Short and long-term outcomes of the Manchester Procedure for Pelvic Organ Prolapse and the impact of major Levator Ani Muscle defects

PhD thesis
by
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LIST OF PAPERS

I. **Oversand SH, Staff AC, Spydslaug AE, Svenningsen R, Borstad E**
Long-term follow-up after native tissue repair for pelvic organ prolapse
*Int Urogynecol J. 2014 January; 25(1): 81-89*

II. **Oversand SH, Staff AC, Sandvik L, Volløyhaug I, Svenningsen R**
Levator ani defects and the severity of symptoms in women with anterior compartment pelvic organ prolapses (POP)
*Int Urogynecol J. 2018 Jan; 29(1):63-69*

III. **Oversand SH, Staff AC, Borstad E, Svenningsen R**
The Manchester Procedure: Anatomical, subjective and sexual outcomes
*Int Urogynecol J, 2018 Mar 12 [Epub ahead of print]*

IV. **Oversand SH, Staff AC, Volløyhaug I, Svenningsen R**
Impact of levator muscle avulsions on Manchester Procedure outcomes in Pelvic Organ Prolapse Surgery
*submitted*

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**ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>CL</td>
<td>Cardinal Ligament</td>
</tr>
<tr>
<td>CRADI-8</td>
<td>Colorectal-Anal Distress Inventory 8</td>
</tr>
<tr>
<td>DAG</td>
<td>Directed Acyclic Graph</td>
</tr>
<tr>
<td>FDA</td>
<td>US Food and Drug Administration</td>
</tr>
<tr>
<td>HRQOL</td>
<td>Health-related Quality of Life</td>
</tr>
<tr>
<td>ICS</td>
<td>International Continence Society</td>
</tr>
<tr>
<td>IUGA</td>
<td>International Urogynecological Association</td>
</tr>
<tr>
<td>IV</td>
<td>Ingrid Volløyhaug</td>
</tr>
<tr>
<td>LAM</td>
<td>Levator Ani Muscle</td>
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<tr>
<td>LUG</td>
<td>Levator-Urethra Gap</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>OR</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>OUH</td>
<td>Oslo University Hospital (Oslo universitetssykehus)</td>
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<tr>
<td>PFDI-20</td>
<td>Pelvic Floor Distress Inventory - Short form 20</td>
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<td>PFM</td>
<td>Pelvic Floor Muscle</td>
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<td>PISQ-12</td>
<td>Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire - Short form 12</td>
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<tr>
<td>PISQ-IR</td>
<td>Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire - IUGA Revised</td>
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<tr>
<td>POP</td>
<td>Pelvic Organ Prolapse</td>
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<td>POPDI-6</td>
<td>Pelvic Organ Distress Inventory 6</td>
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<tr>
<td>POP-Q</td>
<td>Pelvic Organ Prolapse Quantification</td>
</tr>
<tr>
<td>PRM</td>
<td>Puborectal Muscle</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized Controlled Trial</td>
</tr>
<tr>
<td>RS</td>
<td>Rune Svenningsen</td>
</tr>
<tr>
<td>SO</td>
<td>Sissel Oversand</td>
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<tr>
<td>SUI</td>
<td>Stress Urinary Incontinence</td>
</tr>
<tr>
<td>TPUS</td>
<td>Transperineal Ultrasound</td>
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<tr>
<td>TUI</td>
<td>Tomographic Ultrasound Imaging</td>
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<tr>
<td>UDI-6</td>
<td>Urinary Distress Inventory 6</td>
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<tr>
<td>USL</td>
<td>Uterosacral Ligament</td>
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<tr>
<td>UUI</td>
<td>Urgency Urinary Incontinence</td>
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SUMMARY OF THE THESIS

Pelvic Organ Prolapse (POP), defined as the downward displacement of pelvic organs (uterus, bladder, rectum or bowel) through the vagina due to loss of normal tissue support, is a common condition affecting up to 50% of postmenopausal females. Women seek healthcare for POP-related symptoms, such as sensation of heaviness and bulging, lower urinary tract symptoms, obstructed defecation and sexual dysfunction. POP is therefore a burden both personally and on the Health care system, and identification of optimal treatment options with long-term favorable outcomes are necessary.

Anatomically, clinicians are encouraged to stage POP according to the Pelvic Organ Prolapse Quantification Scale (POP-Q), where stage ≥ II is generally considered clinically relevant. The prolapses are classified into anterior, mid- or posterior compartment prolapse according to location in the vagina. The most common form is anterior compartment POP involving the descent of the bladder. Anterior compartment prolapses are often seen in conjunction with descent of the mid-compartment. Elevation of mid-compartment is widely recognized as important for obtaining favorable outcomes after anterior compartment repair procedures. Avulsion of the medial part of the levator ani muscle (LAM) from its insertion at the symphysis pubis is a recognized risk factor for the development of anterior- and mid-compartment POP. LAM avulsions may occur during vaginal childbirth, especially when women are delivered by forceps, causing weakened support for pelvic organs and thereby increased POP risk.
Although some women with POP are successfully treated with conservative measures, most require surgical treatment. A woman’s lifetime risk of POP surgery has been estimated in the range of 6-18%. Long-lasting postoperative cure or improvement has proven difficult to obtain, particularly in the anterior compartment, and recurrence rates in this compartment has been reported as high as 30%. Some have therefore speculated that LAM avulsions may be the cause of a particularly severe type of POP prone to higher postoperative recurrence rates. As a consequence, some surgeons recommend that POP patients with avulsions should receive surgical repair involving vaginal placement of a synthetic mesh.

Synthetic meshes for tissue reinforcement in vaginal POP surgery were introduced at the start of this millennium due to high reported recurrence-rates after POP surgery, strongly supported by economic interests from medical companies. Currently, due to unacceptably high risks for complications such as erosions, pain and chronic infection, most synthetic mesh products for vaginal use have been withdrawn from the market, and the interest for optimization of native tissue repairs in POP surgery has been revived.

The Manchester Procedure, a uterus-sparing native-tissue surgical technique developed in the late 1880ies, is well established at the Department of Gynecology at Oslo University Hospital (OUH) as the preferred method for treating anterior and mid-compartment POP. The procedure was abandoned after the mid 1950ies in many countries, such as the US, due to increasing popularity of hysterectomy on benign indications and a fear of overlooking uterine pathology when leaving the uterus intact. The procedure has however remained popular in
Scandinavia, Turkey and the Netherlands. The Department of Gynecology at OUH has run an internal quality control registry for POP surgery since 2002, and has not experienced the high reoperation rates reported by some other centers. However, women treated for POP at our Department are not routinely screened for LAM avulsions. We therefore do not know whether they clinically differ from other POP patients in regards to preoperative symptoms or objective, subjective and sexual outcomes after surgery.

The aim of this thesis was primarily to investigate the long-term reoperation risks as well as one-year anatomical and subjective outcomes in a population treated for POP with native tissue repair techniques including the Manchester Procedure, using data from our POP surgery internal quality control registry. In our surgical cohort, we wanted to estimate the prevalence of LAM avulsions and explore potential differences between POP patients with and without avulsions with regards to demographic data and symptom load at the time of surgery. Moreover, we aimed at prospectively investigating the one-year anatomical, symptomatic and sexual outcomes for all women undergoing the Manchester Procedure at the Department and explore whether LAM avulsions had a negative impact on these outcomes. Furthermore, we wanted to investigate whether LAM avulsions act as an independent risk factor for a poor postoperative outcome.

Data from all women treated with native tissue repair procedures at our Department during the period 2002 to 2005 (n=699) was reviewed and telephone interviews were performed in order to identify any repeat POP surgery performed at other hospitals. The cumulative incidence of reoperation was calculated using a competing risks model.
For the prospective evaluation of anatomical, symptomatic and sexual outcomes one year after the Manchester Procedure, 160 women with primary anterior compartment POP were included in a prospective cohort study (the MAncester Procedure for Pelvic Organ Prolapse (MAP-POP)-study) at the Department of Gynecology, OUH. In order to estimate the impact of LAM avulsions on pre- and postoperative outcomes, the cohort was extended to include 204 women, due to sample size calculations. The MAP-POP study took place between October 2014 and January 2018.

This thesis concludes that:

i. POP surgery using native tissue repair comprises low reoperation rates (Paper I). The overall five-year reoperation rate for the whole cohort was 4.7%. Comparing the Manchester Procedure (complete repair of all 3 compartments) to partial repairs further demonstrated a significantly lower reoperation rate after the former (2.8%) than after partial repairs (8.9%) (p<0.01). The cumulative incidence for reoperations was also significantly lower among women treated with a Manchester Procedure (p<0.002).

ii. Subjective outcomes at one-year follow-up after native tissue repairs, in particular Manchester Procedures, were excellent. In the registry-based POP population, 93.5% reported to be cured or improved from their POP symptoms (Paper I). Subjective satisfaction tended to be superior after Manchester Procedures (95.0%) compared to partial repairs (90.9%), but this difference was not statistically significant. Among the prospectively included population of women with primary anterior compartment POP
treated with a Manchester Procedure, the subjective cure rate was similar at 96.0% (Paper III).

iii. Satisfactory anatomical outcomes were obtained one year after native tissue repairs, in particular after the Manchester Procedure, but with inferior outcomes in the anterior compartment. In Paper I, a maximum POP-Q stage 0-I in the dominating compartment was obtained in 83.6% after native tissue repair procedures, the outcome being significantly superior after the Manchester Procedure (86.7%) compared to partial repairs (78.3%) (p=0.02). Amongst women with primary anterior compartment POP who were treated with a Manchester Procedure in the prospective cohort study (Paper III), the one-year anatomical outcomes differed from the above findings. Despite excellent anatomical results in mid-compartment (stage 0-I in 99.3%), only 48.6% obtained stage 0-I in the anterior compartment.

iv. Sexual outcomes one year after the Manchester Procedure were difficult to evaluate due to a high percentage of women considering themselves sexually inactive, and thus not answering the questionnaire on sexual distress. De novo dyspareunia was reported in only 4 of 72 women after the Manchester Procedure (5.6%).

v. LAM avulsions were highly prevalent in our cohort of women with primary anterior compartment POP, identified in 50% (Paper II and IV). Avulsions were, however, not associated with pre-or postoperative POP-Q measurements (Paper IV), severity of POP-related symptoms nor sexual dysfunction (Paper II and IV). Neither did LAM avulsions act as an independent risk factor for poor postoperative anatomical or symptomatic outcomes (Paper IV).
The findings of this thesis will be used to counsel women thoroughly before primary POP surgery, giving realistic ideas about expected outcomes and providing comforting messages about risks for symptomatic recurrence and need for reoperations. Moreover, we hope that this thesis will help convincing our fellow urogynecologists globally that vaginal native tissue repair techniques should be the first choice in the treatment of primary POP. Our results show especially favorable outcomes after surgical procedures involving all three compartments, such as the Manchester Procedure. Our findings will act as further argument against the use of synthetic meshes in women with LAM avulsions, as we have shown that these women may be treated adequately with the Manchester Procedure. POP is a benign condition requiring treatment only when symptomatic, supporting that POP research should focus mainly on symptomatic outcomes, in accordance with the conclusions of this thesis.
1. INTRODUCTION

1.1. The female pelvic floor and pelvic organ support

The female pelvic floor is a functional unit with complex anatomy. The bony part, the pelvic girdle, protects the pelvic organs and serves as site of insertion for muscles and fibrous structures. In a pelvis with normal anatomy, the anterior tilt of the pelvic girdle makes its axis dorsocaudal. This tilt avoids that gravity mediates a direct load upon the pelvic floor by the abdominal structures. The deeper muscular layers of the pelvic floor consist, in addition to the urethral and anal sphincter complex, mainly of the levator ani muscle (LAM) in addition to fibers from the coccygeal muscle. Despite attempts to standardize the terminology, disagreement on the definition of muscular structures forming part of the levator ani complex still exists (1).

![Figure 1: Schematic view of the levator ani muscles from below; arcus tendineus levator ani (ATLA); external anal sphincter (EAS); puboanal muscle (PAM); perineal body (PB); puboperineal muscle (PPM); iliococcygeal muscle (ICM); puborectual muscle (PRM).](image)


Most authors agree however that the muscle has three main portions (see Figure 1 and 2) (2-4):

1. The puborectal muscle that is inserted in the pubic bone and forms a sling around the vagina and anorectum.
2. The ileococcygeal muscle that forms a horizontal layer from the arcus tendineus levator ani to the raphe between anus and coccyx.
3. The pubococcygeal or pubovisceral muscle that stretches with an upward horizontal biconvex shape attaching to the pubic bone, pelvic organs and the perineal body. It has three subdivisions: the puboperineal muscle, the pubovaginal muscle and the puboanal muscle. The expression “pubovisceral muscle” is by some used as a common term for the puborectal and pubococcygeal muscles, as these muscles are largely continuous.

![Figure 2: The levator ani muscle seen from above; the sacral promontory (SAC), the pubovaginal muscle (PVM), puboanal muscle (PAM); arcus tendineus levator ani (ATLA); iliococcygeal muscle (ICM).](image)


The pelvic floor muscles have a constant resting tone in order to provide support for the overlying pelvic viscera, maintain continence and to narrow the hiatus. They have the ability to automatically contract during rapid increases of intra-abdominal pressure (coughing, sneezing, jumping etc.) and to relax during micturition or defecation (1).

The connective tissues that occupy the spaces between bone, muscles and viscera are called the endopelvic fascia. This fascia functions in part as a mesenterium supporting nerves and vessels in their trajectory (eg. infundibulopelvic and cardinal ligaments) and partly condenses to fibrous ligaments in order to keep the viscera centered in the pelvis (eg cardinal and sacrouterine ligaments) (1). The rectovaginal space is occupied by the dense fibromuscular rectovaginal septum, by some called the rectovaginal
fascia, and is situated between the rectogenital pouch and the perineal body (the latter is further described below) (5). The term vesicovaginal fascia is widely used for the connective tissue which occupies the vesicovaginal space, despite some authors claiming that it is not a true fascia (6).

In the outer parts of the pelvic floor the endopelvic fascia forms the perineal membrane (sometimes called diafragma urogenitale), and contains the urethral and anal sphincteres and transversus perinei profundus muscle, in addition to the more superficial bulbospongiosus, ischiocavernosus and transversus perinei superficialis muscles (1). The perineal body is the fibromuscular structure between the posterior border of the vagina and the anus which plays an important role in maintaining the integrity of the pelvic floor. Laterally, the perineal body is attached to the ischiopubic rami by the superficial transverse perineal muscles, and fibers from the bulbospongiosus muscle also form part of this structure. The perineal body is suspended anteriorly to the pubic bone by the puborectal and pubovaginal muscles and communicates posteriorly with the anal sphincter complex (see Figure 3) (7).

Figure 3: The perineal body.

The pudendal nerves inervate the voluntary parts of the urethral and anal sphincters whereas the levator ani muscle complex receives its nerve supply from both the pudendal and direct sacral nerves. During the second stage of labor, the nerves to the anal sphincter undergo the most strain (8).

The connective tissue supports of uterus and vagina are commonly divided into 3 levels, as classified by DeLancey (see Figure 4) (9):

i. Level 1 supports the uterus and the upper vagina (= apical support), and is constituted by the cardinal and uterosacral ligaments.

ii. Level 2 provides lateral attachment to the mid-vagina by the adherence of the vagina to the aponeurosis of the levator ani and comprises the endopelvic fascia’s connections to the arcus tendineus fascia pelvis (“white line”).

iii. Level 3 keeps the urethra and the lower third of the vagina in place. Posteriorly, the vagina attaches to the perineal body and muscular fibers from the bulbospongiosus, transversus perinei and

Figure 4: Levels of connective tissue support of uterus and vagina. Reprinted from DeLancey, JOL: Anatomic aspects of vaginal eversion after hysterectomy, Am J Obstet Gynecol 1992; 166:1717, with permission.
external anal sphincter muscles. Laterally, the vagina fuses to the levator ani muscle and anteriorly to the urethra and peri-urethral connective tissues.

Alterations of the normal pelvic floor anatomy may cause Pelvic Floor Dysfunction that can give rise to a wide range and degree of symptoms. The most prevalent manifestations in the female population are Pelvic Organ Prolapse (POP) and Urinary and Anal Incontinence (10-12). The degree of manifestation might be better understood as a life-span interaction between predisposing factors (e.g. genetic constitution affecting connective tissue support), inciting factors (e.g. forceps delivery, prolonged second stage during delivery), and intervening factors (e.g. degree of aging of muscles, nerves and connective tissue, obesity etc.) (13). Anatomical structures that are involved in causing one manifestation (e.g. fecal incontinence) often differ from those involved in other manifestations (e.g. stress urinary incontinence). However, injuries to the levator ani muscles and the pelvic nerves may affect several aspects of the pelvic floor function (13).

