the conclusion that AVW prolapse formation had more association with the paravaginal descent than the side-to-side stretching and lengthening of the pubocervical fascia. They also found a strong correlation between the paravaginal and the apical descent, concluding that these two observations were a result of the same defect. They did not correlate the findings of paravaginal descent with PC muscle defects. In our study, we could not demonstrate a significant difference in the mean apical descent measured by MRI in the women with and without missing H (p value 0.103) or PC muscle defect (p value 0.823). In the Larson study, the mean age was 56.3 years whereas our cohort had a mean age of 40.0 years. We think that the extent of time that the pelvic organs lack support due to various defects that occurred during labor influences the severity of descent. Maybe a correlation between missing H/PC muscle defect and apical descent could have been found if we had waited another 15 years before examination. We hypothesize that defects occurring during vaginal birth primarily involve the PC muscle and the paravaginal attachment. When the lateral support and/or the muscular floor of the pelvis weakens, the forces that pull the pelvic organs downward increase. The ligaments (uterosacral and cardinal ligaments) that support the apical part of the vagina stretch during this downward pulling, causing the cervix to decrease, meaning the apical descent is a condition that arises sometime after the initial birth-related defect. In the cohort of women undergoing PVD operation, 20 had apical suspension as well. We think that the apical descent was a sign of more advanced prolapse compared to the women without. In the group of women who had apical suspension, seven (35%) had recurrence, whereas 11 (42%) had recurrence in the group of women with no apical suspension (p=0.615) showing no difference in recurrence between the two different groups. Knowing that women with advanced

prolapse, have a higher risk of recurrence, one should think, that women, who also had apical descent, should have the highest recurrence, but we could not demonstrate that in our small study[48,106].

We believe that the PVD exists and that the paravaginal attachment plays a role in the support of the AVW. The descent of the AVW and the appearance of the vaginal mucosa looks very different in women with PVD compared to women with AVW prolapse but without the PVD, when evaluated by gynecological examination. In our study, MRI and US could not help us support the PVD diagnosis. Therefore, we believe that focus must be put on the gynecological examination in order to strengthen the procedure of detecting a PVD. We also believe that assessing risk of recurrence before surgery should be performed routinely, and we demonstrated both MRI and US to be useful in that context.

Conclusion

5. Conclusion

In summary, we demonstrated a robust and reliable translation of the questionnaire ICIQ-VS into the Danish language.

We found moderate interrater reliability in diagnosing a PVD by gynecological examination but with substantial bias. We demonstrated no correlation between PVD found by gynecological examination and the observation of missing H configuration by MRI and EAUS. EAUS was not useful in the evaluation of vaginal shape. We concluded that missing H configuration was not a sign of PVD but was found to be correlated to the severity of PC muscle defect measured by MRI.

PVD repair alone or together with concomitant surgery was safe and with significant reduction in objective AVW descent evaluated by gynecological examination and MRI, together with significant reduction in subjective vaginal symptoms, urinary incontinence, and sexual problems six months after surgery. Quality of life was increased. A recurrence rate of 39% was found, and major PC muscle defect, missing H configuration, and increasing bladder base descent measured by MRI were independent risk factors for recurrence.

6. Future perspectives

In this study, we translated the questionnaire ICIQ-VS. A few modified questions from the questionnaire have been used in the Danish nationwide urogynecological clinical database DUGABase since 2006, and it has been discussed whether to keep these questions in the database or replace them with the full validated ICIQ-VS questionnaire or just some of the questions. By replacing the existing questions with the new ones, a huge problem regarding comparison of date from before and after the replacement will arise. On the other hand, data from a questionnaire not validated could result in uncertain results. This issue will be for the database working group to discuss in the future.

MRI and US could not help the clinicians in diagnosing the PVD, and we concluded that focus could be put on enhancing the gynecological examination. We suggest applying a measurement system to the lateral descent of the vagina in the same manner as the POP-Q measurement system. A location 3 centimeters above the hymenal ring in each side of the vagina could serve as a fixed point, and descent of this location measured during straining. This theory needs to be tested in a clinical study in women undergoing surgery for PVD.

In our study, recurrence of AVW prolapse was assessed after six months. We suggest a long-term follow-up on women who had PVD repair both to assess the long-term recurrence rate after the surgery, and also to evaluate preoperative parameters correlated to the risk of long-term recurrence. Parameters correlated to the risk of recurrence could be different for the short-term and the long-term recurrence. We also suggest a follow-up study evaluating whether the recurrent AVW prolapse after PVD repair was due to midline or paravaginal defect assessed by gynecological examination.

