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Doctoral thesis

NTNU
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Summary

Background:

The function of levator ani muscle (LAM) is to maintain continence and prevent pelvic organ prolapse (POP). LAM macro trauma is a risk factor for development of POP, a condition with 20 % prevalence in the western world. LAM trauma is also associated with reduced contraction of the LAM, which should be assessed in women with pelvic floor dysfunctions. Several methods can be used for this purpose, but no gold standard exists. Transperineal ultrasound can be used, but the reliability of the method needs further examination. There is a need to improve outcomes after POP surgery due to a high recurrence rate. Pelvic floor muscle training (PFMT) is an effective treatment for mild to moderate POP, but needs further evaluation as an adjunct to surgery.

Aims:

I. To study associations between LAM trauma, POP and contraction in healthy parous women.
II. To examine the reliability of ultrasound for assessment of pelvic floor contraction in women with incontinence, POP and in pregnancy.
III. To explore the effect of preoperative PFMT as a supplement to POP surgery on anatomy, symptoms and contraction after surgery.
IV. To examine the impact of LAM trauma and contraction on anatomy and symptoms after surgery.

Method:

The women were examined with pelvic organ prolapse quantification system (POP-Q), palpation, ultrasound, vaginal manometry, surface EMG and assessment of symptoms using visual analog scale.
I. Cross-sectional study on associations between LAM trauma, POP and contraction.
II. Cross-sectional study on reliability of ultrasound for assessment pelvic floor contraction using intra- and interrater analysis (ICC).
III. Randomized controlled trial on the effect of preoperative PFMT as an adjunct to surgery on outcomes after POP surgery.
IV. Cohort study on the impact of LAM trauma and contraction on outcomes after POP surgery.

Results:

I. We found an association between LAM trauma, POP and impaired contraction. Macro trauma seems to be the main contributor. Women with LAM trauma can still contract.
II. Ultrasound is reliable for assessment of contraction, with moderate correlation to palpation. The best ICC was found for 2D measures. We created an ultrasound contraction scale
III. Contraction, anatomy and symptoms improved for the overall population after surgery but there was no additional effect of preoperative PFMT for the intervention group.
IV. LAM trauma was associated with increased risk of any POP ≥ 2 after surgery. Absent to weak contraction was associated with reduced risk of bulge sensation after surgery.

Conclusion:

LAM macro trauma is associated with POP and impaired pelvic floor contraction. Ultrasound is a reliable method for assessing pelvic floor contraction. POP surgery improves pelvic floor contraction, but there is no additive effect of preoperative PFMT. LAM trauma is associated with anatomical POP after surgery, while absent to weak contraction is associated with reduced risk of bulge sensation.

Sammendrag

Bakgrunn:
Funksjonen til bekkenbunnen er å opprettholde kontinens og unngå descens. Avrivning av levatormuskelen i bekkenbunnen er en risikofaktor for å utvikle urogenital descens, en tilstand som rammer 20% av kvinner i den vestlige verden. Muskelavrivning er også assosiert med redusert kontraksjonsevne i bekkenbunnen. Det er ingen gullstandard for undersøkelse av kontraksjon i bekkenbunnen. Transperineal ultralyd kan benyttes, men reproduserbarheten av ultralydmål trenger ytterligere kartlegging. Tilbakefall av descens etter operasjon forekommer hyppig og det er behov for å bedre utkommet etter slik kirurgi. Bekkenbunnstrening er effektivt behandling av prolaps, men det trengs ytterligere kunnskap om trening som et supplement til kirurgi.

Mål:
I: Studere assosiasjonen mellom levator muskelskade, descens og bekkenbunns kontraksjon
II: Undersøke reprodserbarheten av bruk av ultralydmål som verktøy for å bedømme bekkenbunns kontraksjon
III: Undersøke effekten av preoperativ bekkenbunnstrening på anatomi, symptomer og kontraksjon etter kirurgi.
IV: Studere betydningen av levator skade og kontraksjonsevne for anatomi og symptomer etter kirurgi.

Metode:
Kvinnene ble undersøkt for anatomisk descens (POP-Q), palpasjon, transperineal ultralyd, vaginal trykkmåling, overflate EMG og visuell analog skala.
I: Tverrsnitts-studie av sammenhengen mellom levator skade, descens og kontraksjonsevne
II: Tverrsnitts-studie på reproduserbarhet av ultralydmål for å bedømme kontraksjon
III: RCT på effekt av bekkenbunnstrening som supplement til kirurgi på anatomi, symptomer og kontraksjon etter kirurgi.
IV: Kohort-studie på betydningen av levator skade for anatomi og symptomer etter kirugi.