1.2. Levator ani muscle avulsions

Damage to the levator ani muscle (LAM) from childbirth was described by Gainey already in the early 1940ies (14), but this field did not attain extensive interest until the development of Magnetic Resonance Imaging (MRI) and Transperineal Ultrasound (TPUS), allowing further detailed anatomical knowledge by means of imaging (15, 16).

The main risk factor for major LAM defects, called avulsions, is vaginal childbirth. LAM avulsions are rarely described in nulliparous women or after cesarean section (17). Loss of levator ani muscular tone and
integrity, resulting in a more open urogenital hiatus, occurs due to direct trauma or denervation. During childbirth, fibers from all portions of the LAM suffer substantial elongation, but simulation studies show that the posteromedial parts of the puborectal muscle suffer the most stretching (18, 19). Despite this, the predominant mechanism of injury due to such substantial stretching of the muscle is detachment from its normal insertion at the site of the pubic bone (20, 21). As LAM in nulliparous women probably are stiffer and have firmer attachments to the pelvic sidewalls than in parous women, the first vaginal birth is likely to cause the major defects (18, 22). Instrumental vaginal deliveries increase the risk of damaging the muscle, especially when forceps are used (23). One study found an Odds Ratio (OR) of almost 26 for LAM avulsion when forceps had been used for prolonged second stage compared to spontaneous vaginal delivery (24).

The traumatic injuries may be uni- or bilateral (20) and they may also be complete or partial (also named incomplete). Minor defects or partial avulsions have not been shown to have the same clinical importance as complete avulsions (21). The diagnosis of partial avulsions is not standardized and some of these injuries recover post-partum (17).

Substantial reduction of the incidence of injuries to the anal sphincter complex during vaginal childbirth has been achieved in the Nordic countries over the last decade due to renewed focus on hands-on techniques to control delivery of the baby’s head (25, 26). A similar attention among obstetricians to avoid injury to the LAM has not been present, although awareness of this challenge is increasing (27-29).
Figure 5: Tranperineal Ultrasound images of intact levator ani muscle (LAM) (A) and bilateral LAM avulsions (B).

LAM avulsions may be diagnosed on vaginal palpation as a lateral discontinuity of the puborectal/ pubococcygeal muscles (30), however this requires substantial clinical experience. Commonly, avulsions are diagnosed by imaging techniques such as MRI or Transperineal Ultrasound (TPUS, see Figure 5) (20, 31). Transperineal Ultrasound, also called Pelvic Floor Ultrasound or Translabial Ultrasound, is an established part of the examination in many urogynecological centers around the world and is cheaper and easier accessible that MRI (32).

In order to diagnose avulsions by TPUS, the examination is most commonly carried out with the woman in a dorsal lithotomy position, using a 3.5 – 8 MHz curved array transducer (standard transducer for obstetric or abdominal use) placed on the perineum in the mid-sagittal direction (33).
Four dimensional TPUS allows the acquisition of cineloops which give insight to dynamic changes that happens during patient maneuvers such as Valsalva and Pelvic Floor Muscle (PFM) contraction. Volumes at maximal PFM contraction facilitate the evaluation of LAM muscle integrity (33). The resulting 3D images display the mid-sagittal (A) plane, the coronal (B) plane and the axial (C) plane. Post–imaging processing by Tomographic Ultrasound Imaging (TUI) divides the image into “slices”, so that the complete thickness of the muscle is visualized (see Figure 6) (33).

If the TPUS diagnosis is challenging due to marked muscle atrophy, scarring, inability to voluntarily contract the PFM or bilateral LAM avulsion (lack of asymmetry), a measurement of the levator-urethra gap (LUG) may be used as a diagnostic aid. However, the LUG measurement
must be interpreted with caution since vaginal hiatal size is correlated with the woman’s height and pubic arch length (34).

Women with LAM avulsions have double the risk for developing Pelvic Organ Prolapse (35). Among women with POP, about 25 -50 % will have major uni- or bilateral LAM defects (35, 36).

1.3. Pelvic Organ Prolapse

Pelvic Organ Prolapse has impacted female health for thousands of years. The earliest written mention of POP is found in the Ebers papyrus, dated from at least 1550 BC (37). Although female reproductive health has changed substantially since then, still one third to half of postmenopausal women will develop some degree of POP (38-40).

Pelvic Organ Prolapse can be defined as the downward displacement of uterus, vaginal compartments or neighboring organs such as bladder, rectum or bowel. The definition is anatomic, but the diagnosis of POP should always be linked to the description of subjective symptoms (41). There is no clear-cut anatomical threshold between normal asymptomatic changes due to childbirth and symptomatic POP, especially in women with smaller prolapses (42). Common POP-related symptoms include a feeling of vaginal bulging, pelvic pressure, bleeding/discharge/infection (due to prolapse ulceration), and POP-related low back pain. Other associated symptoms and signs are often present: lower urinary tract symptoms (including bladder emptying difficulties and urinary incontinence); anorectal dysfunction symptoms (such as constipation and incomplete rectal emptying); and sexual symptoms (including
dyspareunia and obstructed intercourse). Some women have to digitate to help bladder or bowel emptying (41).

Some women may be at a higher baseline risk of developing POP due to hereditary factors, including collagen deficiency or other genetic factors (43). The main inciting factor is however the same as for LAM avulsion, namely vaginal childbirth, with increased risk when the baby is delivered by forceps (2, 35). The development of symptomatic POP and the age at its debut depend on several factors, such as the degree of tissue/neurologic injury suffered during childbirth, aging, estrogen deficiency, chronic straining and chronically increased intra-abdominal pressure from heavy lifting or pulmonary disease (11). Older age at first delivery is an independent risk factor for POP, regardless of delivery method (44, 45).

Figure 7: “The boat in dry dock”, where A depicts normal support of the uterus and B depicts how loss of pelvic support promotes prolapse of the uterus (boat).

“The boat in dry dock” theory postulated by Norton provides a simple structural understanding of POP, particularly of uterine descent (46). The boat represents the pelvic organs, the water represents the pelvic floor muscles (PFM), and the moorings represent their fascia and ligamentous attachments to the pelvic sidewall. If the ligaments (“moorings”) are cut or the PFM tone (“water”) is reduced, increased strain will be put on the remaining structures and thereby increase the risk for POP (see Figure 7) (46).

Different types of POP can be explained by deficiencies at different levels of the pelvic organ support system, which is described and illustrated in 1.1 (see Figure 8) (9):

i. **A mid-compartment or apical** prolapse is present when there is a prolapse of the uterine body, the vaginal vault (the bind-ending top of the vagina after total hysterectomy) or the cervix after subtotal hysterectomy. Level 1 defects lead to mid- and anterior compartment prolapses.

ii. **An anterior compartment** prolapse is the bulging of the anterior vaginal wall into the vagina. It contains a **cystocele**

![Figure 8: Above: Uterovaginal prolapse (involving all three compartments). Below: Anterior compartment prolapse.](image)
(protrusion of the bladder) with or without a concomitant urethrocele (bulging of the urethra). Both level 1, 2 and 3 defects play a role in its development.

iii. A posterior compartment prolapse is the protrusion of the posterior vaginal wall into the vagina and contains most often a rectocele (bulging of the rectum into the vagina). Rectoceles occur due to a combination of Level 2 and 3 defects. However, an enterocele (bulging of the small bowel into the vagina) may be present, and although usually located in the posterior wall, it might be located at the apex or even in the anterior wall. Women who have been operated with hysterectomy are at increased risk for developing enterocele, which is most often caused by fascial (Level 2) defects.

A woman complaining of POP symptoms is most frequently examined in the dorsal lithotomy position while she pushes downward or performs a Valsalva maneuver in order to demonstrate the prolapse at its maximum (47). In case of inability to push/perform Valsalva, a clamp may be applied to the cervix by the examiner to perform downward traction, or the patient may be examined while standing (48). In some countries, examination in Sim´s (left side-lying) position is commonly used (49). The POP measurements obtained with the woman in different positions have been shown to correlate well, although higher degrees of POP tend to be described in the upright position (48, 49), likely due to gravity effects.

Different staging systems for POP exist (50). Due to the low reproducibility of the existing scoring systems, Bump et al proposed in 1996 a standardized system for measuring POP (51). This scoring system was named the “Pelvic Organ Prolapse Quantification (POP-Q) system”
(52) and stages each individual vaginal compartment, from stage 0 (no prolapse) to stage IV (vaginal eversion essentially complete). The International Continence Society (ICS) and the International Urogynecological Association (IUGA) encourage clinicians to adhere to the POP-Q system when describing POP (41). However, poor documentation of POP is still a problem in many clinical settings (53).

1.4. Surgical management of Pelvic Organ Prolapse

Symptomatic POP is present in 6-28% of postmenopausal women (54, 55). The estimated life-time risk of POP in need of surgical treatment ranges from 6-19% (56, 57). As it is a benign condition, Pelvic Organ Prolapse should only be treated when symptomatic (41).

POP treatment has a long history dating back to the Hippocratic days when women were tied to a frame, tipped head-down and then the frame was moved up and down for 3-5 minutes (Hippocratic succussion) (see Figure 9). The first description of a “pessary” dates back to 350 B.C., when half a pomegranate was dipped in vinegar and inserted into the vagina (37). Modern pessaries still have a place in POP treatment and may be the best solution for some women, such as POP in pregnancy or postpartum, as these prolapses often resolve spontaneously. Pessaries may also

![Figure 9: Example of Hippocratic succussion.](image)

be a good treatment alternative for women who do not desire surgical treatment and also for multi-morbid or older women with high perioperative risk (58). Preoperative testing with a pessary in women with POP in order to mimic the postoperative result is sometimes performed by applying a pessary for some weeks/ months to evaluate potential symptom improvement (58).

Pelvic floor muscle training may also reduce symptoms by some degree in women with smaller prolapses (59) and could be attempted as a first-line treatment in motivated women.

Most women with bothersome POP, however, end up being treated surgically (60). In general, POP surgery is often reported to have high risks of recurrence (61), thus there is a constant search for the ideal procedure that permanently resolves the POP problem, but at the same time has low costs and low risks of complications (62). Practices and theoretical convictions differ between countries, but also between hospitals in the same country or region and even between individual gynecologic surgeons at the same hospital (62). As a result, the controversy on how to perform female POP surgery is a minefield in urogynecology. There are several aspects to the discussion, some of which are outlined below.

1. *Synthetic vaginal mesh*

   Synthetic meshes for transvaginal tissue reinforcement were developed due to high reported recurrence rates after POP surgery (61) and approved by the FDA in 2001 (63). Their introduction was promoted by strong interests of medical companies, and premarket clinical testing was insufficient (63). After few years in use, a high incidence of complications such as vaginal mesh erosions, chronic pain and infections
led the FDA to warn against their use (64-67). These warnings, in addition to an enormous amount of litigations against medical professionals and manufacturers, have led to the decline in use of synthetic meshes in vaginal surgery (68).

There are however still controversies concerning if and when to use synthetic meshes and which kinds of meshes to employ (69). Due to heterogeneity in outcome variables, results from studies are often not comparable, but the current general recommendation is that a posterior compartment mesh does not provide any benefits and that anterior compartment mesh placement have limited indications (70). Some find that women with LAM avulsions (see 1.2) have a doubled risk of recurrence after POP surgery and claim that vaginal synthetic mesh is indicated in these women (71, 72). Nonetheless, this association between LAM avulsions and recurrence after POP surgery remains unclear (73).

All mesh types have their advantages and disadvantages. Synthetic non-absorbable polypropylene meshes have dominated the market due to superior performance in regard to anatomical results when used vaginally, but with a high risk of mesh complications (74). Complications are less frequent when the mesh is placed abdominally. Concerning anatomical outcomes, polypropylene mesh has also shown superior performance to other materials in abdominal sacral colpopexies (75).

2. Prevalence of hysterectomy for benign (non-POP) indications

The indications for a hysterectomy diverge substantially between countries and the practice of hysterectomy for benign indications has generally been more restrictive in Europe than in the US (76). Whereas the estimated hysterectomy rates in the US in the 90ies were 5.4 pr. 1000
(76), they were 3.7 pr. 1000 in Italy (77) and as low as 1.6 pr. 1000 in Norway (78). Even though less invasive treatments such as uterine artery embolization (for treating myoma uteri) and transcervical resections (of polyps, endometrium, intracavitary myomas) have caused a decline in hysterectomies on benign indications in the US during the last decade (79), a high percentage of the patients presenting for POP had their uteruses removed more than a decade ago (76). POP occurring in women after a hysterectomy have different characteristics (often involving enteroceles) compared to women with intact uteruses and require other and more elaborate surgical techniques (80).

3. The preferred route of access
As for POP surgery in general, laparoscopy and robotic surgery is often preferred to laparotomy due to a lower risk of complications (81, 82), but beyond this no consensus exists on whether abdominal or vaginal surgery should be performed (70). The advantage of the vaginal route is the access to concomitant anterior and posterior wall repairs (62), whereas the abdominal route allows access to the adnexae and sacrum (62). If a hysterectomy for POP is performed vaginally, the uterus is removed completely, whereas when it is performed abdominally, the cervix may be left in place in order to avoid vaginal mesh erosions after sacral colpopexies (62). In uterus-sparing POP surgery the vaginal route is most frequently used as it allows access to the fascia and ligaments. Another advantage of vaginal surgery (in contrast to abdominal surgery) is that regional (spinal) (83) and even local anesthesia (84) may be sufficient.

4. Hysterectomy as part of POP surgery.
The threshold for removing the uterus in mid-compartment prolapses varies between centers (85). While some gynecologic surgeons tend to
perform hysterectomy whenever the mid-compartment is descended, others only remove the uterus when there is a substantial descent of the corpus uteri (independently of the concomitant existence of cervical elongation) (86). While some surgeons consider that an intact uterus may increase the recurrence rate due to gravity (87), others believe that the intact (not too descended) uterus serves as an anchoring point and thereby provides more favorable postoperative outcomes (88). Therefore, no clear agreement exists regarding which method reduces the recurrence risk the most (89). However, present data do not favor hysterectomy compared to uterus-sparing procedures for mid-compartment POP (90-93).

With easy access to information on Internet, patient skepticism to possible complications from a non-essential hysterectomy has increased (85). Even in the US female population, in which attitudes towards hysterectomy traditionally have been liberal, there is a shift in common opinion. One 2013 study found that 60% would decline hysterectomy for POP if presented with an equally efficient uterus-sparing option (94).

Advantages of leaving the uterus intact include reduced operation time, less blood loss and thereby fewer complications (91, 95). Ovarian function is reduced even after ovarian-sparing hysterectomies (96, 97), whereas the effect of hysterectomy on sexual function remains unclear (98, 99). Hysterectomy, regardless of surgical route, has also been associated with worsening of and de-novo urinary incontinence (100, 101).

A disadvantage of uterus-sparing POP surgery is that uterine pathology (such as endometrial or cervical cancer) not evident at the time of surgery may be left undetected due to postoperative cervical obliteration from
scarring and thus no evident abnormal vaginal bleeding as an early warning of potential malignancy (102). The same applies to postoperative risk of later uterine/cervical malignancies. However, the risk is low, estimated to be 2.6% and minimized if proper preoperative evaluations, such as vaginal ultrasound and, if indicated, endometrial and cervical biopsies are performed (102).

Although there are reports of successful pregnancies after uterus-sparing POP surgery (103-106), postoperative childbearing is usually discouraged. Since the main risk factor for POP is pregnancy and vaginal delivery, the risk of POP increases with increasing parity (107), and the effect of a subsequent pregnancy on POP recurrence is unknown (85). If a cervical amputation was performed during POP surgery, this may in addition imply an increased risk of cervical insufficiency and late abortion or premature labour, as well as cervical dystocia (108).