Assessing defects in the PC muscle should be performed in all women scheduled for a POP repair so that information on the risk of recurrence could be reported to the women. Information on muscle defect could also support the surgeon's choice of suture material, especially in a country like Denmark where native tissue repair and resorbable sutures are the preferred choices. To evaluate whether non-absorbable sutures or mesh implant could reduce the recurrence after PVD repair, a study on a matched group of women undergoing PVD repair with non-absorbable material could be conducted.

We also suggest a further investigation of the paravaginal edges of the vagina in the 3-D MRI coordinate system as described earlier. The study by Larson et al. [45] compared women with and without AVW prolapse and found the paravaginal descent

to be involved in the formation of AVW prolapse. No information on whether these women had missing H or PVD evaluated by gynecological examination was presented in the paper, and therefore, we think it would be interesting to compare the location of paravaginal edges in women with presumed PVD and women with presumed midline defect. It could also be interesting to evaluate the vaginal edges in women before and after PVD repair to see if surgery changes the location of the pubocervical fascia. We could not demonstrate that in our study.

7. References

[1] Maher C, Feiner B, Baessler K, Schmid C. Surgical management of pelvic organ prolapse in women. Cochrane Database Syst Rev. 2013;4

[2] Hall AF, Theofrastous JP, Cundiff GW, Harris RL, Hamilton LF, Swift SE, et al. Interobserver and intraobserver reliability of the proposed international continence society, Society of Gynecologic Surgeons, and American Urogynecologic Society pelvic organ prolapse classification system. Am J Obstet Gynecol. 1996;175(6): 1467–70

[3] E.Gutman, Daniel E.Ford, Lieschen H.Quiroz, Stuart H.Shippey, Victoria L.Handa. Is there a pelvic organ prolapse threshold that predicts pelvic floor symptoms? American Journal of Obstetrics and Gynecology Volume 199, Issue 6, December 2008, Pages 683.e1-683.e7

[4] Swift SE, Tate SB, Nicholas J. Correlation of symptoms with degree of pelvic organ support in a general population of women: what is pelvic organ prolapse? Am J Obstet Gynecol.2003;189(2):372–7.

[5] Arenholt LTS, Glavind-Kristensen M, Bøggild H, Glavind K. Translation and validation of the International Consultation on Incontinence Questionnaire Vaginal Symptoms (ICIQ-VS): the Danish version. Int Urogynecol J. 2018 Jan 10. [Epub ahead of print]

[6] Vrijens D, Berghmans B, Nieman F, van Os J, van Koeveringe G, Leue C. Prevalence of anxiety and depressive symptoms and their association with pelvic floor dysfunctions-A cross sectional cohort study at a Pelvic Care Centre Neurourol Urodyn. 2017 Sep;36(7):1816-1823..

[7] Lone F, Thakar R, Sultan AH. One-year prospective comparison of vaginal pessaries and surgery for pelvic organ prolapse using the validated ICIQ-VS and ICIQ-UI (SF) questionnaires. Int Urogynecol J. 2015 Sep;26(9):1305-12.

[8] Barber MD, Walters MD, Bump RC. Short forms of two condition-specific quality-of-life questionnaires for women with pelvic floor disorders (PFDI-20 and PFIQ-7). Am J Obstet Gynecol. 2005 Jul;193(1):103-13.

[9] Digesu GA, Khullar V, Cardozo L, Robinson D, Salvatore S. P-QOL: a validated questionnaire to assess the symptoms and quality of life of women with urogenital prolapse. Int Urogynecol J Pelvic Floor Dysfunct. 2005 May-Jun;16(3):176-81

[10] Jones G, Radley S, Lumb J, Jha S. Electronic pelvic floor symptoms assessment: tests of data quality of ePAQ-PF. International Urogynecology Journal, 2008, Vol.19(10), pp.1337-1347

[11] Terwee CB, Bot SD, de Boer MR, van der Windt DA, Knol DL, Dekker J, Bouter LM, de Vet HC. Quality criteria were proposed for measurement properties of health status questionnaires. J Clin Epidemiol. 2007 Jan;60(1):34-42.

[12] Cheon C, Maher C. Economics of pelvic organ prolapse surgery. Int Urogynecol J. 2013 Nov;24(11):1873-6

[13] Løwenstein E, Ottesen B, Gimbel H. Incidence and lifetime risk of pelvic organ prolapse surgery in Denmark from 1977 to 2009. Int Urogynecol J. 2015;26(1):49–55.

[14] Hendrix SL, Clark A, Nygaard I, Aragaki A, Barnabei V, McTiernan A. Pelvic organ prolapse in the Women's Health Initiative: gravity and gravidity. Am J Obstet Gynecol 2002; 186**:** 1160–66.