Resultater:
I: Det er en sammenheng mellom levatorskade, descens og bekkenbunnskontraksjon
II: Ultralydmål for å bedømmelse av bekkenbunnskontraksjon er pålitelige, med god reproduserbarhet. De beste resultatene fant vi for prosentvisendring i 2D-ultralydmål av levatorhiatus fra hvile til kontraksjon.
III: Kontraksjonsevne, anatomi og symptomer bedret seg etter kirurgi, men det var ingen tilleggseffekt for kvinner som trente bekkenbunnen før operasjonen.
IV: Levatorskade var assosiert med økt risiko for POP-Q$\geq$ 2 etter operasjonen, mens ingen eller svak kontraksjonevnen var assosiert med redusert risiko for symptomer i form av kulfølelse.

Konklusjon:
Kvinner med levatorskade har redusert bekkenbunnskontraksjon sammenlignet med kvinner med intakt muskel, og den største bidragsyteren til svekket kontraksjonsevne synes å være avrivning av muskelen. Ultralydmål for å vurdere kontraksjonsevvne har god reproduserbarhet. Vi har utviklet en skala for å bedømme kontraksjonsevne. Kontraksjonsevnen bedres etter framfallsoperasjon, men preoperativ bekkenbunnstrening gir ingen tilleggseffekt. Avrivning av levator er en risikofaktor for anatomisk descens etter operasjon, mens redusert kontraksjonevne i bekkenbunn gir en redusert risiko for symptomer etter kirurgi.

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I Association between pelvic floor muscle trauma and contraction in parous women from the general population

II Ultrasound assessment of pelvic floor muscle contraction: reliability and development of an ultrasound-based contraction scale

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IV Impact of levator ani muscle trauma and pelvic floor muscle contraction on recurrence after pelvic organ prolapse surgery

Abbreviations

2D	Two dimensional
3D	Three dimensional
4D	Four dimensional
ANCOVA	Analysis of covariance
aOR	Adjusted odds ratio
AP	Anteroposterior
BMI	Body Mass Index
CI	Confidence interval
EMG	Electromyography
ICC	Intraclass Correlation coefficient
MOS	Modified Oxford scale
MRI	Magnetic resonance imaging
MVC	Maximum voluntary contraction
OR	Odds ratio
PFD	Pelvic floor disorder
PFMT	Pelvic floor muscle training
POP	Pelvic organ prolapse
POP-Q	Pelvic organ prolapse quantification
POP-Q ≥ 2	Pelvic organ prolapse equal to or larger than stage two
SD	Standard deviation

1 Introduction

In my period as an intern after medical school I was introduced to the field of urogynecology by an experienced gynecologist looking for assistance in the operation theater. This was an eye-opener. I was amazed by the history of these women, the condition itself and not least I found the surgical technique appealing. After ended internship, I started as a resident in obstetrics and gynecology, and my interest and fascination for urogynecology continued. I was lucky to end up at the section for urogynecology at St. Olavs hospital in Trondheim, surrounded by inspirational gynecologists full of knowledge and commitment, with a goal of providing the best possible care for women with pelvic floor dysfunctions.

The evaluation and treatment of women with pelvic floor dysfunctions is complex and time consuming, dealing with conditions with major influence on the individual woman's life and great impact for society.[1] The term pelvic floor dysfunction involves a wide spectrum of conditions including pelvic pain, urinary- and anal incontinence, sexual dysfunctions and pelvic organ prolapse (POP). In the field of urogynecology the focus is mainly on women presenting with POP and urinary incontinence. The lifetime risk for undergoing surgery for POP or urinary incontinence is 1 in 5 women at age 80 in the Western world.[2] In addition to this, many women are treated with conservative methods, so the prevalence of the conditions is ever higher.[3]

The anatomy of the female pelvis is complex and several structures interact to maintain continence and prevent pelvic organ descent.[4, 5] In addition to connective tissue and the bony pelvis, the pelvic floor muscle plays a crucial role.[6, 7] The function of the muscle is important both at relaxation and during contraction.[4]

There are several known risk factors for development of POP and levator ani muscle (LAM) macro trauma is one of them.[8-10] Obstetric LAM trauma is seen in up to 20 % of cases after vaginal delivery.[11-13] LAM trauma is also associated with reduced contraction of the pelvic floor[6, 14-19], and symptomatic pelvic floor dysfunction postpartum.[6] Impaired pelvic floor function is also associated with development of POP.[20, 21] Most studies on pelvic floor function and LAM trauma are conducted in populations of women postpartum or with previously diagnosed pelvic floor disorders.[16-18, 21] We found no previous studies focusing on a possible association between pelvic floor muscle contraction and LAM trauma in parous women from the general population.