5. How to anchor the vaginal apex
Regardless of the woman having an intact uterus, adequate support of the vaginal apex improves the outcomes of anterior and mid-compartment POP surgeries, as mid- and anterior compartment defects very often coexist (62). There is however no consensus concerning how the vaginal apex best is anchored (109), as illustrated in Figure 10.
When the uterus is intact the corpus uteri and its uterosacral and cardinal ligaments (when shortened and fixated to the proximal anterior aspect of the remaining cervix) could serve to anchor the vaginal apex. The apex would further be held in place by the resulting anteflexion of the corpus uteri (see 1.5 “The Manchester Procedure”) (110). However, several gynecologic surgeons distrust this concept, arguing that uterosacral/cardinal ligament suspension alone would not provide sufficient strength to support the vaginal apex (111). Alternatively, in uterus-sparing procedures apical fixation could be achieved vaginally by anchoring the uterus to the sacrospinous ligament (sacrospinous hysteropexy) (112) or by reinforcement using synthetic vaginal meshes (75, 89).
When the uterus is totally or sub-totally removed, the vaginal vault or remaining cervix could be secured/anchored by a range of different procedures.

Vaginally the apex could be attached to:

i. The sacrospinous ligament (sacrospinous cervicopexy or sacrospinous vault fixation), usually to the right side in order to avoid the rectum which enters the small pelvis at the left side (113), but it may also be performed bilaterally (114).

ii. The ileococcygeus fascia (70). Data on the latter is scarce, but one study indicates that the vaginal length may be longer after ileococcygeous fixation than after sacrospinous fixation (115).

iii. The uterosacral ligaments (uterosacral ligament suspension), usually performed intraperitoneally (116), but the extraperitoneal alternative exists (117), especially if the cervix is intact. In Mayo/McCalls culdoplasty the anterior parts of the uterosacral ligament are plicated in the midline to achieve obliteration of the posterior cul-de-sac (75).

iv. The levator ani muscles (levator myorrhaphy), a wide mid-line plication of the levator muscles is performed and the vaginal cuff is fixated to it (118).

v. A synthetic vaginal mesh (75).

Abdominally, the apex could be attached to the uterosacral ligaments (119) but is usually attached to the sacrum by a bridging mesh (sacral colpopexy) (75). Presently, the latter is usually performed laparoscopically, and robotic surgery has not proven superior (70).
6. Additional procedures to prevent recurrence

The use of additional procedures in anterior and mid-compartment repairs to prevent recurrence is highly controversial. Based on their finding of increased risk of recurrence in patients with LAM avulsions and increased hiatal dimensions (120), Dietz et al have advocated the reconstruction of the medial part of the LAM, the puborectal muscle, in order to reduce hiatal circumference (121). Among gynecologists performing the Manchester Procedure (see below) some advocate the prophylactic reconstruction of the perineal body as part of the procedure, in order to recuperate the normal shape of the vaginal axis as this will reduce the load upon the pelvic organs from intra-abdominal pressure (122).

7. Obliterating procedures

The extent to which vaginal obliterating procedures, called colpocleises, are performed in POP surgery differs widely (75). In selected older women who do not desire to maintain the possibility of vaginal intercourse, a colpocleisis may be considered the best option due to a very low POP recurrence risk (123). Studies of high quality supporting this are however lacking (124). In the older age group, concomitant hysterectomy should probably be avoided unless uterine or cervical pathology exists, due to higher perioperative morbidity (124).

1.5. The Manchester Procedure

After the industrial revolution, young women in industrialized regions started performing heavy factory work for long hours (125). As a result, the prevalence of Pelvic Organ Prolapse in the fertile female population
increased, and a surgical option for women who desired further childbearing was needed (until then treated with pessaries) (126).

The first uterus-sparing surgical procedures described in modern times were cervical amputations or variations of anterior and posterior colporrhaphies. Combinations of these procedures were invented in the late 1880ies by surgeons at the Women’s Hospital in Berlin (127) at the same time as by professor Archibald Donald’s staff at St. Mary’s Hospital in Manchester (128). The Manchester group strongly advocated the additional importance of mid-compartment support in POP surgery (129, 130). Professor Donald was first and foremost interested in hands-on teaching of students, residents and external visitors (128), so the written description of the procedure was mainly performed by Dr. Donald’s junior colleague Fothergill (131). Therefore, although invented by Donald, the procedure has become known as the “Fothergill” (132), the “Manchester-Fothergill” (133), or the “Manchester” Procedure (128). Fothergill presented some modifications by means of type of incision and degree of dissection, but Donald’s original principles remained mainly unchanged (134). However, the importance of narrowing the hiatus by reconstructing the perineal body exhaustively stressed by Donald was less explicit in Fothergill’s papers (135). Due to this, the “Manchester Procedure” is by some referred to as a three-compartment procedure, whereas by others understood and performed as a two-compartment procedure, omitting the reconstruction of the perineal body (136).

Due to excellent results the procedure became popular around the world (131, 137). However, after the mid-fifties its popularity decreased (especially in the US) mainly due to the increased use of hysterectomy on benign indications (138) in addition to an increased worry of
undiscovered endometrial cancer related to postoperative cervical permeability (139).

In recent years the desire for uterus-sparing options and the awareness of the potential serious complications of vaginal synthetic meshes have revived the use of procedures using native tissue repairs, such as the Manchester Procedure (69). Since transvaginal ultrasound is an established part of the gynecological preoperative examination today (140), the fear of overlooking uterine or adnexal pathology is of less concern.

At the Department of Gynecology at Oslo University Hospital (OUH), the Manchester Procedure is the established procedure for primary anterior and mid-compartment POP in women with intact uteruses. About 60% of all POP operated women receive a Manchester Procedure, which is performed as a three-compartment procedure (122);

1. An anterior colporrhaphy, where the mucosa of the anterior wall is being opened longitudinally and dissected off the vesicouterine fascia. The fascia is also dissected off the cervix and mobilized as proximal as possible on the cervix. Sutures to pull together the over-stretched and ruptured fascia are placed as lateral as possible on the anterior wall in a transverse or u-shaped fashion to ensure an overlap of the fascia when the sutures are tied in the midline. The proximal (closest to the cervix) part of the fascia is furthermore sutured as high as possible on the anterior part of the cervix enabling the anterior wall to be pulled upwards and inwards in the pelvis by the shortening and repositioning of the cardinal and uterosacral (C/US) ligaments (see paragraph 2).
2. The cardinal and uterosacral (C/US) ligaments are dissected off the cervix, shortened and sutured as proximal as possible on the anterior part of the cervix to ensure an upward and inward traction of the apical/mid-compartment, pulling the anterior wall with it (see paragraph 1 and Figures 11 and 12). Cervical amputation is usually performed as it facilitates the access to the ligaments, but amputation is not essential when the cervix is short.

![Figure 11: C/US ligaments shortened, ligated and fixated at the proximal anterior aspect of the cervix.](image)


3. A reconstruction of the perineal body (perineoplasty) in order to reconstruct the height and thickness of the perineal body. The perineal body is almost always damaged to some degree in women with POP. The rationale behind a perineoplasty is that it is thought to prevent POP recurrence by restoring a correct anatomical axis of the vagina, reducing the hiatal area and thereby giving support to the anterior wall (see Figure 12) (122). In sexually active women
care is taken not to place the sutures in the levator ani, using only the superficial perineal muscles (transversus perinei and bulbospongiosus muscles). Levator sutures (pulling the levator ani closer together) are only used in older women. A posterior colporrhaphy or enteroccele repair is performed on indication.

![Illustration of the importance of perineal body repair after shortening and repositioning of the ligaments. SP: Symphysis Pubis; B: Bladder; U: Uterus; V: Vagina; C/US ligaments: Cardinal/uterosacral ligaments; PB: Perineal body](image)

**Figure 12**: Illustration of the importance of perineal body repair after shortening and repositioning of the ligaments. SP: Symphysis Pubis; B: Bladder; U: Uterus; V: Vagina; C/US ligaments: Cardinal/uterosacral ligaments; PB: Perineal body

Upper image: Printed with permission from E. Borstad

1.6. POP surgery internal quality control

Quality control is essential in all types of enterprises to ensure that the product or service offered fulfil quality requirements (141). This is especially true in health services, where legal requirements regulate quality control of services offered. Quality control of health services involves
controlling that diagnostics, treatment and service provision lead to the expected results and to certify that quality requirements are fulfilled (142).

In order to keep track of the Oslo University Hospital Gynecological Department’s performance on POP surgery, the former head of the unit Dr. Borstad, established an internal quality control registry for POP surgery in January 2002. All POP operated patients have since then been scheduled for routine one-year postoperative controls to evaluate objective and subjective surgical outcomes. To ensure standardization of the clinical interview and examination, dr. Borstad developed a short-form physician checklist, which is currently in use, but has not been validated. The clinician fills out the short-form physician checklist on paper (see Appendix 4). A database responsible secretary then enters the data in a coded form into the internal quality control registry. The main quality control parameters are revised and discussed yearly at the Department.

1.7. Outcome measures in POP surgery

“Success” after POP surgery has many dimensions, and although clinicians are concerned about anatomical results, what matters for the individual woman is symptom relief and improved health-related quality of life (HRQOL). The latter refers to the woman’s total sense of well-being, including the physical, emotional and social aspects (62). Traditionally the focus of research has lacked the symptomatic and quality of life aspect, less easily definable than anatomical outcomes. Even anatomical outcomes were for a long time not standardized, making studies difficult to compare (143).
In 1996, Bump et al proposed the standardized POP-Q System (see 3.2 and Appendix 1) for anatomical evaluation of POP (51). However, the system still lacked definitons of normality. Based on the POP-Q System, the 2001 National Institutes of Health Workshop on Standardization of Terminology for Researchers in Pelvic Floor Disorders proposed definitions for optimal (stage 0), satisfactory (stage I) and unsatisfactory (≥ stage II) POP surgery outcomes (144). From early 2000s, with the development of validated questionnaires (145-147), the symptomatic and HRQOL aspect attracted more focus (148). Parallel to this, several papers described that a large proportion of asymptomatic women had stage II prolapses (148, 149).

Most POP-related symptoms correlate from weak to moderate with the worsening of pelvic organ support (143), only the feeling of vaginal bulging being relatively consistent among women with advanced prolapse (143). As the hymenal plane is the most accepted anatomical level below which a prolapse is thought to become symptomatic (62), Barber et al proposed in 2009 that the optimal outcome goal after POP surgery should be the combination of anatomical POP above the hymenal plane and the absence of the symptom of bulging (143).

Later, in 2015, the FIGO assessment scoring system (FASS) was developed. The scoring system includes three dimensions; POP severity on physical examination, presence or absence of symptoms, and severity of bother (150). Both the above papers provide the same definition of optimal outcome (any prolapse above the hymenal plane) for all compartments. However, anatomical cut-offs for optimal outcomes probably differ between compartments (151, 152), and further investigations are needed to define these individual compartment cut-offs.
When reporting outcomes after POP surgery, the ICS/IUGA joint report recommend combining anatomical, symptomatic and HRQOL outcomes including the sexual aspect (153).

1.8. Cost – effectiveness

Health care professionals often focus on the patients subjective and anatomical outcomes after POP surgery, and fail to consider the economical perspectives of a Health care system with limited resources (154).

The most commonly used economic analysis in health care is cost-effectiveness, typically by comparing two alternatives, such as treatment/no treatment, screening/no screening etc. It is a term that often is misused and misunderstood by medical professionals, ignoring the complexity of the expression. The term implies a societal perspective beyond the individual health-care provider and analyses are meant to provide basis for political decision-making. Thus, more effective methods are not necessarily cost-effective (155).

For a given intervention, costs may be related to (156):

i. Direct medical care

ii. Direct non-medical care

iii. Indirect mortality or morbidity

The measure of effectiveness depends on the condition studied and health related quality of life aspects should be considered. There is consensus
that some methods and assumptions must be defined and standardized to ensure that studies are comparable (157).

The most common manifestation of primary POP in patients with an intact uterus is prolapse of the anterior vaginal compartment (39). High quality cost-effectiveness analyses for different anterior compartment POP repairs are not available (154). Systematic reviews comparing native tissue anterior colporrhaphy with anterior compartment mesh repairs have however concluded that transvaginal mesh should not be used in primary POP repairs unless special risk factors are present (69, 70, 158) due to the cost of serious mesh-related complications requiring surgical re-intervention or intensive care treatment (158,159).
Which native tissue repair technique combines the lowest costs with the best postoperative outcomes remains unknown. A recent paper found that health-care costs were three times lower in women treated with the Manchester Procedure compared to Vaginal Hysterectomy, based on Danish registry data (160).
2. AIMS OF THE THESIS

Due to international concern following vaginal synthetic mesh complications after POP surgery, the interest in how to repair POP efficiently by using native tissue techniques has been revived. Ideally a POP repair should be performed only once in a symptomatic woman and symptom relief should last her remaining life. Unfortunately, the international field of POP surgery is far from achieving this, as recurrence is a major issue, especially after anterior compartment repairs.

Vaginal native tissue repair procedures for POP are well established at the Department of Gynecology at Oslo University Hospital. The preferred surgical method for anterior compartment POP with concomitant mid-compartment descent is the uterus-sparing Manchester Procedure, a surgical technique which in our Department involves the repair of all three vaginal compartments. Recent publications on the Manchester Procedure are scarce and in design almost exclusively retrospective or special case reports. The success rate of the procedure in women with POP and LAM avulsions is largely unexplored.

The main aims of this thesis were to:

1) Evaluate the long-term re-operation rate after native tissue repairs for POP, with special focus on comparing a “complete” repair technique such as the Manchester Procedure (including repair of all three vaginal compartments) with “partial” repairs (one and two-compartment procedures).

2) Estimate the prevalence of LAM avulsions in a cohort of women with anterior compartment POP in need of surgical treatment, explore differences in demographic data on basis of the presence of
LAM avulsions and investigate the potential impact of LAM
avulsions on preoperative symptom load.

3) Investigate failure-rates, anatomical outcomes, patient-reported
POP-related symptoms and sexual function one year after POP
surgery with native tissue repairs, focusing on the Manchester
Procedure.

4) Explore the impact of LAM avulsions on one-year postoperative
failure-rates as well as anatomical, symptomatic and sexual
outcomes after the Manchester Procedure.

5) Investigate whether LAM avulsions act as an independent risk
factor for poor anatomical and subjective outcomes at one-year
follow-up after the Manchester Procedure.
3. MATERIAL AND METHODS

3.1. Patient selection

Two separate patient populations were investigated in this PhD thesis, both from the Department of Gynecology at Oslo University Hospital (OUH); a historical cohort of women registered in the Department’s POP surgery internal quality control registry (Paper I) and the prospective “Manchester Procedure for Pelvic Organ Prolapse (MAP-POP)” study population (Papers II-IV), see Figure 13.

![PhD Study Populations](image)

*Figure 13: Illustration of the included study populations of this PhD thesis, according to patient inclusion years.*

Paper I

The Department’s POP surgery internal quality control registry was used in order to identify all women undergoing surgery for POP during the period January 2002 to December 2005. The basis of the registry is the POP surgical protocol, where any POP operation is registered by the surgeon. All women registered in this protocol receive a one-year outpatient follow-up invitation. At this follow-up, subjective and objective outcomes are registered and transferred to the quality control registry. The completeness of follow-up is very good, above 90%.
Only women who had procedures involving synthetic or biological meshes were excluded from this cohort, since the scope of the study was native tissue repair procedures. Paper I was thus based on the remaining non-selected population of women who had received POP surgery with native tissue repair techniques at our Department during the described time-span (see Figure 13), including both primary surgeries and surgeries for recurrent POP. For a more detailed overview of the study population, please refer to the flowchart (Figure 1) in Paper I.

The Department’s internal quality control registry for POP surgery has been running since 2002 and includes multiple variables, of which the following were extracted for Paper I; demographic data, procedures performed, preoperative and one-year postoperative anatomical data in terms of the dominating compartment (with the highest POP-Q stage) and subjective satisfaction at one-year follow-up. We also extracted information on postoperative complications and recurrent POP surgeries from the registry. For this study (Paper I), the patients´ medical charts at our hospital were reviewed until the end of February 2012 to rule out any missed surgery for recurrent POP or complications not entered into the quality control registry. In order to identify patients with repeat POP surgeries performed at other hospitals, telephone interviews were performed by the PhD student from 2011 until the end of February 2012. All patients still alive were contacted, with the exception of women already registered as having received treatment for recurrent POP at our Department.

The MAP-POP Study (Papers II - IV)

Women prospectively included for the MAP-POP (The Manchester Procedure for Pelvic Organ Prolapse) Study, form the basis for Papers II -
IV. In Paper III a sub-cohort was analyzed to evaluate one-year postoperative outcomes after the Manchester Procedure (see Figure 13). Due to power calculations, we extended the planned inclusion period to increase patient numbers (sample size) beyond what was needed for Paper III in order to study the impact of LAM avulsions on baseline data (Paper II) as well as on one-year postoperative outcomes (Paper IV). The inclusion period started in October 2014, and ended in January 2016 for Paper III (with n = 160 women included), whereas the inclusion period was concluded in June 2016 for Paper II and IV (totalling n = 204 women included). Surgeries were performed between October 2014 and June 2016 for Paper III, and until January 2017 for Paper IV. Detailed overviews of the study populations are presented in flowcharts in Papers II-IV.