[15] Lavelle RS, Christie AL, Alhalabi F, Zimmern PE. Risk of Prolapse Recurrence after Native Tissue Anterior Vaginal Suspension Procedure with Intermediate to Long-Term Followup J Urol. 2016 Apr;195(4 Pt 1):1014-20.**.**

[16] Guzmán Rojas R, Kamisan Atan I, Shek KL, Dietz HP. Defect-specific rectocele repair: medium-term anatomical, functional and subjective outcomes. Aust N Z J Obstet Gynaecol. 2015 Oct;55(5):487-92.

[17] National survey on the management of prolapse in the UK. Jha S, Moran PA. Neurourol Urodyn. 2007;26(3):325-31

[18] DeLancey JO. Anatomic aspects of vaginal eversion after hysterectomy. Am J Obstet Gynecol. 1992;166(6 Pt 1):1717–24.

[19] Santoro GA, Shobeiri SA , Petros PP, Zapater P, Wieczorek AP. Perineal body anatomy seen by three-dimensional endovaginal ultrasound of asymptomatic nulliparae Colorectal Disease 2015 The Association of Coloproctology of Great Britain and Ireland. 18, 400–409

[20] De Landsheere L, Munaut C, Nusgens B, Maillard C, Rubod C, Nisolle M, Cosson M, Foidart JM. Histology of the vaginal wall in women with pelvic organ prolapse: a literature review. Int Urogynecol J. 2013 Dec;24(12):2011-20.

[21] Delancey JO. Fascial and muscular abnormalities in women with urethral hypermobility and anterior vaginal wall prolapse. Am J Obstet Gynecol. 2002;187(1):93–8.

[22] Huddleston HT, Dunnihoo DR, Huddleston 3rd PM, Meyers Sr PC. Magnetic resonance imaging of defects in DeLancey's vaginal support levels I, II, and III. Am J Obstet Gynecol. 1995;172(6):1778–82.

[23] Mauroy B, Goullet E, Stefaniak X, Bonnal JL,Amara N. Tendinous arch of the pelvic fascia: application to the technique of paravaginal colposuspension. Surg Radiol Anat. 2000;22(2):73–9.

[24] Pit MJ, De Ruiter MC, Lycklama A, Nijeholt AA, Marani E, Zwartendijk J. Anatomy of the arcus tendineus fasciae pelvis in females. Clin Anat. 2003;16(2):131–7.

[25] Fritsch H, Zwierzina M, Riss P. Accuracy of concepts in female pelvic floor anatomy: facts and myths!World J Urol. 2012;30:429–35.

[26] Ersoy M, Sagsoz N, BozkurtMC, Apaydin N, Elhan A, Tekdemir I. Important anatomical structures used in paravaginal defect repair: cadaveric study. Eur J Obstet Gynecol Reprod Biol. 2004;112(2):206–13.

[27] Albright TS, Gehrich AP, Davis GD, Sabi FL, Buller JL. Arcus tendineus fascia pelvis: a further understanding. Am J Obstet Gynecol. 2005;193(3 Pt 1):677–81.

[28] Larson KA, Hsu Y, Chen L, Ashton-Miller JA, DeLancey JO. Magnetic resonance imaging-based three-dimensional model of anterior vaginal wall position at rest and maximal strain in women with and without prolapse. Int Urogynecol J. 2010;21(9):1103–9.

[29] Ramanah R, BergerMB, Parratte BM, DeLancey JO. Anatomy and histology of apical support: a literature review concerning cardinal and uterosacral ligaments. Int Urogynecol J. 2012;23(11):1483–94.

[30] Summers A,Winkel LA, Hussain HK, DeLancey JO. The relationship between anterior and apical compartment support. AmJ Obstet Gynecol. 2006;194(5):1438–43.

[31] Rooney K, Kenton K, Mueller ER, FitzGerald MP, Brubaker L. Advanced anterior vaginal wall prolapse is highly correlated with apical prolapse. Am J Obstet Gynecol. 2006;195(6):1837–40.

[32] Hsu Y, Chen L, Summers A, Ashton-Miller JA, DeLancey JO. Anterior vaginal wall length and degree of anterior compartment prolapse seen on dynamic MRI. Int Urogynecol J Pelvic Floor Dysfunct. 2008;19(1):137–42

[33] Berger MB, Morgan DM, DeLancey JO.Levator ani defect scores and pelvic organ prolapse: is there a threshold effect? Int Urogynecol J. 2014 Oct;25(10):1375-9

[34] Lammers K, Fütterer JJ, Prokop M, Vierhout ME, Kluivers KB. Diagnosing pubovisceral avulsions: a systematic review of the clinical relevance of a prevalent anatomical defect., Int Urogynecol J. 2012 Dec;23(12):1653-64

[35] Kearney R, Sawhney R, DeLancey JO. Levator ani muscle anatomy evaluated by origin-insertion pairs. Obstet Gynecol. 2004 Jul;104(1):168-73

[36] Margulies RU, Hsu Y, Kearney R, Stein T, Umek WH, DeLancey JO. Appearance of the levator ani muscle subdivisions in magnetic resonance images. Obstet Gynecol. 2006 May;107(5):1064-9

[37] DeLancey JO, Starr RA. Histology of the connection between the vagina and levator ani muscles. Implications for urinary tract function. J Reprod Med. 1990;35(8):765–71.