There are several methods used for direct and indirect assessment of pelvic floor muscle contraction available in the clinical setting, including vaginal palpation of the levator muscle, vaginal manometry and electromyography (EMG), but there is no evidence-based gold standard.[22-26] Imaging of the pelvic floor was initially conducted using magnetic resonance imaging (MRI) for describing the LAM and hiatal dimensions.[27-30] Recently, ultrasound has become an easy, low cost and minimally invasive method.[31-33] Studies have demonstrated moderate correlation between MRI and ultrasound measures,[34,35] and today ultrasound is the preferred method used in a clinical setting. When it comes to assessing pelvic floor contraction with ultrasound, however, further research is needed to examine which measurements are most reliable in a clinical setting.

The recurrence rate after primary surgery up to 36 %, and many women need more than one procedure.[36] There is a need to identify ways to improve the outcome of POP surgery. Surgery for POP includes an arsenal of different procedures, and the techniques and terminology varies in the surgical community.[37, 38] One can divide the procedures in to different sub-categories, such as native repair and procedures including synthetic mesh. The use of vaginal mesh is controversial, and its use is decreasing due to high profile medico-legal cases and products being withdrawn from the marked.[39, 40]

Conservative treatment with intensive pelvic floor exercise has been proven to be effective for prevention and treatment of POP.[41-43] LAM trauma is a risk factor recurrence after primary surgery.[36] In addition, a study has shown that a diminished contraction also is associated with recurrence after primary surgery.[44]

A Cochrane review from 2018 showed no benefit of peri-operative pelvic floor exercise, but the results were based on small studies and the intervention was mainly performed postoperatively.[45] This shows lack of evidence on the effect of preoperative optimization of the pelvic floor muscles on contraction, recurrence and symptoms after surgery.

This raises four main research questions

1. Is there an association between levator ani muscle trauma and impaired muscle contraction?
2. Is ultrasound a reliable method for evaluation of pelvic floor muscle contraction?
3. Can a combination of conservative treatment and surgery improve the results of POP surgery?
4. Can pelvic floor contraction and pelvic floor muscle trauma impact recurrence rates after prolapse surgery?

The following thesis aims to use our research to contribute to answering these questions.

2 Background

2.1 Functional anatomy

2.1.1 General anatomy and physiology of skeleton muscle

Whilst skeletal muscles in the human body have differences in anatomy custom to function,[46] there are several common defining features. Skeletal muscles consist of muscle fibers joint together in fascicles, and muscle fibers are the smallest anatomical unit with the potential to contract. In skeletal muscle the fibers have a motoric end-plate. The motoric unit is the smallest functional element and consists of a motoric neuron, the axon of the neuron and the muscle fiber that is innervated by the neuron. A discharge of a motor neuron causes an interaction between myosin and actin filaments, forming cross-bridges and initiating a cascade of molecular events. The end-point of this cascade is a contraction in the muscle fibers connected to the neuron.[47]

2.1.2 The bony pelvis

The anatomy of the female pelvis is complex and the function depends on an intricate interaction between bony structures, muscles and connective tissue. The bony structures are arranged in a circular pelvic girdle and functions as anchor point for ligaments, tendons and muscles. In addition, the bones protect the pelvic organs from exterior trauma.[48] The bone structure consists of two halves, which are made up of a fusion between the ilium, the ischium and the pubic bone. Posteriorly the halves are fused to the sacrum, and anteriorly they are connected to each other through the pubic symphysis.[49]

The anterior tilt of the pelvis contributes to a minimal load on the pelvic floor as the gravity effect from the abdominal and pelvic organs is placed on the bony part of the pelvis instead of the soft pelvic floor, see Figure 1. Women without a spinal lordosis will have a less pronounced pelvic tilt and have a higher risk of POP development.[50] The pelvis consists of two portions: the major pelvis which contains the abdominal organs and the minor pelvis which contains the genital organs and rectum. The pelvic outlet is closed in the minor pelvis by the pelvic floor, see Figure 2.[49]