All patients referred to the outpatient clinic of the Department of Gynecology at OUH for preoperative evaluation of POP during the study period received a study information sheet with their assigned appointment. Women with symptomatic anterior compartment POP who had not previously received POP surgery were considered eligible. Exclusion criteria were previous hysterectomy (total or subtotal) or any coexisting indication for hysterectomy (such as endometrial pathology) revealed during the preoperative evaluation. Women were also excluded if they were unable to understand and communicate in Scandinavian or English language.

At our Department, the Manchester Procedure is the standard technique for repairing anterior compartment prolapse with concomitant mid-compartment prolapse due to cervical elongation up to stage III. Potential study participation did therefore not impact the choice of surgical POP
repair technique. In the few cases with a prolapsed uterine body beyond stage ≥ II (not counting cervical elongation), other procedures were preferred and the women therefore not offered study participation.

Eligible women not included were kept track of through our POP surgery internal quality control registry in order to ensure that the included cohort did not differ significantly from the total cohort undergoing POP surgery at our Department during the study period.

3.2. Surgical techniques

In Paper I, women treated for POP with all types of native tissue repair techniques performed at the Department were analysed. All procedures except for colpocleises and Manchester Procedures were classified as partial repairs, involving repairs of one or two compartments.

In the MAP-POP study (Papers II-IV), all women received POP-repair with the uterus-sparing Manchester Procedure, which in our Department is performed as a three compartment procedure involving:

i. An anterior colporrhaphy.

ii. A uterosacral/cardinal ligament suspension allowing the cervix to be pulled upwards and inwards in the pelvis.

iii. A reconstruction of the perineal body, reducting the hiatal area and restorting the normal anatomical axis of the vagina, thereby preventing recurrence.

For a detailed description of the Manchester Procedure see 1.5.
3.3. Anatomical evaluation tools

Pelvic Organ Prolapse Quantification (POP-Q) system (Appendix 1)(41, 51)

Patients were examined preoperatively (Papers I-IV) and at one-year follow-up (Papers I, III-IV) in the dorsal lithotomy position with the head of the table elevated 30-45 degrees and the POP scored according to the standardized joint ICS /IUGA POP-Q system (41, 51). According to this system, each compartment is staged separately while the woman is performing maximum Valsalva (see Figure 14).

- **Stage O**: no prolapse demonstrated
- **Stage I**: Most distal portion of the prolapse is more than 1 cm above the level of the hymen
- **Stage II**: Most distal portion of the prolapse is 1 cm or less proximal or distal to the hymenal plane
- **Stage III**: Most distal portion of the prolapse protrudes more than 1 cm below the plane of the hymen but protrudes no further than 2 cm less than the total vaginal length.

![Figure 14: Prolapse staging (mid-compartment).](image)

**Stage IV**: Vaginal eversion is essentially complete

The staging is based on six defined points measured on maximal Valsalva; Aa and Ba for the anterior compartment, C and D for the mid-compartment and Ap and Bp for the posterior compartment. Further three landmarks are measured at rest; gh (genital hiatus), tvl (total vaginal length) and pb (perineal body), see Figure 15.

For the mid-compartment, C refers to the maximal descent of the cervix or vaginal cuff and D to the maximal descent of the vaginal posterior fornix. Ba refers to the maximal descent of the anterior compartment. The hymenal plane is in the POP-Q system defined as the zero (reference) level, with points proximal to the hymen being negative and points distal to the hymen being positive. For further details on the POP-Q system, see Appendix 1.

Stage ≥ II was considered anatomically significant in our present study, as stage <II may be considered normal in women who have been pregnant and given birth vaginally (149). Only POP-Q stages were recorded in the internal quality control registry (Paper I), whereas in the MAP-POP study (Papers II - IV) all nine defined points and landmarks in the POP-Q system were registered (see Figure 15), in addition to stages.
4D Transperineal Ultrasound

In the MAP-POP study, all patients were examined preoperatively for the diagnosis of LAM avulsions with 4D Transperineal Ultrasound (TPUS) using a GE Voluson S8 ultrasound machine with a 2-8 MHz 4D abdominal probe. All TPUS examinations were performed by the primary investigator and PhD candidate, with the women in a dorsal lithotomy position, after voiding. The probe was placed on the perineum with the anterior part of the transducer quite firmly pressed against the symphysis pubis. Ultrasound volumes at rest and on maximal pelvic floor muscle contraction were obtained.

Tomographic Ultrasound imaging (TUI), as standardized by Dietz et al (161), was employed for diagnosing LAM avulsions; The zero level is set at the *plane of minimal dimensions*, which is a line at the mid-sagital view tilted in a ventrocaudal to dorsocranial direction running from the posterior surface of the symphysis to the anterior margin of the most central aspect of the puborectal muscle (162). Slices are obtained with 2.5 mm steps from 5mm below this plane to 12.5 mm above this plane (163).

In cases of diagnostic difficulties, because of marked muscle atrophy, scarring, inability to voluntarily contract the pelvic floor muscles or bilateral avulsion (lack of asymmetry), measurement of the levator-urethra gap (LUG) was used as a diagnostic aid. The LUG is evaluated in the axial plane and defined as the distance from the center the urethra lumen to the insertion of the LAM on the inferior pubic ramus. A LUG of 25 mm or more may indicate LAM injury (164).

The analyses were confirmed at a later date on a separate computer using 4D View software (GE Healthcare, Zipf, Austria). After a minimum of
three months post initial examination, intra- and inter-rater validation was performed for the diagnosis of uni- and bilateral LAM avulsions. Ultrasound volumes from 50 randomly selected women were re-examined by both the PhD student and an external evaluator (IV). To ensure blinding of both ultrasound image interpreters, the SPSS randomization function was used by a third person (RS) to randomize and renumber the volumes. Inter- and intra-observer reliabilities were determined using Cohen’s Kappa (Paper II). When discrepancies, the original interpretations by the first author (the PhD candidate) were used in the further analyses.

3.4. Patient-reported evaluation tools

Subjective satisfaction

For both study cohorts, subjective satisfaction at the one-year follow-up was evaluated by response to a single question on subjective satisfaction (Papers I, III and IV). Possible categorical options were; Cured, improved, unchanged or deteriorated/worse. This question, which was used as a simple measure of the patient’s overall postoperative treatment satisfaction, has not been validated.

Pelvic Floor Distress Inventort Short Form-20 (PFDI-20) (Appendix 2)

In Papers II-IV, the validated questionnaire Pelvic Floor Distress Inventory Short Form-20 (PFDI-20) was used for patient-reported preoperative and one-year postoperative symptoms of pelvic floor dysfunction. The women were instructed to consider their symptoms over the last three months. The questionnaire consists of three sub-domains, the POP Distress Inventory 6 (POPDI-6), the Colorectal - Anal Distress
Inventory 8 (CRADI-8) and the Urinary Distress Inventory 6 (UDI-6) (see Appendix 2). Item (single question) nr.3 from the PFDI-20; “Do you usually have a bulge or something falling out that you can see or feel in your vaginal area?” has been shown to be one most strongly related to POP severity (42, 148). Therefore, this was used as an additional separate outcome in the analyses for Paper II and III.

All items offer the same options on the responsive scale; No (value 0) or yes. If yes, the patient responds to the following categories: not at all (value 1), somewhat (value 2), moderately (value 3), quite a bit (value 4). Scale scores and summary scores are obtained by multiplying the mean of the items with 25. Missing data are accounted for by using the mean of the answered items, as indicated in Barber´s original paper on the questionnaire (146).

At the MAP-POP study initiation, PFDI-20 had been validated into Swedish (165), but not yet into Norwegian (the Norwegian version was published in January 2017) (166). Since the languages are similar, our own translation from the Swedish version was used. The English version was offered at the patients’ preference.

Telephone interview
In Paper I a telephone interview was performed 5-10 years after the index POP surgery. The women were asked about any recurrent POP-related symptoms, as well any repeat POP surgery performed in another center during the postoperative years. Women complaining of relapse of POP symptoms were offered an outpatient consultation in order to evaluate the need for further POP treatment. Furthermore, patients who complained of
urinary incontinence (regardless if postoperative or preexisting) were offered a urodynamic evaluation.

Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire Short Form-12 (PISQ-12) (Appendix 3) (145)

Sexual function before surgery (Paper II) and one year after the Manchester Procedure (Papers III - IV) was evaluated using the validated Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire Short Form-12 (PISQ-12, see Appendix 3). Since a Norwegian translation of the questionnaire is not yet validated, our Norwegian translation from the validated Swedish version was used (165). The original English version was offered to patients not fluent in Scandinavian language, but who were fluent in English. The women were told to consider sexual activity during the last 6 months.

The questionnaire consists of 12 questions, all with five responsive options (except item 12 which goes from “much less intense” to “much more intense”): always, usually, sometimes, seldom, never.

The scoring ranges from 0 to 4, and the PISQ-12 is evaluated as a total score. Missing items are dealt with by multiplying the mean of the answered items with the number of answered items as indicated in Rogers` original publication (145). If more than two items are missing, the PISQ-12 questionnaire cannot be analyzed due to reduced validity (145).

Dyspareunia

In Paper I postoperative dyspareunia one year after native tissue repairs was evaluated with a direct, non-validated question about pain during
vaginal intercourse. Unfortunately, this question did not discriminate between pre-existing (before surgery) dyspareunia and postoperative de-novo dyspareunia. In Paper III, therefore, preoperative and one-year postoperative responses to question 5 from PISQ-12; “Do you feel pain during sexual intercourse?” were used to evaluate the mean change in dyspareunia one year after the Manchester Procedure.

3.5. Outcome measures

Various outcome measures and combinations of outcome measures were used in Papers I, III, IV, as outlined in Figure 16. Paper II was a cross-sectional analysis of preoperative data.

<table>
<thead>
<tr>
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<th>PAPER I</th>
<th>PAPER III</th>
<th>PAPER IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FAILURE DEFINITION</strong></td>
<td>Reoperation-rate</td>
<td>Reoperation, pessary or referral to physiotherapist</td>
<td></td>
</tr>
<tr>
<td><strong>ANATOMICAL OUTCOMES</strong></td>
<td>Maximum stage in dominating compartment</td>
<td>Anterior and mid-compartment</td>
<td>Anterior and mid-compartment Impact of LAM avulsions on anatomical outcomes</td>
</tr>
<tr>
<td><strong>PATIENT-REPORTED OUTCOMES</strong></td>
<td>Subjective satisfaction</td>
<td>Subjective satisfaction PFDI-20 PISQ-12</td>
<td>Subjective satisfaction PFDI-20 PISQ-12 Impact of LAM avulsions on patient-reported outcomes</td>
</tr>
<tr>
<td></td>
<td>Dyspareunia Complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>COMPOSITE OUTCOMES</strong></td>
<td>Correlations anatomical and symptomatic changes</td>
<td>Percentage optimal anatomical and subjective outcome</td>
<td></td>
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</tbody>
</table>
3.5.1. Failure rate

Postoperative POP failure rate was a main objective outcome in Paper I and IV. In Paper I, it was defined as any reoperation for POP, and one and five-year reoperation rates were calculated comparing complete (three-compartment procedures), such as the Manchester Procedure, with partial (one- and two-compartment procedures). In addition, the cumulative risk of reoperation was calculated with up to 10 years follow-up, comparing complete with partial procedures. Women treated with a colpoleisis, an oblitative technique used for elderly women who do not desire to maintain the possibility of having vaginal intercourse, were excluded from parts of the analyses since this is a procedure which per definition will have an extremely low risk of recurrence (Paper I).

In Paper IV, failure rate was defined more widely as any repeated treatment for POP performed within the first postoperative year or planned at one-year follow-up after the Manchester Procedure, including also the need of a pessary or pelvic floor muscle training. Failure rates were then compared between the groups of women with and without LAM avulsions.

3.5.2. Anatomical outcomes

Main anatomical outcome in Paper I was maximum stage in the dominating compartment one year after POP surgery with native tissue repairs. Partial repairs were compared to complete repairs, and among the latter there was a special focus on the Manchester Procedure. In Paper III, the primary anatomical outcomes were the percentage of patients with POP-Q stage 0-I in mid- and anterior compartment, as well as the percentage of women who obtained point C ≤ -5 cm (approximately equivalent to stage 0) at the one-year follow-up. Secondary anatomical
outcomes were mean reductions from preoperative to postoperative measurements of anterior and mid-compartment POP-Q points (Ba, C and D).

In Paper II the main anatomical outcome was the prevalence of LAM avulsions, diagnosed on TPUS. Preoperative anatomical differences in anterior compartment stages between women with and without avulsions were used as secondary outcomes.

In Paper IV, a comparison between women with and without LAM avulsions was performed at the one-year follow-up using the main anatomical outcomes; “Stage 0-I in the anterior compartment”, “Stage 0 in the mid-compartment” and mean changes in Ba and C.

3.5.3. Patient-reported outcomes
Subjective satisfaction at the one-year follow-up was the primary patient-reported outcome in Papers I, III and IV. In Paper I, subjective satisfaction was compared between women who received partial repair procedures and women who had complete repairs, including the Manchester Procedure. Paper III reports on subjective satisfaction for its whole cohort, and in Paper IV the degree of subjective satisfaction was compared between women with and without avulsions.

For the analysis of the impact from avulsions on the symptom load before surgery, the preoperative total PFDI-20 scores, POPDI-6 and UDI-6 domain scores as well as the single item 3 (on bulging) were used as primary outcomes in Paper II. For the comparison of the impact from avulsions on sexual function before surgery, the total PISQ-12 score was used as primary patient-reported outcome (Paper II). The changes from
pre- to one-year postoperative mean values of theses questionnaires, in
addition to the single item 5 of PISQ-12 (on dyspareunia) were analyzed
as secondary outcomes in paper III. In Paper IV, the impact of LAM
avulsions on the postoperative total PFDI-20 scores in addition to the
POPDI-6 and the UDI-6 domain scores were analyzed.

The secondary patient-reported outcomes analyzed in Paper I were;
   i.  De novo urinary incontinence (sub-classified as stress urinary
       incontinence, urgency urinary incontinence and mixed urinary
       incontinence).
   ii. Urinary retention, classified as “minimal” or “severe”
   iii. Dyspareunia (not further classified).

3.5.4. Complications

Paper I and III report on per- and postoperative complications registered
in the Department’s POP surgery internal quality control registry, in the
patients’ medical charts and/or reported by the women at the one-year
follow-up. In Paper I, the rate of postoperative complications was
stratified into “hematoma”, “infection” and “other”. In Paper III, the
following complication sub-groups were presented; ureteric kink/injury,
minor bleeding/hematoma, profuse bleeding, prolonged postoperative
pain, minor infection and cervical stenosis.

3.6. Statistical analyses and power calculations

Categorical outcome data were mainly presented as percentages, and the
differences between groups calculated using Pearson’s Chi Squared test.
Mean differences between groups were analyzed with independent
samples t-tests and paired samples t-test was used to evaluate mean
within-group changes from pre- to postoperative measurements. Log-
transformation was performed prior to analysis when outcome data could not be assumed normally distributed (Paper IV). In some cases of not normally distributed data, Mann-Whitney U-test was used.

The cumulative risk of reoperation was calculated in Paper I to illustrate the long-term reoperation risk in women after “partial” (one-or two compartment) repairs compared to “complete” (three-compartment) repairs such as the Manchester Procedure, using a competing risks model. This model was chosen in order to adequately present the long-term risk of POP reoperation in our population consisting of relatively elderly women, with an implicit high risk of death due to causes unrelated to POP.

In Paper III, Pearson’s correlation was used to analyze bivariate correlations between anatomical changes in the anterior (Ba) and Mid-(C) compartments with the above POP-related and sexual symptom scores.