[38] Jung SA, Pretorius DH, Padda BS, WeinsteinMM, Nager CW, den Boer DJ, et al. Vaginal high-pressure zone assessed by dynamic 3-dimensional ultrasound images of the pelvic floor. Am J Obstet Gynecol. 2007;197(1):52.e1–7.

[39] Gyhagen M, Bullarbo M, Nielsen TF, Milsom I. Prevalence and risk factors for pelvic organ prolapse 20 years after childbirth: a national cohort study in singleton primiparae after vaginal or caesarean delivery. BJOG. 2013;120(2):152–60

[40] Géry Lamblin, Emmanuel Delorme, Michel Cosson, Chrystèle Rubod. Cystocele and functional anatomy of the pelvic floor: review and update of the various theories Int Urogynecol J (2016) 27: 1297-1305

[41] Richardson AC, Edmonds PB, Williams NL. Treatment of stress urinary incontinence due to paravaginal fascial defect. Obstet Gynecol. 1981;57(3):357–62.

[42] Richardson AC, Lyon JB, Williams NL. A new look at pelvic relaxation. Am J Obstet Gynecol. 1976;126(5):568–73.

[43] Claydon CS, Maccarone JL, Grody MH, Steinberg A, Oyama I, Holzberg AS, et al. The distance between the perceived and the actual arcus tendineus fascia pelvis during vaginal paravaginal repair. Am J Obstet Gynecol. 2005;192(5):1707–11.

[44] Miklos JR, Kohli N. Laparoscopic paravaginal repair plus burch colposuspension: review and descriptive technique. Urology. 2000;4(56):64–9.

[45] Larson KA, Luo J, Guire KE, Chen L, Ashton-Miller JA,DeLancey JO. 3D analysis of cystoceles using magnetic resonance imaging assessing midline, paravaginal, and apical defects. Int Urogynecol J. 2012;23(3):285–93.

[46] DeLancey JOL, Kearney R, Chou Q, Speights S, Binno S. The Appearance of Levator Ani Muscle Abnormalities in Magnetic Resonance Images After Vaginal Delivery. Obstet Gynecol. 2003 Jan; 101(1): 46–53

[47] Dietz HP, Simpson JM. Levator trauma is associated with pelvic organ prolapse. BJOG. 2008 Jul;115(8):979-84.

[48] Vergeldt TF, van Kuijk SM, Notten KJ, Kluivers KB, Weemhoff M. Anatomical Cystocele Recurrence: Development and Internal Validation of a Prediction Model Obstet Gynecol. 2016 Feb;127(2):341-7.

[49] Friedman T, Eslick GD, Dietz HP, Risk factors for prolapse recurrence: systematic review and meta-analysis. Int Urogynecol J. 2018 Jan;29(1):13-21

[50] Rodrigo N, Wong V, Shek KL, Martin A, Dietz HP. The use of 3-dimensional ultrasound of the pelvic floor to predict recurrence risk after pelvic reconstructive surgery. Aust N Z J Obstet Gynaecol. 2014 Jun;54(3):206-11.

[51] Morgan DM, Umek W, Stein T, Hsu Y, Guire K, DeLancey JO. Interrater reliability of assessing levator ani muscle defects with magnetic resonance images. Int Urogynecol J Pelvic Floor Dysfunct. 2007 Jul;18(7):773-8

[52] Rostaminia G, Manonai J, Leclaire E, Omoumi F, Marchiorlatti M, Quiroz L, Shobeiri SA. (2014) Interrater reliability of assessing levator ani deficiency with 360° 3D endovaginal ultrasound. Int urogynecol J. 25(6):761–6

[53] Shull BL. Clinical evaluation of women with pelvic support defects. Clin Obstet Gynecol. 1993;36(4):939–51.

[54] Barber MD, Cundiff GW, Weidner AC, Coates KW, Bump RC, Addison WA. Accuracy of clinical assessment of paravaginal defects in women with anterior vaginal wall prolapse. Am J Obstet Gynecol. 1999;181(1):87–90.

[55] Segal JL, Vassallo BJ, Kleeman SD, Silva WA, Karram MM. Paravaginal defects: prevalence and accuracy of preoperative detection. Int Urogynecol J Pelvic Floor Dysfunct. 2004;15(6):378–83.