The impact of LAM avulsions and other independent variables on preoperative (Paper II) and postoperative (Paper IV) POP-related symptom scores (PFDI-20 total and domain scores) was analyzed using linear regression models. In Paper II the impact of avulsions on preoperative sexual dysfunction (PISQ-12) was also evaluated. For Paper II, bivariate correlations using Spearman’s rho were used to determine which independent variables to include in the model, whereas for Paper IV, univariate linear regression analyses were used. In Paper II, independent variables with a $p < 0.1$ on Spearman’s Correlation were analyzed in the models, whereas in Paper IV, the cut-off was set to $p < 0.2$. Relevant interactions were checked for.
Logistic regression analyses were used to evaluate the impact of avulsions and other independent variables on a poor anatomical anterior compartment outcome (defined as stage ≥ II) at the one-year follow-up (Paper IV). Independent variables with a p-value < 0.2 on univariate analyses were included in the multivariate model and the variables which maintained a p value < 0.2 were kept in the final model. Relevant interactions were tested, and the model was also tested with a goodness-of-fit (Hosmer-Lemeshow test) test.

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS-PC) version 18 (Paper I), version 22 (Paper II) and version 24 (Papers III and IV). In Paper I, R version 2.15 was used to calculate the cumulative risk of reoperation. For Paper IV, Stata version 14.2 was used for the regression analyses.

No sample size power calculations were performed for Paper I due to its retrospective design and since it was based on an unselected population including all the patients registered as treated with native tissue repairs in the Department’s POP surgery internal quality control registry between 2002 and 2005.

For the MAP-POP study, all sample size calculations were performed with a power of 80% and a significance level of 0.05. Calculations for two individual samples were completed prior to study start, one which was planned as an extension of the other. For Paper III the sample size was estimated according to the assumption that 85% would achieve a postoperative point C (maximal cervical descent) ≤ -5 cm. This assumption was based on unpublished data from our POP surgery internal
quality control registry, in which 85% of the 431 women who underwent the Manchester Procedure from 2002 to 2005 obtained a mid-compartment POP-Q stage 0 at the one-year follow-up. Using a statistical table for paired data, the estimated number of patients needed was 138 (167).

Since only 81.1% instead of the assumed 85% obtained a postoperative point C ≤ -5 cm at one-year follow-up (Paper III), a post hoc sample size estimation with the aim of confirming adequate sample size was performed. This was performed by using a paired t-test for changes in C, generating a required sample size of n = 101 for effect size 0.81 and SD of change 2.9 (from our own data).

For Paper IV, we assumed that 25% of our patients would have a levator ani muscle (LAM) avulsion. This was based on a pragmatic “average” of estimated LAM avulsion prevalences from previous publications. Dietz et al described 23% avulsions in a general urogynecology setting, whereas DeLancey et al found 55% major levator defects in a POP population (35, 36). We also assumed a priori that women with avulsions would have a risk of recurrence of 20% compared to 3% in women without avulsions (122). As we were unable to find any publications describing potential impact of LAM avulsions on the postoperative result of a Manchester Procedure, the assumptions had to be based on best clinical practice. Dietz et al described, in a study with a mean follow-up time of 4.5 years, a cystocele recurrence rate of 69% (stage ≥ 2 on clinical examination) after anterior colporrhaphy in patients with avulsions (168). The supposed risk of recurrence in women without avulsions was based on our results from Paper I, in which we found a five-year reoperation rate for women operated with the Manchester
Procedure of 2.8%, this in a population with unknown prevalence of LAM avulsions. A total sample size of 189 was estimated, 142 without avulsion and 47 with avulsion (Fleiss with CC) (167).

To confirm appropriate test-power, a post study power analysis was performed for Paper II, including a 50% prevalence of LAM avulsions and proposing a clinically relevant difference of 25 in PFDI-20 total score (1 point increase in mean score of one of the domains). With a SD of 55 (from our own data), the resulting sample size was 152 (two sample t-test).

3.7. Legislation and research ethics

The Declaration of Helsinki was respected in all papers that form basis for this thesis. The studies were approved by the Head of Department and by the Insititutional Data Protection Officer (“Personvernombud”- PVO) at Oslo University Hospital. Paper I was performed as an internal quality control study and thus covered by the Health Personnel Act of 2. July 1999 no.64 § 26. Such studies are in Norway exempt from regional ethical committee evaluation. Written patient consent was not deemed necessary for Paper I since the quality control parameters were evaluated on a group level and for treatment already given.

The MAP-POP study (Papers II -IV) was approved by the Regional Committees for Medical and Health Research Ethics, South-Eastern Norway, and written informed consent was obtained from all participants on inclusion. The Institutional Data Protection Officer at Oslo University Hospital approved data handling, including the transfer of anonymized ultrasound volumes between Oslo University Hospital and St. Olav’s
Hospital in Trondheim, Norway. The limited use of data from non-included women registered in the internal quality control registry in order to assure the adequacy of sample selection was approved by the Data Protection Officer without need for individual patient consent.
4. SUMMARY OF RESULTS

4.1. Short and long-term failure rates

In Paper I, 699 women operated with native tissue repair techniques registered in the Department’s POP surgery internal quality control registry were analyzed. More than 60% (n=431) were treated with a Manchester Procedure (Paper I). Failure rate was defined as reoperation for POP. Both short-term (one-year) and long-term (five years) reoperation rates were calculated. The overall reoperation rate was 1.1% at one-year follow-up and 4.7% five years after the index surgery. When excluding women treated with a colporrhaphy, the numbers remained similar, 1.2% up and 4.9%, respectively. The five-year reoperation rate was significantly lower among women operated with a Manchester Procedure (a complete repair procedure, involving repair of all three

![Cumulative incidence of reoperation chart](image)

*Figure 17: Cumulative risk of POP reoperation, comparing women treated with a Manchester Procedure to women treated with partial repair procedures.*

*Figure based on data from Paper I (previously unpublished).*
compartments) compared to the partial (one or two compartment) repair group, with 2.8% vs. 8.9% (p< 0.001).

The cumulative incidence of reoperation had a slight, but steady increase over the years in both groups. However, complete repairs had a significantly lower cumulative risk of reoperation compared to partial repairs (p< 0.001). The latter was also true when Manchester Procedures were analyzed separately against partial repairs (p=0.002) (Figure 17).

In Paper IV, the one-year failure rate was evaluated using follow-up data of 189 women from our prospective cohort of women operated with the MP. The one-year failure rate in Paper IV, defined as any repeated treatment for POP (new surgery, use of a pessary or referral to a physiotherapist for pelvic floor muscle training), was 1% in the LAM avulsion group vs 3.2% in the non-avulsion group, p = 0.36.

4.2. Prevalence of LAM avulsions and impact on preoperative status

We performed a cross-sectional analysis of the baseline data from our prospective cohort of 197 women with anterior compartment POP scheduled for a Manchester Procedure (Paper II). The prevalence of LAM avulsions was 50% in this cohort, of which two thirds were bilateral avulsions and one third were unilateral. For the diagnosis of LAM avulsions on Transperineal Ultrasound, the inter-rater and intra-rater Cohen’s Kappa (after the reanalysis of 50 randomly selected ultrasound volumes) were 0.82 and 0.80 respectively, indicating excellent agreement.
Compared to women without LAM avulsions, women with avulsions were younger at presentation for symptomatic POP (mean age 58.6 vs. 63.1 years) and had lower mean BMI (24.1 vs. 25.6 kg/m²), both p < 0.01. Furthermore, women with LAM avulsions were older when they gave birth to their first child (mean 27.7 vs 25.0 years, p < 0.001) and had more often been delivered by forceps (25.3 vs 8.7%, p < 0.01). Preoperative descent of anterior compartment was similar between groups. Also, preoperative mean values and distribution of pelvic floor (PFDI-20) and sexual (PISQ-12) symptom scores were similar. On linear regression analyses LAM avulsions were not significantly associated with neither preoperative pelvic floor symptoms (PFDI-20 total and domain scores) nor sexual distress (PISQ-12). Preoperatively, the only factor significantly associated with all domains of the PFDI-20 questionnaire was chronic disease (causing pain, fatigue or increased intra- abdominal pressure) (p<0.05) and only age was associated with PISQ-12 (p<0.05) (Paper II).

4.3. Impact of LAM avulsions on one-year postoperative outcomes
The one-year follow-up data from our prospective cohort of 189 women operated with the Manchester Procedure was used to analyze the impact of LAM avulsions on postoperative outcomes (Paper IV). Comparing women with and without LAM avulsions, no significant differences were found, neither in anatomical (anterior- and mid-compartment POP-Q measurements), symptomatic (PFDI-20 total and domain scores) nor sexual (PISQ-12 score) outcomes. Subjective satisfaction was also similar between groups, 94.8% vs. 93.5%.
On univariate logistic regression analyses, a poor postoperative outcome in the anterior compartment (defined as POP-Q stage ≥ II) was found significantly associated with age (p < 0.05), chronic disease (p = 0.01) and a preoperative POP-Q stage ≥ III in the anterior compartment (p < 0.001). On multivariate analysis, however, only a preoperative anterior compartment stage ≥ III (p < 0.01) remained significantly associated with a poor anatomical postoperative outcome.

Using univariate linear regression analyses, preoperative use of estrogen, chronic disease and the preoperative symptom load (total PFDI-20 score) were significantly associated with the total postoperative PFDI-20 score (p < 0.05). On multivariate linear regression analysis, only the preoperative PFDI-20 score remained significantly associated with the postoperative total PFDI-20 score. Thus, LAM avulsions did not significantly impact neither poor postoperative anterior compartment outcome nor postoperative pelvic floor symptom load (PFDI-20).

4.4. Anatomical and patient-reported outcomes one year after native tissue POP repairs, with main focus on the Manchester Procedure

Anatomical and patient-reported outcomes at the one-year follow-up were both analyzed in our retrospective cohort of 699 women operated on with native tissue repairs (Paper I) and in a sub-cohort (n=148) from our prospectively included cohort of women undergoing the Manchester Procedure for primary anterior compartment POP (Paper III).

With regards to anatomical results in Paper I, the outcome analyzed was maximum POP-Q stage in the dominating compartment. Optimal
anatomical outcome (postoperative stage 0-I) was obtained significantly more often in women having undergone the Manchester Procedure as compared to women having undergone partial repairs (86.7% vs. 78.3%, p=0.02). In Paper III, the POP-Q stages and points were analyzed for each compartment individually. Stage 0-I was found at one-year follow-up in 99.3% in the mid-compartment and in 48.6% in the anterior compartment. However, even if only 48.6% obtained anterior compartment stage 0-I, 87.2% of all women had a maximum anterior compartment descent (point Ba) at or above the hymenal level. The mean reduction in maximum descent from preoperative to postoperative measurements were significant in all compartments (< 0.01); - 4.8 cm (C) in mid-compartment and -2.9 cm (Ba) in the anterior compartment (see Paper III).

In Paper I, the subjective satisfaction at one-year follow-up, defined as being subjectively cured or improved from prolapse symptoms, was significantly superior among women with three-compartment procedures (Manchester Procedures and colpocleises) compared to partial repairs (p=0.04). When comparing only the Manchester Procedures to the partial repairs the trend was maintained, however not statistically significant (95.0% vs. 90.9%, p=0.06).

Subjective satisfaction among the cohort treated with a Manchester Procedure in Paper III was similar to the cohort in Paper I; 96%. After a Manchester Procedure, significant reduction in pelvic floor symptoms (PFDI- 20 total and domain scores) as well as sexual distress (total PISQ-12 score) was obtained (p < 0.01). The percentage of women who reported to be cured or improved was 89.8% for pelvic floor symptoms and 51.5% for sexual distress (Paper III).
Postoperative dyspareunia was in Paper I described by 8.9% of the women after a Manchester Procedure and by 10.7% after a partial repair (non-significant difference), however no data was available on preexisting (before surgery) dyspareunia in the Department’s POP surgery internal quality control registry. Among the prospectively included cohort of women operated with a Manchester Procedure in Paper III, no significant mean changes from pre- to postoperative dyspareunia (item 5, PISQ-12) were found. Improvement of dyspareunia was reported by 24.6% whereas 49.2% expressed being unchanged and 26.2% reported aggravation. De-novo dyspareunia was described by 5.6% of the women.

Among women treated with the Manchester Procedure, correlations between one-year anatomical and subjective (including sexual) outcomes were analyzed (Paper III). Dichotomizing women with postoperative anterior compartment POP stage II into maximum decent (Ba) above vs. below the hymenal plane, we found a trend towards increased symptoms of bulging in the latter group (p = 0.08). The changes between pre-and postoperative POP-Q measurements in the anterior compartment (Point Ba) were significantly correlated with POP specific symptoms (POPDI-6, p = 0.01), urinary distress symptoms (UDI-6, p < 0.01) and the isolated symptom of vaginal bulging (q.3, POPDI-6, p < 0.01). However, anatomical change in the mid-compartment (point C) was only correlated with the response to the question of bulging (q.3, POPDI-6, p = 0.04). No correlations were found between anatomical anterior- or mid-compartment changes and sexual outcomes.

In the retrospective cohort in Paper I, de-novo urinary incontinence was similar among Manchester Procedures (8.5%) compared to partial repairs
(12.7 %). In total, de-novo urgency incontinence (UUI) was reported by 5.7%, stress incontinence (SUI) by 3.8% and mixed by 0.5%. In the prospective cohort treated with the Manchester Procedure (Paper III), more women reported to be cured or improved from urinary incontinence than worsened, both regarding SUI (24.3 vs.10.4%) and UUI (32.4 vs.16.6%). Incomplete bladder emptying was cured/improved in 49% and worsened in 6.9%.

Postoperative complications, in the retrospective cohort (Paper I) subclassified as hematoma, infection and “other” were found to be similar in women after the Manchester Procedure (8.7%) compared to after partial repairs (9.5%). Over-all severe urinary retention, in need of prolonged intermittent self-catheterization was 1.8%. In the prospective MAP-POP cohort, the over-all complication-rate was 11.8% (18/148), mainly due to hematomas and postoperative pain (Paper III). Three women were identified with serious complications, two with profuse bleeding and one with ureteric kink.
5. DISCUSSION

5.1. Methodological considerations

5.1.1. Study design and study populations

Paper I

Paper I was designed as a historical cohort study with data from the Department’s POP surgery internal quality control registry including all women registered with vaginal native tissue repair procedures (n=699) during the study period. The only selection was the exclusion of the few women who had received procedures not classified as vaginal native tissue repairs (n=28). Registry-based studies might better reflect the average female POP population than prospective studies which are more prone to selection bias due to stringent selection criteria. Such selection criteria would likely have included proficiency in Norwegian or English, which may have excluded the participation of some of the immigrated populations.

Whereas invaluable in providing insight into long-term safety and effectiveness of interventions, the restricted nature of such registry data may be challenging (169). Especially is this the case if the study aims differ from the purpose of the registry, so that important variables are lacking among the registered variables (169). At our Department, the internal quality control registry was set up in 2002, in the era of increasing popularity of vaginal synthetic mesh, with the intention of testing the efficacy of native tissue repair procedures. Thus, our study aims of evaluating short and long-term outcomes after native tissue POP repairs were within the predefined aims of the registry and all essential variables were collected in the registry. However, questions on self-
reported sexual activity were not extensive (in line with what was feasible within the time frame of a regular clinical one-year follow-up setting).

The MAP-POP study (Paper II-IV)

Internal quality control registries must per definition be simple, in order to ensure their adequate coverage in an everyday busy clinical setting. When the study goal is to evaluate specific pre- and postoperative variables and compare women with similar baseline anatomical POP, such registries may be less useful. We therefore decided to start a prospective study and considered performing a Randomized Controlled Trial (RCT), which often is considered the gold-standard for evaluating the efficacy of an intervention (170). However, we soon realized that such a design would include too many pitfalls as there are several obstacles to randomization in POP surgery, such as; the surgeon cannot be “blinded”, individual women have specific requirements and indications, individual surgeons have different skills etc. Moreover, since excellent Manchester Procedure outcomes were observed in Paper I, we found it ethically questionable to randomize women to another procedure in which we had less confidence. We therefore considered that a poorly conducted RCT would not be superior to a well performed observational study (171), and the MAP-POP study was thus designed as a prospective cohort study.

As mentioned above, prospective design comprises a risk of selection (sampling) bias (172). To ensure that the study participants represented the average women receiving primary POP repair with the Manchester Procedure at the Department, we used our internal quality control registry to keep track of women not included listed as having undergone a primary Manchester Procedure within the study period. When comparing
all women not included primarily operated on with a Manchester Procedure to women included in the MAP-POP study, they were similar by means of age and POP-Q stage in anterior and mid-compartment, but women not included had a significantly higher mean BMI. One of the exclusion criteria for the study was the inability to communicate fluently in Norwegian or English. A proportion of non-western immigrants were therefore systematically excluded. Obesity is known to be highly prevalent among some immigrant groups in Norway (173) and was therefore thought to explain this BMI discrepancy between participants and non-participants. When we excluded non-western immigrants from the analysis, this difference in BMI disappeared. Although high BMI is a risk factor for POP development (11), its role as a risk factor for POP recurrence has yet to be determined (174). Since the anatomical POP staging was similar among included and non-included women, we believe the cohort to be representative of women undergoing this procedure at our Department.