[56] Whiteside JL, Barber MD, Paraiso MF, Hugney CM, Walters MD. Clinical evaluation of anterior vaginal wall support defects: interexaminer and intraexaminer reliability. Am J Obstet Gynecol. 2004;191(1):100–4.

[57] Macura KJ. Magnetic resonance imaging of pelvic floor defects in women. Top Magn Reson Imaging. 2006;17(6):417–26.

[58] Athanasiou S, Chaliha C, Toozs-Hobson P, Salvatore S, Khullar V, Cardozo L. Direct imaging of the pelvic floor muscles using twodimensional ultrasound: a comparison of women with urogenital prolapse versus controls. BJOG. 2007;114(7):882–8.

[59] Adekanmi OA, Freeman RM, Jackson SA, Puckett M, Bombieri L, Waterfield MR. Do the anatomical defects associated with cystocele affect the outcome of the anterior repair? A clinical and radiological study. Int Urogynecol J Pelvic Floor Dysfunct. 2009 Nov;20(11):1369-77.

[60] Ochsenbein N, Kurmanavicius J, Huch R, Huch A, Wisser J. Volume sonography of the pelvic floor in nulliparous women and after elective cesarean section. Acta Obstet Gynecol Scand. 2001;80(7):611–5.

[61] Dietz HP, Pang S, Korda A, Benness C. Paravaginal defects: a comparison of clinical examination and 2D/3D ultrasound imaging. Aust N Z J Obstet Gynaecol. 2005;45(3):187–90.

[62] Cassadó-Garriga J, Wong V, Shek K, Dietz HP. Can we identify changes in fascial paravaginal supports after childbirth? Aust N Z J Obstet Gynaecol. 2015;55(1):70–5.

[63] Aronson MP, Bates SM, Jacoby AF, Chelmow D, Sant GR. Periurethral and paravaginal anatomy: an endovaginal magnetic resonance imaging study. Am J Obstet Gynecol. 1995;173(6):1702–8.

[64] Huebner M, Margulies RU, DeLancey JO. Pelvic architectural distortion is associated with pelvic organ prolapse. Int Urogynecol J Pelvic Floor Dysfunct. 2008;19(6):863–7.

[65] Tillack AA, Joe BN, Yeh BM, Jun SL, Kornak J, Zhao S, et al. Vaginal shape at resting pelvic MRI: predictor of pelvic floor weakness? Clin Imaging. 2015;39(2):285–8.

[66] Morse AN, O'dell KK, Howard AE, Baker SP, Aronson MP, Young SB. Midline anterior repair alone vs anterior repair plus vaginal paravaginal repair: a comparison of anatomic and quality of life outcomes. Int Urogynecol J Pelvic Floor Dysfunct. 2007 Mar;18(3):245-9.

[67] Reid RI, You H, Luo K. Site-specific prolapse surgery. I. Reliability and durability of native tissue paravaginal repair. Int Urogynecol J, 2011;22:591-9

[68] Young SB, Daman JJ, Bony LG. Vaginal paravaginal repair: one-year outcomes. Am J Obstet Gynecol. 2001 Dec;185(6):1360-6

[69] Richardson AC, Edmonds PB, Williams NL. Treatment of stress urinary incontinence due to paravaginal fascial defect. Obstet Gynecol. 1981;57(3):357–62.

[70] HosniMM, El-Feky AE, AgurWI, Khater EM. Evaluation of three different surgical approaches in repairing paravaginal support defects: a comparative trial. Arch Gynecol Obstet. 2013;288(6):1341–8.

[71] Price N, Jackson SR, Avery K, Brookes ST, Abrams P. Development and psychometric evaluation of the ICIQ vaginal symptoms questionnaire: the ICIQ-VS. BJOG. 2006;113(6):700–12.

[72] Ekanayake CD, Pathmeswaran A, Herath RP, Perera HS, Patabendige M, Wijesinghe PS. Validation of the International Consultation on Incontinence Questionnaire-Vaginal Symptoms(ICIQ-VS) in two south- Asian languages. Int Urogynecol J. 2017 16. [Epub ahead of print].

[73] Athanasiou S, Grigoriadis T, Kyriakidou N, Giannoulis G, Antsaklis A. The validation of international consultation on incontinence questionnaires in the Greek language. Neurourol Urodyn. 2012;31(7):1141–4.

[74] Banerjee C, Banerjee M, Hatzmann W, Schiermeier S, Sachse K, Hellmich M, et al. The German version of the 'ICIQ vaginal symptoms Questionnaire' (German ICIQ-VS): an instrument validation study. Urol Int. 2010;85(1):70–9.

[75] Tamanini JT, Almeida FG, Girotti ME, Riccetto CL, Palma PC, Rios LA. The Portuguese validation of the international consultation on incontinence questionnaire-vaginal symptoms (ICIQ-VS) for Brazilian women with pelvic organ prolapse. Int Urogynecol J Pelvic Floor Dysfunct. 2008;19(10):1385–91.