5.1.2. Missing data

A well-known problem in all types of health registries is missing/incomplete data, affecting their internal validity (175). It is generally accepted that if the amount of missing data (or participants) is greater than 10%, the results of successive data analyses may be biased (176). In order to enhance the quality of our internal quality control registry, women are informed about the invitation to a one-year routine clinical follow-up at the day of discharge after POP surgery.

The registry’s one-year follow-up coverage of women operated for POP between 2002 and 2005 was 94.1% (see Figure I, Paper I), which according to prevailing standards is considered to be of good quality
(177). For the analyses in Paper I, we therefore did not consider the use of methods (e.g. imputation) to deal with missing data. However, as all variables were not complete for all registered women, we performed available-case analyses based on the assumption that the missing data were non-differential. This means that the probability of missing values was assumed not to be related to any other variable in the dataset (known or unknown) (178). For long-term data on reoperations, we were unable to obtain information from 42 women only (6.1%). The high number of deceased women during the study follow-up (n=88) added further challenges to the analyses, as described in 5.1.8.

Prospective cohort studies, such as the MAP-POP study (Paper III-IV) are susceptible to loss to follow-up/withdrawals (172). The study participants were therefore thoroughly informed at inclusion about the planned follow-up. The women were also given the opportunity to reschedule their one-year appointment or, if desired, to meet for afternoon controls after regular outpatient clinic opening hours. This way, we managed to reduce the loss to follow-up to a minimum. In Paper IV one-year loss to follow-up was only 3.1%, as one woman did not attend, whereas further five women were not clinically followed-up due to ongoing cancer treatment, emigration, or POP reoperation (Figure I, Paper IV).

The main challenge in regards to missing data in the MAP-POP study was related to self-reported questionnaires. For the PFDI-20, several women completed the questionnaires incorrectly. Items responded with “Yes” without being scaled according to degree of bother had to be discarded. Missing answers to individual items within a domain were dealt with using the mean of the answered items, as described in the
original paper (146). Although no maximum limit for missing responses is described for PFDI-20, three questionnaires were so poorly filled in that we decided to exclude them from the analyses (Paper IV). The amount of incomplete items could have been reduced if a clinician had been present while the women filled out their questionnaires, but this option was not chosen as it would have increased the risk of influencing the responses given. Incomplete answers to individual items were, however, not a major problem regarding the PISQ-12 questionnaire. For this questionnaire the major limitation was the large amount of women considering themselves not sexually active and thus not answering the questionnaire at all (see 5.1.5).

5.1.3. Pelvic Organ Prolapse-Quantification scale (POP-Q)

POP-Q is a validated, reproducible and well-established tool to measure the objective anatomical degree of POP and is the standard method in clinical research recommended by the International Urogynecological Association (IUGA) and the International Continence Society (ICS) (41). However, there are objections to the use of POP-Q, and several clinicians have requested its revision (151). First of all, the system lacks a definition of normality. Women who have given birth often have asymptomatic stage I or II “prolapses” (38). In the POP-Q system a stage II prolapse is a genital descent on Valsalva to between 1 cm above and 1 cm below the hymenal plane. However, in clinical experience the hymenal plane is often considered the most important reference point, at least for the anterior compartment, below which prolapses become symptomatic (143, 179).

The POP-Q system also stages all three compartments equally, assuming the threshold for symptomatic POP to be the same in all compartments,
which probably is false (151). Therefore, whereas stage 0-I as a definition of optimal outcome in anterior compartment may be too strict, the same definition may not be strict enough for the mid-compartment (151).

Another objection to the use of POP-Q is that whereas a substantial part of the examination is supposed to be performed under Valsalva, not all patients are able to perform Valsalva correctly. Therefore, if not additional measures are applied, such as using a cervical clamp or performing examination in a standing position, POP-Q measures may be underestimated (180).

5.1.4. Transperineal Ultrasound

Transperineal Ultrasound (TPUS) is a commonly used tool for diagnosing LAM avulsions, especially by Tomographic Ultrasound Imaging (TUI) (21). The technique was developed by Prof. Dietz and his team at the Nepean Hospital (University of Western Sydney, Australia), and although generally accessible, some training is required for correct TPUS image orientation and interpretation (33), as described in 3.2. To avoid bias from poorly performed ultrasound examinations and volume analyses, the PhD student (SO) was trained in TPUS at Dietz’ Department prior to study start. All study TPUS volumes (Paper II) were obtained and interpreted by the same person (SO). To further ensure the correct interpretation of ultrasound volumes, another clinician (IV), also previously trained at Dietz’ Department, was involved in the inter-rater evaluation process. Only three women had incomplete/non-interpretable ultrasound volumes causing them to be excluded from the analyses of baseline data (Paper II). Although this number is small, it could to have impacted the interpretation of outcomes. Fortunately, we were able to repeat the TPUS examinations prior to surgery in two of these three
women, enabling the evaluation of LAM integrity. Thus, in Paper IV, the amount of non-interpretable ultrasound volumes was reduced to one.

It is widely accepted that nulliparous women do not have LAM avulsions (181). However, two studies on nulliparous women have shown abnormalities in LAM structure in 18-20% (182, 183), probably due to technical limitations. Theoretically, however, these abnormalities could have represented hereditary anatomical variations (181), and if that is the case, a revision of the concept of LAM avulsions may have to be performed.

5.1.5. Questionnaires

Validated questionnaires are used in research to ensure that the questions asked measure what they are supposed to measure. They are validated for use in a certain context, language and population and ought therefore to be revalidated before presenting it to another population than it was originally designed for (184).

The questionnaires used for patent-reported outcomes in the MAP-POP study (Paper II-IV) were the PFDI-20 for pelvic floor distress symptoms and the PISQ-12 for sexual distress. As neither of the questionnaires were validated into Norwegian at study start, we translated the validated Swedish PFDI-20 and PISQ-12 versions into Norwegian. The populations are culturally similar and spoken and written Swedish is understood by native Norwegians. The PFDI-20 was validated into Norwegian in 2017 (166). Comparing the latter with our translation, minor differences of expression were found. Therefore, a large extent of information bias due to misinterpretations is unlikely to have occurred. In line with this, none of the patients ever asked about the meaning of a question.
The sexual PISQ-12 questionnaire (still not validated into Norwegian) is widely used in research concerning female pelvic floor distress (185). It is however not validated for lesbian women and only developed for sexually active individuals, assuming that “sexually active” implies having vaginal intercourse (145). In our study population, we experienced that only half of the women considered themselves “sexually active” and thereby answered the PISQ-12 questionnaire (Paper II, III and IV). Therefore, our study might not have been sufficiently powered to study sexual outcomes. We could have used another sexual questionnaire, the Pelvic Organ Prolapse/Incontinence Sexual Questionnaire, IUGA-Revised (PISQ-IR) (186) which was developed in 2013 in order to address both “sexually active” and “sexually inactive” women. However, as the PISQ-IR is more extensive, we feared that less women would be willing to respond to it. Moreover, at the time of study planning, only the English PISQ-IR version existed.

The evaluation of sexual outcomes was further complicated by the fact that women who considered themselves “sexually active” before surgery became “sexually inactive” after surgery and vice versa, as illustrated in 5.2, Figure 18.

5.1.6. Telephone interview

In Paper I, a telephone interview was performed five to ten years after the initial POP surgery, in order identify women who had received repeat POP surgery at other hospitals/centers or who had symptoms potentially indicating recurrent POP. As the mean age at the index operation in this population was 67 years, several patients had quite an advanced age when interviewed. Reduced auditory, communicative or
mental capacity due to aging could have contributed to information bias due to misunderstandings. On the other hand, only non-institutionalized women (functioning well enough to live at home) were interviewed. Therefore, we considered this risk to be of minor importance.

5.1.7. Strenghts and limitations

Paper I

One of the main strengths of Paper I is the study population of 699 women, representing the total population of women treated with vaginal native tissue POP repairs at one of the largest urogynecology units in Norway during a four-year period (January 2002 to December 2005). We believe that the outcomes of this study better reflect the everyday surgical urogynecology setting compared to a prospective study, minimizing the risk of selection bias and thus rendering a high external validity. Furthermore, the variety of procedures performed made it possible to group the procedures and compare groups. The prolonged follow-up time also enabled the estimation of long-term risk of POP reoperation.

The study also had weaknesses. The subjective symptoms registered at the one-year follow-up were based on a clinical interview using a non-validated questionnaire. Questions which are not validated imply a risk that they are misunderstood and not answered the way they were intended. Moreover, since the questionnaire was only used at the one-year follow-up and not prior to or at the time of surgery, some information went missing. For instance, postoperative dyspareunia could not be well evaluated, as information on preexisting symptoms was lacking. Clinicians performing the one-year follow-ups were not blinded for the preoperative data, and in some situations the same surgeon performing the POP repair also conducted the follow-up. This could have
biased the registered outcomes, as previous studies have shown that surgeons tend to underestimate the patient’s bother due to an eagerness of favorably interpreting results from self-performed surgery (187, 188). The relatively high median age in this population of 67 years compared to other study populations might have affected the external validity of our findings (189-191). However, previous studies have not shown that age per se impact outcomes after POP surgery (192, 193).

The Department’s internal quality control registry includes POP-Q stages in each compartment, but not individual POP-Q points and landmarks. Only the maximum stage in the dominating compartment was evaluated in Paper I, and not each compartment separately, which could perhaps be criticized as being too simplistic. However, as most women had their maximum POP-Q stage in the anterior compartment, we do not believe that the analysis of each compartment separately would have added vital information to the Paper.

The MAP-Pop study

The MAP-Pop study population was well-defined, consisting exclusively of women with primary anterior compartment prolapses and intact uteruses, thus increasing the comparability of outcomes between groups and also enhancing the interpretability of within-group changes. All women were treated with a Manchester Procedure, and sample sizes were adequate according to pre-study sample size calculations (Paper III and IV). To our knowledge, only two recent studies on the Manchester Procedure have been performed prospectively (194, 195), therefore we consider this study to add substantial information to the field.
The ultrasonographic diagnosis of LAM avulsions (Paper II) was deemed well performed, as the calculated Kappa scores for inter- and intra-rater reliabilities were high, 0.82 and 0.80 respectively. Further, the prevalence of avulsions of 50% allowed us to compare two groups of equal size (Paper II and IV). The median age in this population of 62 years was lower than in Paper I, thus more similar (an thus perhaps more comparable) to other published studies (189-191).

Whereas the use of the validated questionnaires PFDI-20 and PISQ-12 may be considered a study strength, some limitations also applies to the interpretation of these questionnaires, as outlined in 5.1.5. None of the questionnaires include cut-offs for high/low symptom load as they are developed for before/after comparisons. This made our study results less easy to interpret clinically. Neither were we able to find any publications indicating what is to be considered the minimum symptom reduction desired.

The MAP-POP population consisted of mainly women of European heritage, possibly affecting the external validity of the study results. However, although the expression of sexual symptoms has been found to differ between ethnic groups (196), ethnicity per se has not been demonstrated to significantly impact pelvic floor symptoms (197).

5.1.8. Statistical analyses

Failure rate calculations

The most common way of presenting short- and even long term reoperation (failure) risks are in percentages (174, 179). Although clinically simple to understand and to compare, this presentation of risks would often not be statistically correct, especially when considering long-
term risks. Women treated for POP are in general elderly, therefore such populations have a risk of disease/death not related to the POP surgery which must be taken into concern when calculating risks for POP reoperation.

Some publications on long-term risk of reoperation use proportional Hazards models (198). The problem with such models is, however, that the censored cases are equally weighed, meaning that senstation due to death is considered equivalent to senstation due to recurrence. In order to take into account the difference between censored cases, we calculated the cumulative incidence of POP reoperation using a competing risks model (Paper I). For the simplicity and easy interpretation, we additionally presented the five-year reoperation risks in percentages. Since few patients were lost to follow-up at one year after POP surgery, presenting the one-year failure risks only in percentages was deemed adequate (Paper I and IV).

Power calculations

Sample size estimations are considered essential when planning a prospective study. The estimations has four main components (199):

1) The type I error (α) level (often set to 0.05) = the probability of falsely rejecting the null hypothesis (H₀) (false positive).

2) The study power (typically set to 80 or 90%) = the probability of correctly rejecting H₀ (avoiding type II error (β) (false negative)).

3) Smallest effect of interest = the minimal clinically relevant difference between groups.

4) Variance (based on pilot studies or previously published studies).
Since the smallest effect of interest is highly subjective and variance often is unknown, sample size estimations are often based on highly inaccurate assumptions (199).

Prior to the initiation of the MAP-POP study, two individual sample size estimations were performed in which one cohort was planned as an extension of the other.

*Sample size for Manchester Procedure outcomes*

For the evaluation of within-group changes at one-year follow-up after the Manchester Procedure (Paper III), the sample size estimation was calculated with an effect size of 0.85 (assuming that 85% would achieve a postoperative point C ≤ -5). At one-year follow-up, only 81.1 % obtained the latter. Thus, with the aim of confirming adequate sample size, we decided to perform a post hoc sample size estimation by means of paired t-test for changes in C, generating a required sample size of n = 101 for effect size 0.81 and SD of change 2.9.

Commonly, researchers like us want to perform post hoc analyses in order to check the power of our studies, and such analyses are often requested by reviewers. However, to consider that the effect size observed in actual data equals the pre-study effect size set as cut-off for clinical importance is statistically incorrect. After the study has been performed, the observed data determine the size of the treatment effect and the width of confidence interval estimates (200). The estimated study power will then change according to the p-value for the observed data. This means that for any two group comparisons, if the p-value is above 0.05, the study power has to be low (200).
The only part of the *a priori* sample size estimation that needs to be considered when analysing the study outcomes, is the effect size that was set as clinically meaningful, to which the observed effect size with the correspondent confidence intervals should be compared (199, 200).

*Sample size for evaluating the impact of levator ani muscle avulsions on demographic data and preoperative symptom load.*

No *a priori* sample size estimation was performed for Paper II. This was a cross-sectional analysis of the preoperative data from all women included in the MAP-POP study. Also in this case, a post study power analysis for this cross-sectional study was performed. However, in this calculation the effect size was based on the hypothetical clinical relevance of a difference in total PFDI-20 score of 25 points and was not based on observed data. Thus this post hoc calculation was probably a more statistically correct estimate than the one performed for Paper III. We estimated sample size of 152, but decided to include all study participants in the analyses as the minimal relevant difference in PFDI-20 scores was not established in any previous papers, meaning that our sample size estimation was still highly uncertain.

*Sample size for evaluating the impact of levator ani muscle avulsions on Manchester Procedure outcomes*

For the calculation of the sample size needed to estimate the impact of LAM avulsions on Manchester Procedure outcomes at one-year follow-up (Paper IV), we assumed that the proportion of avulsions would be 25% (based on previous publications (35, 36), see 3.4.5 ), whereas it turned out to be 50% in our population. Thus we felt confident in having included enough women for adequate study power. However, the deduced effect size (between group difference in recurrence rate) of 17%
(20% vs. 3%), turned out to be highly overestimated compared with the observed effect size. The estimates were in part based on results from previous publications (35, 36, 122), but mostly based on best clinical practice, as we were not able to find published data on the impact of LAM avulsions on Manchester procedure outcomes (see 3.4.5). Still, the clinically relevant effect size could probably have been set lower, perhaps at 10%, but at the cost of having to further prolong the inclusion period, which for the MAP-POP study lasted 21 months.

**Linear and logistic regression analyses**

Linear regression models were used for the evaluation of impact of LAM avulsions on preoperative (Paper II) and postoperative (Paper IV) symptom scores. In order to evaluate the potential association between avulsions and poor anatomical outcome, a logistic regression model was built (Paper IV).

Whereas multiple regression models may be useful for investigating how independent variables impact the dependent variable, their interpretation must be extremely cautious (201). No strict rules exist on how to select variables into a regression model (201-203), therefore this selection is at least in part, dependent on the researcher’s clinical experience and subjective opinion. Therefore, the same data may be turned into widely different models.

In our study, we used a forward selection method, starting by analyzing each independent variable against the dependent variable. For the selection of variables to the linear regression models, Spearman’s rank correlation was used in Paper II whereas univariate linear regression was used in Paper IV. The advantage of using Spearman’s rank correlation is
its robustness against extreme values (204), but was not found necessary in Paper IV due to the absence of extreme outliers.

Using p-value cut-offs for variable selection as we did in our studies (Paper II and Paper IV) is disputed among biostatisticians and no consensus exists on where the cut-offs in p-levels should be set (205, 206), since p-levels are driven by sample size (207). The variable selection would be arbitrary if not combined with clinical knowledge about variables with biological importance or variables previously shown to be associated with the outcome (202). The latter is, however, more complicated in fields where such knowledge is basically unknown, such as factors related to baseline POP symptom load analysed in Paper II.

In none of the regression models were LAM avulsions found to be associated with any of the outcomes, thus we feel confident concluding that avulsions seem to be of lesser importance regarding baseline symptom load and postoperative outcomes when the Manchester Procedure is used. Furthermore, other significant associations found in the regression models used in Paper II and IV, such as the impact of Chronic Disease on preoperative symptom load, do not necessarily represent causative relationships with the outcome.

In our study planning, drawing DAGs (Directed Acyclic Graphs) helped clarifying potential causal relationships as well as to identify which factors were important to measure and how these factors related to each other, in order to point out confounders and risk modifiers (208). Although representing an excellent tool in planning statistical analyses, clinical knowledge is essential when drawing DAGs and therefore difficult to draw in cases where the relations between variables are not
established. For instance, if LAM avulsions are thought to be important for both the development of POP and the postoperative outcome, the avulsions is a confunder in the relationship between pre- and postoperative anatomical outcomes. On the other hand, if avulsions are not thought to act on the postoperative outcome, then avulsions is per definition not a confunder and should not be adjusted for in the regression analyses.

5.2. Discussion of results

Short- and long-term failure rates

In both our general POP population (Paper I) and our selected population of women with anterior compartment POP (Paper IV), failure rates were very low at one-year follow-up. In Paper I, the one-year reoperation rate among women treated with the Manchester Procedure was only 0.9%, even lower than previously reported failure rates after native tissue repair procedures (179). In Paper IV, one-year surgical failure (defined as reoperation for POP, the need of a pessary or referral to a physiotherapist for pelvic floor muscle training due to recurrent POP symptoms) still turned out exceptionally low (2.1%) and was similar among women with and without LAM avulsions.

Recurrence after anterior compartment repairs is often found to occur within the first one or two years (62, 195, 209), but most of these papers define failure as anatomical recurrence on clinical examination and not symptomatic POP in need of repeat POP surgery. Therefore, one could claim that our choice of endpoint being surgical failure (by the definition given above) at one-year follow-up is too soon as longer follow-up is needed for the recurrence of symptoms leading to the need of further
treatment. However, whereas long-term follow-up is important in order to establish the long-lasting efficacy of a POP repair, a recent Danish population-based registry study with up to 20 years follow-up, including more than 11,000 women treated for POP, showed that the reoperation rate is highest during the first year after primary surgery (210). In the latter study, the increase in cumulative incidence of reoperation for the anterior compartment declined after 2 years (210). This decline is in accordance with our finding in Paper I where the increase in cumulative reoperation risk fell with increasing years post-surgery (see 4.1, Figure 17).

Our study published in Paper I and others have found that symptomatic POP recurrences may be registered several years after the initial surgery (211), but these “late recurrences” in populations of advanced age (such as our study population) may not in fact be recurrences but rather new POP due to weakening of connective tissue support with advancing age.

Although median age was similar in women having undergone the Manchester Procedure and those only treated with partial repairs in Paper I, we found that the cumulative incidence of reoperation after the Manchester Procedure was significantly lower and with a slower increase over the years compared to the group with partial repairs. The five-year reoperation-rate was also significantly lower for women treated with the Manchester Procedure. We believe that the superior performance of the Manchester Procedure is due to the procedure providing thorough repair of all three vaginal compartments and as such not only being a repair of anatomical defects but also a prophylactic procedure, as discussed in detail below (under “Anatomical and patient-reported outcomes one year after native tissue repairs, with main focus on the Manchester Procedure”).
Prevalence of levator ani muscle (LAM) avulsions and the impact on preoperative status

The prevalence of LAM avulsions in our POP population of 50% (Paper II and IV) was in the upper range of what has previously been published (36, 73, 212-214). Most previous prevalence estimations have been performed in mixed urogynecological populations, where a significant part of the women were seen for stress urinary incontinence without having POP. The relationship between LAM avulsions and urinary incontinence is still controversial, whereas avulsions is an established risk factor for POP development (181). Therefore, the prevalence of avulsions in a study population such as ours in which all women had anterior compartment POP, would be expected to be higher. This is supported by the fact that the two papers we have identified to report on LAM avulsions in populations where all women had POP (with or without concomitant urinary incontinence) showed similar prevalences of avulsions compared to our population (36, 73).

Uni- and bilateral avulsions were juxtaposed in the MAP-POP study (Paper II and IV), as done in most previous studies (181). However, since unilateral avulsions at least theoretically could be interpreted as less severe than bilateral avulsions, we performed sub-group analysis in Paper II, which did not add any significant differences between the study groups.

An association between a high intensity of pelvic floor symptoms three months post-partum and LAM avulsions has previously been shown (215, 216). In our cohort of women with POP, no such association was
revealed concerning preoperative symptom load. It may be that symptoms due to tissue injury caused by vaginal birth in some women with avulsions are reversible over time, and therefore detectable at three months post partum but not later in life. A more plausible explanation could also be that since all women in our study had POP symptoms severe enough to warrant surgical treatment, this fact could potentially have masked any between-group differences. A retrospective study published in 2015 also supports the lack of association between avulsions and prolapse symptoms in POP patients (217). Furthermore, the POP stage has in another study been shown as the only factor associated with the severity of symptoms (148). It may therefore be a plausible explanation that the size of prolapse is more important for symptom expression than LAM integrity.

By comparing demographic data from women with and without avulsions, we found that women in the avulsion group were younger when presenting for POP in need of surgery whereas they were older when they gave birth to their first child. Most avulsions occur during the first vaginal delivery (22), and older primiparas have an increased risk of obstetric trauma (218) possibly due to the fact that the pelvic floor becomes more vulnerable and less elastic with age (71). Our findings therefore support what has been pointed out by others, that older age at first delivery shortens the time gap between pelvic floor trauma and symptomatic POP development (219).

Forceps delivery is an established risk factor for LAM avulsions due to tissue trauma (23), therefore we were not surprised to find that also women in the avulsion group of the MAP-POP study had significantly more often been delivered by forceps. A more unexpected finding was
that women in the avulsion group had lower BMI compared to women with intact LAM. High BMI is a commonly accepted risk factor for POP development (220), therefore our finding may be interpreted in support of the idea that due to the importance of LAM integrity for normal female pelvic floor function, women with injured LAM may need less additional cofactors in order to develop POP. It is also possible that women with low BMI are more susceptible to suffering pelvic floor trauma during delivery due to less adipose tissue and therefore more exposed muscular tissues, as proposed by others (221, 222).

Anatomical and patient-reported outcomes one year after native tissue repairs, with main focus on the Manchester Procedure

In Paper I, one-year anatomical outcomes after POP surgery were superior for the Manchester Procedure compared to partial repair procedures, as anatomical stage 0- I in any compartment was obtained by 86.7% vs. 78.3% (p=0.02). Therefore, it was somewhat surprising to find that among the included women treated with the Manchester Procedure in the MAP-POP observational study (Paper III), only 48.6% obtained stage 0- I in the anterior compartment, albeit stage 0-I in the mid-compartment was obtained in 99.3%. We believe that the divergent anterior compartment findings in Paper I and III could be explained by the fact that the clinical examination in Paper I only included staging without measuring actual POP-Q points and therefore some stage II prolapses at or above the hymenal level might have been misjudged as stage I. We suspect that when the clinician found “some genital descent” without symptoms, the prolapse was staged as I, as long as it did not protrude beyond the hymenal level during maximal Valsalva. This suspicion is supported by the fact that in the MAP-POP study 87.2% (129/148) had a maximum
anterior compartment descent (point Ba) at or above the hymeneal level, an almost exactly identical percentage as the ones staged as 0-I in Paper I.

Subjective satisfaction, defined as being improved or cured from the prolapse problem, was excellent in both our unselected (Paper I) and selected (Paper III) POP populations. POP-related subjective symptoms are often found to correlate poorly with anatomical POP findings (195), the symptom of “bulging” being the one best correlated with anatomical findings (42). This is supported by the trend we found in Paper III, in which women with maximum descent of the anterior compartment (point Ba) tended to have more intense symptoms of bulging (p=0.08). The anatomical threshold below which a prolapse is thought to become symptomatic is not fully established, and probably different for each vaginal compartment (223). According to the anterior compartment, some advocate that the symptomatic threshold is situated at the hymenal level (143, 179), others at 0.5-1 cm below the hymen (223, 224) and others again at 0.5 cm above the hymen (151).

For mid-compartment, cut-offs are even less defined, but several studies indicate that compared to anterior compartment, less descent is needed to become symptomatic (151, 223). Therefore, whereas our definition of stage 0-I as optimal may have been too strict in anterior compartment, for mid-compartment it was probably more correct or could even have been stricter (Paper I and III) (see also 5.1.3). In Paper III; maximum descent of mid-compartment (point C) to 5 cm above the hymen during maximum Valsalva was found in 81.1% (120/148). Based on what is found in previous papers, “optimal mid-compartment outcome” is probably a point C situated somewhere more than one centimeter, but less than five centimeters, above the hymen (151, 223).
It is commonly accepted that anterior and mid-compartment prolapses most often occur together (109). We therefore believe that the favourable subjective outcomes after the Manchester Procedure in our study, despite less optimal anatomical outcomes in anterior compartment, are explained by the procedure combining anterior repair with adequate apical support. The fact that the Manchester Procedure does not fully restore the anterior compartment has also been shown by others (225). Adequate apical support, however, will help reducing the anterior prolapse proximal to the level of the hymen and thereby significantly decreasing POP symptoms and improving patient satisfaction (143). The Manchester Procedure in our understanding of its definition always includes a reconstruction of the perineal body, reducing the genital hiatus (see also1.5 ). We believe that such a reconstruction of the perineal body restores the floor upon which the anterior wall rests during strain and thereby may counteract any remaining symptoms from a moderately bulging anterior wall.

The absence of performing a posterior repair (assumed to include a reconstruction of the perineal body) has also been shown by Dällenbach et al to increase the POP reoperation risk (192). Similarly, Abdool et al have shown that the subjective awareness of prolapse is associated with the hiatal area size (226). A main argument against performing a prophylactic reconstruction of the perineal body is the risk of dyspareunia. However, we believe that this risk is minor if care is taken to avoid placing deep sutures into the LAM. In Paper I, reported dyspareunia was similar among women after the Manchester Procedure (8.9%), compared to women treated with partial repairs (10.7%; p=0.46). As the registry data used for Paper I was collected one year after
surgery, information on preoperative dyspareunia was lacking. The rate of de-novo dyspareunia could therefore not be evaluated in this paper.

In Paper III, however, using a validated questionnaire evaluating sexual function (PISQ-12), 5.6% reported de-novo dyspareunia following three compartment repairs by the Manchester Procedure. This rate is in accordance with the dyspareunia rates reported in a systematic review from 2015 on sexual outcomes after native tissue repairs (227). The same review also indicated that 47% improved their sexual function after POP surgery. This is similar to our findings of 51.6% of the women reporting that they were improved or cured from their sexual distress (Paper III). Therefore, we feel confident that the sexual outcomes after the Manchester Procedure are not inferior to other procedures. However, since some sexually active women became sexually inactive after surgery and vice versa, sexual outcomes turned out difficult to evaluate, as illustrated in Fig. 19.
Some still argue strongly against the use of a more than 100 years old surgical technique such as the Manchester Procedure in POP surgery. They claim that the poor outcomes previously reported after native tissue anterior compartment repairs (which led to the introduction of synthetic meshes in vaginal POP surgery) still present a significant problem. However, during recent years optimal anatomical outcome has been redefined as the importance of patient symptomatic outcomes have become more emphasized and integrated to a larger extent in the defined outcomes. Accordingly, outcomes after native tissue repair techniques have to a larger extent been deemed as highly acceptable (69). An excellent example of the latter is the original Weber study published in
2001 in which high anatomical recurrence rates after native tissue techniques were described. Recurrence was in this study defined purely as an objective finding of more than stage I in anterior compartment, resulting in a recurrence rate of 70% (228). Ten years later, however, the data were reanalyzed and re-published with the hymen used as the reference point for surgical success. This alternative definition of a successful outcome after a median follow-time of 23 months resulted in only 10% having anatomical recurrence, 5% having symptomatic recurrence and less than 1% having a need for new surgery (229).

*Impact of levator ani muscle (LAM) avulsions on one-year postoperative outcomes after the Manchester Procedure*

In several studies, even with relatively short follow-up time, LAM avulsions have been shown to exert a negative impact on anatomical outcomes after anterior compartment repair procedures (120, 174, 230, 231). Therefore, we were surprised to discover that our study was not able to reproduce this finding when comparing anatomical outcomes in women with and without LAM avulsions at one-year follow-up. Although less women with LAM avulsions tended to obtain stage 0-I in the anterior compartment (46.9% vs. 58.1%; p = 0.08) in our study, both mean Ba and mean changes in Ba from preoperative to postoperative values were similar in both groups (p=0.50 and p=0.55, respectively). Furthermore, LAM avulsions were not found to be associated with a poor one-year anatomical anterior compartment outcome using logistic regression. The only factor we identified as associated with a poor anatomical postoperative outcome was having a preoperative POP-Q stage of ≥ III in the anterior compartment, in line with what has been found by others (232).
The lack of an independent impact from avulsions on anatomical outcomes in our population may be explained by the surgical technique. Several previous studies that describe impact of LAM on postoperative outcomes were performed after isolated anterior colporrhaphies (71, 72, 231, 233). Women with LAM avulsions have larger hiatal areas (234, 235), which has previously been identified as an independent risk factor for POP development (236). Given that an isolated anterior repair does not restore the hiatal area to its normal dimensions, one would expect a higher degree of failure after this procedure in women with avulsions. One could therefore argue that it is not the LAM avulsion per se that exerts an impact on the outcome, but rather the hiatal dimensions. Women in our study group were all treated with a three-compartment Manchester Procedure that includes a reconstruction of the perineal body, thereby reducing the hiatal dimensions (Paper IV).

The effect of avulsions on symptomatic recurrence is unclear from previous studies (230, 237). In our study population, similar symptomatic outcomes in terms of subjective satisfaction, symptom load (PFDI-20) and sexual distress (PISQ-12) were found comparing women with and without LAM avulsions. On linear regression analyses, the only factor associated with the postoperative PFDI-20 score (symptom load) was the preoperative PFDI-20 score.

Some would claim that a one-year follow-up is too short in order to identify symptomatic differences between groups and that a poor postoperative symptomatic outcome may emerge at a later date (143). However, as previously mentioned, most POP reoperations (and thereby symptomatic recurrences) are found to occur during the first
postoperative year (210). We therefore believe that if LAM avulsions have a true independent negative impact on POP recurrence, it ought to have manifested itself already at the one-year follow-up. Still, a five year follow-up is planned for the MAP-POP cohort in order to evaluate whether the lack of impact from LAM avulsions on anatomical and patient-reported outcomes is sustained in the long term.
6. CONCLUSIONS

This thesis demonstrates that native tissue repair techniques for POP repair, in particular the Manchester Procedure as a complete repair technique comprising all three vaginal compartments, provide good anatomical and patient reported outcomes with low failure rates both in women with and without LAM avulsions. The need for using synthetic meshes in primary POP surgery is therefore in our opinion non-existent.

In Paper I, the overall five-year reoperation rate for women treated surgically for POP using native tissue repair techniques was only 4.7% and as such very different from the high recurrence risks reported in several previous papers from other research groups. The five-year risk of reoperation in women treated with the Manchester Procedure as a three-compartment procedure was only 2.8%, significantly lower than for women treated with one- or two compartment procedures (partial repairs). Furthermore, the cumulative risk of reoperation was also significantly lower in the Manchester Procedure group, with a decreasing rate over the years.

On short-term follow-up after the Manchester Procedure, the one-year failure rate was very low (1-2%) for all groups of women, both the heterogenous group in Paper I and the selected groups with and without LAM avulsions in Paper III and Paper IV.