[76] Guillemin F, Bombardier C, Beaton D. Cross-cultural adaptation of health-related quality of life measures: literature review and proposed guidelines. J Clin Epidemiol. 1993;46(12):1417–32.

[77] http://www.iciq.net/validationprotocol.htm

[78] Srikrishna S, Robinson D, Cardozo L. Validation of the patient global impression of improvement (PGI-I) for urogenital prolapse. Int Urogynecol J. 2010;21(5):523–8.

[79] Baden W, Walker T. Surgical repair of vaginal defects. Philadelphia: JB Lippincott, 1992.

[80] Bump RC, Mattiasson A, Bø K, Brubaker LP, DeLancey JO, Klarskov P, Shull BL, Smith AR. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. Am J Obstet Gynecol. 1996 Jul;175(1):10-7

[81] Avery K, Donovan J, Peters TJ, Shaw C, Gotoh M, Abrams P. ICIQ: a brief and robust measure for evaluating the symptoms and impact of urinary incontinence. Neurourol Urodyn. 2004;23(4):322-30.

[82] Broekhuis SR, Kluivers KB, Hendriks JC, Vierhout ME, Barentsz JO, Fütterer JJ. Dynamic magnetic resonance imaging: reliability of anatomical landmarks and reference lines used to assess pelvic organ prolapse.Int Urogynecol J Pelvic Floor Dysfunct. 2009 Feb;20(2):141-8.

[83] Kearney R, Miller JM, Ashton-Miller JA, DeLancey JO. Obstetric factors associated with levator ani muscle injury after vaginal birth. Obstet Gynecol. 2006 Jan;107(1):144-9.

[84] El Sayed RF, Alt CD, Maccioni F, Meissnitzer M, Masselli G, Manganaro L, Vinci V, Weishaupt D; ESUR and ESGAR Pelvic Floor Working Group. Magnetic resonance imaging of pelvic floor dysfunction - joint recommendations of the ESUR and ESGAR Pelvic Floor Working Group. Eur Radiol. 2017 May;27(5):2067-2085.

[85] Broekhuis SR, Fütterer JJ, Barentsz JO, Vierhout ME, Kluivers KB. A systematic review of clinical studies on dynamic magnetic resonance imaging of pelvic organ prolapse: the use of reference lines and anatomical landmarks. Int Urogynecol J Pelvic Floor Dysfunct. 2009 Jun;20(6):721-9.

[86] Broekhuis SR, Fütterer JJ, Hendriks JC, Barentsz JO, Vierhout ME, Kluivers KB. Symptoms of pelvic floor dysfunction are poorly correlated with findings on clinical examination and dynamic MR imaging of the pelvic floor. Int Urogynecol J Pelvic Floor Dysfunct. 2009 Oct;20(10):1169-74

[87] Lakeman MM1, Zijta FM, Peringa J, Nederveen AJ, Stoker J, Roovers JP. Dynamic magnetic resonance imaging to quantify pelvic organ prolapse: reliability of assessment and correlation with clinical findings and pelvic floor symptoms. Int Urogynecol J. 2012 Nov;23(11):1547-54

[88] Broekhuis SR, Kluivers KB, Hendriks JC, Fütterer JJ, Barentsz JO, Vierhout ME. POP-Q, dynamic MR imaging, and perineal ultrasonography: do they agree in the quantification of female pelvic organ prolapse? Int Urogynecol J Pelvic Floor Dysfunct. 2009 May;20(5):541-9.

[89] Chamié LP, Ribeiro DMFR, Caiado AHM, Warmbrand G, Serafini PC. Translabial US and Dynamic MR Imaging of the Pelvic Floor: Normal Anatomy and Dysfunction. Radiographics. 2018 Jan-Feb;38(1):287-308

[90] Hegde A, Aguilar VC, Davila GW, Levator ani defects in patients with stress urinary incontinence: three-dimensional endovaginal ultrasound assessment. Int Urogynecol J. 2017 Jan;28(1):85-93.

[91] Shobeiri SA, Leclaire E, Nihira MA, Quiroz LH, O'Donoghue D, Appearance of the levator ani muscle subdivisions in endovaginal three-dimensional ultrasonography, Obstet Gynecol. 2009 Jul;114(1):66-72.

[92] Federative Committee on Anatomical Terminology . Terminologia anatomica: international anatomical terminology. Thieme; Stuttgart, Germany: 1998

[93] Jeppson PC, Balgobin S, Washington BB, Hill AJ, Lewicky-Gaupp C, Wheeler T, Ridgeway B, Mazloomdoost D, Balk EM, Corton MM, DeLancey J, Society of Gynecologic Surgeons Pelvic Anatomy Group. Recommended standardized terminology of the anterior female pelvis based on a structured medical literature review.Am J Obstet Gynecol. 2018 Jul;219(1):26-39.