Subjective satisfaction, defined as being cured or improved from the prolapse bother, was excellent at one-year follow up after all native tissue repair techniques (Paper I) and in particular after Manchester Procedures (Paper I-IV). Among the total cohort of women treated with native tissue
repair procedures, 93.5 % reported to be cured or improved from their POP symptoms (Paper I). Women tended to be more satisfied after the Manchester Procedure (95%) when compared to partial repairs (90.9%), although this difference did not prove statistically significant. In the selected cohort of women with anterior compartment POP treated with the Manchester Procedure, the subjective cure-rate was similar (96%, Paper III).

Satisfactory anatomical outcomes were obtained at one-year follow-up after native tissue repairs, in particular after the Manchester Procedure. However, whereas the anatomical outcomes were excellent in the mid-compartment, inferior outcomes were found in the anterior compartment. In Paper I, 83.6% of women treated with native tissue repair procedures obtained a maximum POP-Q stage of 0-I in the dominating compartment, and again the outcome being significantly superior after the Manchester Procedure (86.7%) compared to partial repairs (78.3%) (p=0.02). In the prospective MAP-POP study, however, women with primary anterior compartment POP treated with a Manchester Procedure were found to have excellent anatomical results in mid-compartment (99.3% stage 0-I), but not in the anterior compartment (Paper III). But although only 48.6% were registered as having obtained Stage 0-I in the anterior compartment, 87.2% obtained a maximal anterior compartment descent (point Ba) at or above the hymenal level, the most commonly accepted cut-off for optimal anatomical anterior compartment outcome. In support of this, we found that women with point Ba above the hymen tended to have less symptoms of bulging (Paper III).

Sexual outcomes one year after POP surgery turned out to be difficult to evaluate. However, de- novo dyspareunia and sexual outcomes after the
Manchester Procedure were similar to outcomes reported after other native tissue repair procedures. In paper I, the dyspareunia rate was similar after the Manchester Procedure compared to partial repairs, but information on preexisting dyspareunia was lacking. In the MAP-POP study (Paper III) the de novo dyspareunia rate was 5.6% one year after the Manchester Procedure and 51.6% reported improvement or being cured from sexual distress.

This thesis also demonstrates that LAM avulsions are highly prevalent among women with primary anterior compartment POP in need of surgery. Although established as an independent risk factor for POP development, avulsions do not seem to impact baseline symptom load or one-year postoperative anatomical or patient-reported outcomes in women treated with a Manchester Procedure.

In the MAP-POP study LAM avulsions were diagnosed in 50 %, one third being unilateral whereas the rest were bilateral (Paper II and IV). Women with avulsions had more often been delivered by forceps, were older when giving birth to their first child, had lower BMI and were younger when presenting with symptomatic POP. These factors mirror the importance of avulsions in POP development and indicate that LAM avulsions shorten the time-gap between the inciting vaginal birth and development of POP bother.

LAM avulsions were however not associated with pre-or postoperative POP-Q measurements (Paper IV), severity of POP-related symptoms nor sexual dysfunction (Paper II and IV). The only variable associated with preoperative pelvic floor symptoms (PFDI-20 score) was having a chronic disease, causing pain, fatigue or increased intra-abdominal
pressure. Furthermore, the PFDI-20 score at one-year follow-up was only associated with the preoperative PFDI-20 score and a poor one-year anatomical outcome was only associated with having a preoperative anterior compartment prolapse stage \( \geq \) III.
7. RECOMMENDATIONS AND CLINICAL PERSPECTIVES

No consensus exists among vaginal surgeons on how to treat POP in order to obtain low recurrence rates and high patient satisfaction. Especially the treatment of anterior compartment prolapses has proven to be a challenge. The findings of this thesis should in our opinion be used to counsel women properly before POP surgery, offering comforting information on expected excellent subjective outcomes and low recurrence risks.

We hope that this thesis will help convincing our fellow vaginal surgeons that, due to high performance and low complication risks, native repair techniques should be the first choice when treating women with primary POP, at least when not previously treated with a hysterectomy. Our results show that outcomes are especially favorable after the Manchester Procedure as it provides repair of all three compartments. Furthermore, we also hope the thesis will act as an argument for a more limited use of hysterectomy, particularly in the treatment of POP, as the use of cardinal/uterosacral ligament shortening and repositioning performed as part of the Manchester Procedure provide excellent apical suspension. Concerning women with LAM avulsions, we have shown that outcomes are not inferior to women with intact LAM when treated with the Manchester Procedure. We again hope that these findings will convince colleagues that vaginal synthetic meshes have no place in primary POP repair, neither in women with LAM avulsions.

Finally, as POP is a benign condition that should only be treated when symptomatic, our findings support the importance of focusing mainly on patient-reported outcomes. Many papers reporting on POP recurrence still
focus solely on anatomical findings, and we hope and believe that the symptomatic aspect will be given more importance in future research.
8. ERRATA

Reference 93 is a duplication of reference 136.
9. OTHER PUBLICATIONS DURING THE PHD PERIOD

**Oversand SH, Atan IK, Shek KL, Dietz HP**

The association between different measures of pelvic floor muscle function and female pelvic organ prolapse

*Int Urogynecol J, 2015 December; 26(12): 1777-81*

**Oversand SH, Kamisan Atan I, Shek KL, Dietz HP**

The association of urinary and anal incontinence with measures of pelvic floor muscle contractility

*Ultrasound Obstet Gynecol, 2016 May; 47(5):642-5*
10. REFERENCE LIST


66. FDA. FDA issues proposals to address risks associated with surgical mesh for transvaginal repair of pelvic organ prolapse 2014 [Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm395192.htm.]


APPENDICES

APPENDIX I
THE PELVIC ORGAN PROLAPSE QUANTIFICATION (POP-Q) SYSTEM (41, 51)
POP-Q POINTS AND LANDMARKS

(ii) Defined Points. The anatomic position of the six defined points (two on the anterior vaginal wall, two in the superior vagina, and two on the posterior vaginal wall) for measurement should be centimeters (cm) above or proximal to the hymen (negative number) or cm below or distal to the hymen (positive number) with the plane of the hymen being defined as zero (0). For example, a cervix that protruded 3 cm distal to the hymen would be +3 cm. All points are measured on maximal straining (except total vaginal length).

(iii) Anterior Vaginal Wall.
(a) Point Aa. A point located in the midline of the anterior vaginal wall three (3) cm proximal to the external urethral meatus. By definition, the range of position of Point Aa relative to the hymen is -3 to +3 cm.
(b) Point Ba. A point that represents the most distal (i.e., most dependent) position of any part of the upper anterior vaginal wall from the vaginal cuff or anterior vaginal fornix to Point Aa. By definition, Point Ba is at -3 cm in the absence of prolapse and would have a positive value equal to the position of the cuff (Point C) in women with total uterine prolapse or post-hysterectomy vaginal eversion.

(iv) Superior Vagina. These points represent the most proximal locations of the normally positioned lower reproductive tract. The two superior sites are as follows:
(c) Point C. A point that represents either the most distal (i.e., most dependent) edge of the cervix or the leading edge of the vaginal cuff (hysterectomy scar) after total hysterectomy.
(d) Point D. A point that represents the location of the posterior fornix in a woman who still has a cervix. It is included as a point of measurement to differentiate suspensory failure of the uterosacral-cardinal ligament "complex" from cervical elongation. When the location of Point C is significantly more positive than the location of Point D, this is indicative of cervical elongation which may be symmetrical or eccentric. Point D is omitted in the absence of the cervix.

(v) Posterior Vaginal Wall.
(e) Point Ap. A point in the midline of the posterior vaginal wall three (3) cm proximal to the hymen. By definition, the range of position of Point Ap relative to the hymen is -3 to +3 cm.
(f) Point Bp. A point that represents the most distal (i.e., most dependent) position of any part of the upper posterior vaginal wall from the vaginal cuff or posterior vaginal fornix to Point Ap. By definition, Point Bp is at -3 cm in the absence of prolapse and would have a positive value equal to the position of the cuff in women with total post-hysterectomy vaginal eversion.

(vii) Other Landmarks and Measurements.
(g) The genital hiatus (GH) is measured from the middle of the external urethral meatus to the posterior margin of the hymen.
(h) The total vaginal length (TVL) is the length of the vagina (cm) from posterior fornix to hymen when Point C or D is reduced to its full normal position. [See Figure 46 - Appendix].
(i) The perineal body (PB) is measured from the posterior margin of the hymen to the mid-anal occlusus.
POP-Q STAGES

Stage 0: No prolapse is demonstrated.
Stage I: Most distal portion of the prolapse is more than 1cm above the level of the hymen.
Stage II: The most distal portion of the prolapse is situated between 1 cm above the hymen and 1cm below the hymen. FN3. See also Appendix.
Stage III: The most distal portion of the prolapse is more than 1cm beyond the plane of the hymen but everted at least 2cm less than the total vaginal length.
Stage IV: Complete eversion or eversion at least within 2 cm of the total length of the lower genital tract is demonstrated.
APPENDIX 2
THE PELVIC FLOOR DISTRESS INVENTORY SHORT FORM 20 (PFDI-20) (146)
Pelvic Floor Distress Inventory—short form 20

**Instructions:** Please answer all of the questions in the following survey. These questions will ask you if you have certain bowel, bladder, or pelvic symptoms and, if you do, how much they bother you. Answer these by putting an X in the appropriate box or boxes. While answering these questions, please consider your symptoms over the last 3 months.

The PFDI-20 has 20 items and 3 scales. All items use the following format with a response scale from 0 to 4.

<table>
<thead>
<tr>
<th>Do you ________________?</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ No  □ Yes</td>
</tr>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

If yes, how much does it bother you?

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not at all</td>
<td>Somewhat</td>
<td>Moderately</td>
<td>Quite a bit</td>
</tr>
</tbody>
</table>

**Scales**

Pelvic Organ Prolapse Distress Inventory 6 (POPDI-6):

1. Usually experience *pressure* in the lower abdomen?
2. Usually experience *heaviness or dullness* in the pelvic area?
3. Usually have a bulge or something falling out that you can see or feel in your vaginal area?
4. Ever have to push on the vagina or around the rectum to have or complete a bowel movement?
5. Usually experience a feeling of incomplete bladder emptying?
6. Ever have to push up on a bulge in the vaginal area with your fingers to start or complete urination?

Colorectal-Anal Distress Inventory 8 (CRADI-8):

7. Feel you need to strain too hard to have a bowel movement?
8. Feel you have not completely emptied your bowels at the end of a bowel movement?
9. Usually lose stool beyond your control if your stool is well formed?
10. Usually lose stool beyond your control if your stool is loose?
11. Usually lose gas from the rectum beyond your control?
12. Usually have pain when you pass your stool?
13. Experience a strong sense of urgency and have to rush to the bathroom to have a bowel movement?
14. Does part of your bowel ever pass through the rectum and bulge outside during or after a bowel movement?

Urinary Distress Inventory 6 (UDI-6):

15. Usually experience frequent urination?
16. Usually experience urine leakage associated with a feeling of urgency, that is, a strong sensation of needing to go to the bathroom?
17. Usually experience urine leakage related to coughing, sneezing, or laughing?
18. Usually experience small amounts of urine leakage (that is, drops)?
19. Usually experience difficulty emptying your bladder?
20. Usually experience *pain or discomfort* in the lower abdomen or genital region?

**Scale scores:** Obtain the mean value of all of the answered items within the corresponding scale (possible value 0 to 4) and then multiply by 25 to obtain the scale score (range 0 to 100). Missing items are dealt with by using the mean from answered items only.

**PFDI-20 Summary Score:** Add the scores from the 3 scales together to obtain the summary score (range 0 to 300).
APPENDIX 3
THE PELVIC ORGAN PROLAPSE/URINARY INCONTINENCE SEXUAL QUESTIONNAIRE SHORT FORM-12 (PISQ-12) (145)
Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire (PISQ-12)

Instructions: Following are a list of questions about you and your partner’s sex life. All information is strictly confidential. Your confidential answers will be used only to help doctors understand what is important to patients about their sex lives. Please check the box that best answers the question for you. While answering the questions, consider your sexuality over the past six months. Thank you for your help.

1. How frequently do you feel sexual desire? This feeling may include wanting to have sex, planning to have sex, feeling frustrated due to lack of sex, etc.
   - [ ] Always
   - [ ] Usually
   - [ ] Sometimes
   - [ ] Seldom
   - [ ] Never

2. Do you climax (have an orgasm) when having sexual intercourse with your partner?
   - [ ] Always
   - [ ] Usually
   - [ ] Sometimes
   - [ ] Seldom
   - [ ] Never

3. Do you feel sexually excited (turned on) when having sexual activity with your partner?
   - [ ] Always
   - [ ] Usually
   - [ ] Sometimes
   - [ ] Seldom
   - [ ] Never

4. How satisfied are you with the variety of sexual activities in your current sex life?
   - [ ] Always
   - [ ] Usually
   - [ ] Sometimes
   - [ ] Seldom
   - [ ] Never

5. Do you feel pain during sexual intercourse?
   - [ ] Always
   - [ ] Usually
   - [ ] Sometimes
   - [ ] Seldom
   - [ ] Never

6. Are you incontinent of urine (leak urine) with sexual activity?
   - [ ] Always
   - [ ] Usually
   - [ ] Sometimes
   - [ ] Seldom
   - [ ] Never

7. Does fear of incontinence (either stool or urine) restrict your sexual activity?
   - [ ] Always
   - [ ] Usually
   - [ ] Sometimes
   - [ ] Seldom
   - [ ] Never

8. Do you avoid sexual intercourse because of bulging in the vagina (either the bladder, rectum or vagina falling out)?
   - [ ] Always
   - [ ] Usually
   - [ ] Sometimes
   - [ ] Seldom
   - [ ] Never

9. When you have sex with your partner, do you have negative emotional reactions such as fear, disgust, shame or guilt?
   - [ ] Always
   - [ ] Usually
   - [ ] Sometimes
   - [ ] Seldom
   - [ ] Never

10. Does your partner have a problem with erections that affects your sexual activity?
    - [ ] Always
    - [ ] Usually
    - [ ] Sometimes
    - [ ] Seldom
    - [ ] Never

11. Does your partner have a problem with premature ejaculation that affects your sexual activity?
    - [ ] Always
    - [ ] Usually
    - [ ] Sometimes
    - [ ] Seldom
    - [ ] Never

12. Compared to orgasms you have had in the past, how intense are the orgasms you have had in the past six months?
   - [ ] Much less intense
   - [ ] Less intense
   - [ ] Same intensity
   - [ ] More intense
   - [ ] Much more intense

Scoring:

Scores are calculated by totaling the scores for each question with 0=never, 4=always. Reverse scoring is used for items 1.2.3 and 4. The short form questionnaire can be used with up to two missing responses. To handle missing values the sum is calculated by multiplying the number of items by the mean of the answered items. If there are more than two missing responses, the short form no longer accurately predicts long form scores. Short form scores can only be reported as total or on an item basis. Although the short form reflects the content of the three factors in the long form, it is not possible to analyze data at the factor level. To compare long and short form scores multiply the short form score by 2.58 (12/31).
APPENDIX 4
SHORT FORM PHYSICIAN CHECKLIST FOR THE POP SURGERY INTERNAL QUALITY CONTROL REGISTRY, DEPARTMENT OF GYNECOLOGY, OSLO UNIVERSITY HOSPITAL
<table>
<thead>
<tr>
<th>Patient ID.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td></td>
</tr>
<tr>
<td>Procedure</td>
<td></td>
</tr>
<tr>
<td>Surgeon</td>
<td></td>
</tr>
<tr>
<td>Date of Surgery</td>
<td><em><strong>/</strong></em>/___</td>
</tr>
<tr>
<td>Date of Follow-up</td>
<td><em><strong>/</strong></em>/___</td>
</tr>
<tr>
<td>Previous POP Surgery?</td>
<td>No</td>
</tr>
<tr>
<td>Preop. POP-Q Stage</td>
<td>Anterior compartment</td>
</tr>
<tr>
<td>Postop. POP-Q Stage</td>
<td></td>
</tr>
<tr>
<td>Subjective Satisfaction (for POP Bother)</td>
<td>Cured</td>
</tr>
<tr>
<td>Urinary Incontinence DE-NOVO:1 PREEXISTING:2</td>
<td>None</td>
</tr>
<tr>
<td>Urinary Retention</td>
<td>None</td>
</tr>
<tr>
<td>Obstructed Defecation</td>
<td>Not relevant</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>None</td>
</tr>
<tr>
<td>Use of Estrogen</td>
<td>None</td>
</tr>
</tbody>
</table>