[94] Tolstrup CK, Husby KR, Lose G, Kopp TI, Viborg PH, Kesmodel US, Klarskov N. The Manchester-Fothergill procedure versus vaginal hysterectomy with uterosacral ligament suspension: a matched historical cohort study. Int Urogynecol J. 2018 Mar;29(3):431-440

[95] Kolberg Tennfjord M, Hilde G, Staer-Jensen J, Siafarikas F, Engh ME, Bø K. Effect of postpartum pelvic floor muscle training on vaginal symptoms and sexual dysfunction-secondary analysis of a randomised trial. BJOG. 2016 Mar;123(4):634-42.

[96] Cooper J, Annappa M, Dracocardos D, Cooper W, Muller S, Mallen C. Prevalence of genital prolapse symptoms in primary care: a cross-sectional survey. Int Urogynecol J. 2015 Apr;26(4):505-10.

[97] Kupelian AS, Vashisht A, Sambandan N, Cutner A. Laparoscopic wrap round mesh sacrohysteropexy for the management of apical prolapse. Int Urogynecol J. 2016 Dec;27(12):1889-1897.

[98] Carati D, Zizza A, Guido M, De Donno A, Stefanizzi R, Serra R, Romano I, Ouedraogo C, Megha M, Tinelli A. Safety, efficacy, and tolerability of differential treatment to prevent and treat vaginal dryness and vulvovaginitis in diabetic women. Clin Exp Obstet Gynecol. 2016;43(2):198-202

[99] de Oliveira MS, Cavalcanti Gde A, da Costa AA. Native vaginal tissue repair for genital prolapse surgical treatment: a minimum of 30 months of results. Eur J Obstet Gynecol Reprod Biol. 2016 Jun;201:75-8.

[100] Ulrich D, Dwyer P, Rosamilia A, Lim Y, Lee J. The effect of vaginal pelvic organ prolapse surgery on sexual function. Neurourol Urodyn. 2015 Apr;34(4):316-21

[101] Edwards PJ, Roberts I, Clarke MJ, Diguiseppi C, Wentz R, Kwan I, Cooper R, Felix LM, Pratap S. Methods to increase response to postal and electronic questionnaires. Cochrane Database Syst Rev. 2009 Jul 8;(3)

[102] Haylen BT, Maher CF, Barber MD, Camargo S, Dandolu V, Digesu A, Goldman HB, Huser M, Milani AL, Moran PA, Schaer GN, Withagen MI. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic organ prolapse (POP).Int Urogynecol J. 2016 Apr;27(4):655-84.

[103] Toozs-Hobson P, Freeman R, Barber M, Maher C, Haylen B, Athanasiou S, Swift S, Whitmore K, Ghoniem G, de Ridder D. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for reporting outcomes of surgical procedures for pelvic organ prolapse. Neurourol Urodyn. 2012 Apr;31(4):415-21

[104] Barber MD1, Maher C. Epidemiology and outcome assessment of pelvic organ prolapse. Int Urogynecol J. 2013 Nov;24(11):1783-90.

[105] Guldberg R, Brostrøm S, Hansen JK, Kærlev L, Gradel KO, Nørgård BM, Kesmodel US. The Danish Urogynaecological Database: establishment, completeness and validity. Int Urogynecol J. 2013 Jun;24(6):983-90.

[106] Whiteside JL, Weber AM, Meyn LA, Walters MD. Risk factors for prolapse recurrence after vaginal repair. Am J Obstet Gynecol. 2004 Nov;191(5):1533-8.

[107] Vergeldt TF, Weemhoff M, IntHout J, Kluivers KB. Risk factors for pelvic organ prolapse and its recurrence: a systematic review. Int Urogynecol J. 2015 Nov;26(11):1559-73

[108] Reimers C, Siafarikas F, Stær-Jensen J, Småstuen MC, Bø K, Ellström Engh M. Risk factors for anatomic pelvic organ prolapse at 6 weeks postpartum: a prospective observational study. Int Urogynecol J. 2018 Apr 14.

[109] Rostaminia G, White D, Quiroz LH, Shobeiri SA. 3D pelvic floor ultrasound findings and severity of anal incontinence. Int Urogynecol J. 2014 May;25(5):623-9.

[110] Schwertner-Tiepelmann N1, Thakar R, Sultan AH, Tunn R. Obstetric levator ani muscle injuries: current status. Ultrasound Obstet Gynecol. 2012 Apr;39(4):372-83.

[111] van Delft KW, Sultan AH, Thakar R, Shobeiri SA, Kluivers KB. Agreement between palpation and transperineal and endovaginal ultrasound in the diagnosis of levator ani avulsion. Int Urogynecol J. 2015 Jan;26(1):33-9.

[112] Majida M, Braekken IH, Bø K, Benth JS, Engh ME. Validation of three-dimensional perineal ultrasound and magnetic resonance imaging measurements of the pubovisceral muscle at rest. Ultrasound Obstet Gynecol. 2010 Jun;35(6):715-22.

[113] Rodríguez LV, Bukkapatnam R, Shah SM, Raz S. Transvaginal paravaginal repair of high-grade cystocele central and lateral defects with concomitant suburethral sling: report of early results, outcomes, and patient satisfaction with a new technique. Urology. 2005 Nov;66(5 Suppl):57-65.

[114] Zebede S, Smith AL, Lefevre R, Aguilar VC, Davila GW. Reattachment of the endopelvic fascia to the apex during anterior colporrhaphy: does the type of suture matter? Int Urogynecol J. 2013 Jan;24(1):141-5.

[115] Chung CP, Miskimins R, Kuehl TJ, Yandell PM, Shull BL. Permanent suture used in uterosacral ligament suspension offers better anatomical support than delayed absorbable suture. Int Urogynecol J. 2012 Feb;23(2):223-7.

[116] Mateu Arrom L, Errando Smet C, Gutierrez Ruiz C, Araño P, Palou Redorta J. Pelvic Organ Prolapse Repair with Mesh: Mid-Term Efficacy and Complications. Urol Int. 2018 Jun. [Epub ahead of print]

[117] Milani AL, Damoiseaux A, IntHout J, Kluivers KB, Withagen MIJ. Long-term outcome of vaginal mesh or native tissue in recurrent prolapse: a randomized controlled trial. Int Urogynecol J. 2018 Jun;29(6):847-858

[118] Maher C, Feiner B, Baessler K, Christmann-Schmid C, Haya N, Brown J. Surgery for women with anterior compartment prolapse. Cochrane Database Syst Rev. 2016

[119] Dietz HP, Chantarasorn V, Shek KL. Levator avulsion is a risk factor for cystocele recurrence. Ultrasound Obstet Gynecol. 2010 Jul;36(1):76-80.

[120] Model AN, Shek KL, Dietz HP. Levator defects are associated with prolapse after pelvic floor surgery. Eur J Obstet Gynecol Reprod Biol. 2010 Dec;153(2):220-3.

[121] Morgan DM, Larson K, Lewicky-Gaupp C, Fenner DE, DeLancey JO. Vaginal support as determined by levator ani defect status 6 weeks after primary surgery for pelvic organ prolapse. Int J Gynaecol Obstet. 2011 Aug;114(2):141-4

[122] Weemhoff M, Vergeldt TF, Notten K, Serroyen J, Kampschoer PH, Roumen FJ. Avulsion of puborectalis muscle and other risk factors for cystocele recurrence: a 2-year follow-up study. Int Urogynecol J. 2012 Jan;23(1):65-71

[123] Betschart C, Chen L, Ashton-Miller JA, Delancey JO. On pelvic reference lines and the MR evaluation of genital prolapse: a proposal for standardization using the Pelvic Inclination Correction System. Int Urogynecol J. 2013 Sep;24(9):1421-8.

[124] Reiner CS, Williamson T, Winklehner T, Lisse S, Fink D4, DeLancey JOL, Betschart C. The 3D Pelvic Inclination Correction System (PICS): A universally applicable coordinate system for isovolumetric imaging measurements, tested in women with pelvic organ prolapse (POP). Comput Med Imaging Graph. 2017 Jul;59:28-37.

[125] Larson KA, Luo J, Yousuf A, Ashton-Miller JA, Delancey JO. Measurement of the 3D geometry of the fascial arches in women with a unilateral levator defect and "architectural distortion". Int Urogynecol J. 2012 Jan;23(1):57-63.

[126] Leerasiri P, Wachasiddhisilpa P, Hengrasmee P, Asumpinwong C. Relationship of degree of uterine prolapse between pelvic examination in lithotomy position with cervical traction and pelvic examination in standing position. Int Urogynecol J. 2018 Mar 6. [Epub ahead of print]

[127] Rodríguez-Mias NL, Subramaniam N, Friedman T, Shek KL, Dietz HP. Prolapse assessment supine and standing: do we need different cutoffs for "significant prolapse"? Int Urogynecol J. 2018 May;29(5):685-689.

[128] Friedman B, Stothers L, Lazare D, Macnab A. Positional pelvic organ prolapse (POP) evaluation using open, weight-bearing magnetic resonance imaging (MRI). Can Urol Assoc J. 2015 May-Jun;9(5-6):197-200

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