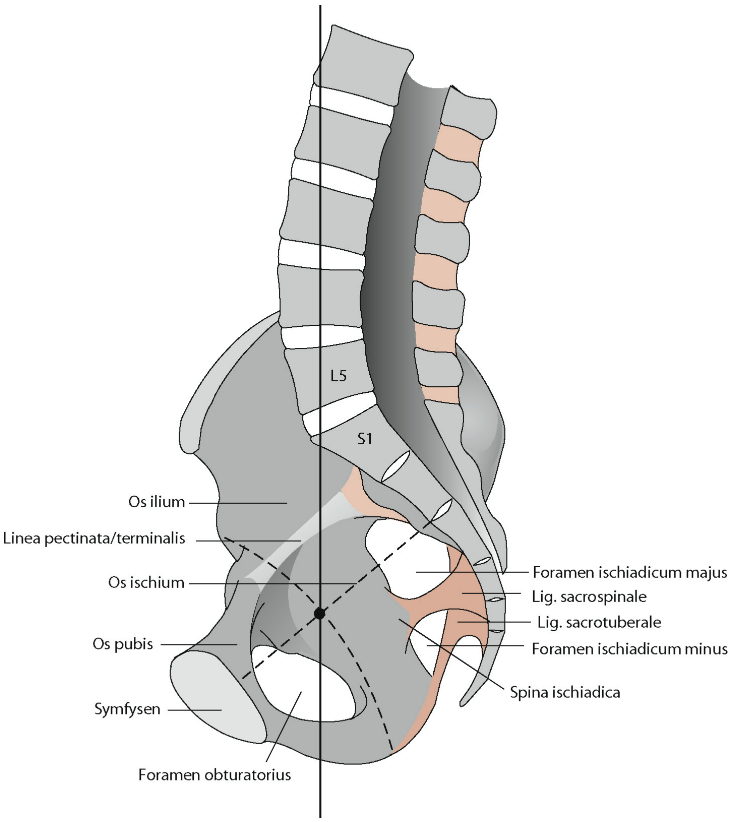


Figure 1 The bony pelvis with ligaments. With permission from illustrator Lena Lyons and Studentlitteratur.

2.1.3 Pelvic floor muscles

Large parts of the inside of the pelvis is covered with muscle; the obturatorius-, piriformis- and coccygeus muscles (Figure 2).[48]

The levator ani muscle (LAM) forms a diaphragm, the pelvic floor, over the pelvic outlet and is inserted to the bony structures through arcus tendinous laterally (Figure 2) and consists of ileococcygeus and pubovicerale muscle. The pubovicerale muscle again consists of the puborectalis- and the pubococcygeus muscle (Figure 3).[4]

The puborectalis sling is inserted on the pubic bone and the anterior part of arcus tendinous, and defines the levator hiatus (Figure 3).[48, 51] Urethra, vagina and rectum passes through the levator hiatus, which is also referred to as the body´s largest hernia port.[52]

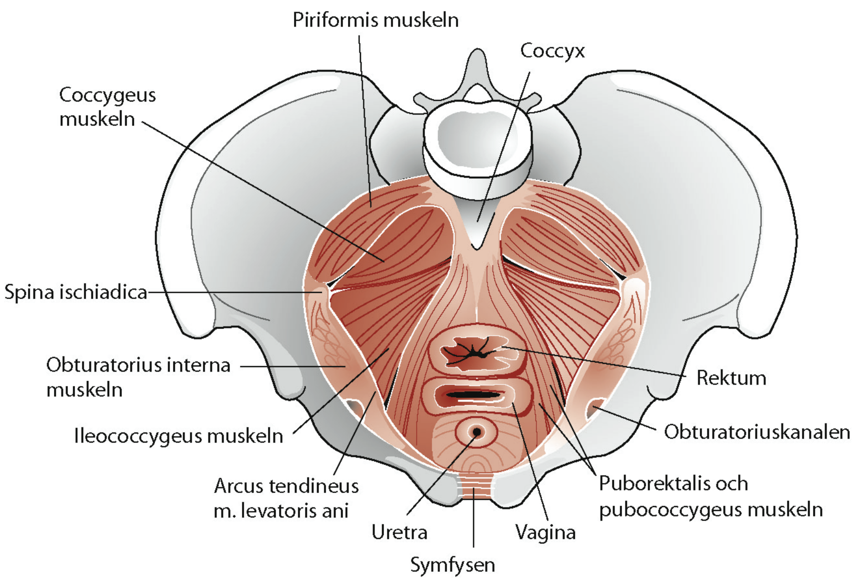


Figure 2 The muscles of the pelvic floor. With permission from illustrator Lena Lyons and Studentlitteratur.

Women with intact pelvic floor muscle and support will, in an upright position have a vagina that extends almost horizontally, resting on the LAM.[4, 49] At contraction the diaphragm lifts cranial and forms a horizontal plate.[5]

Leakage of urine, feces and flatus is prevented when urethra, rectum and vagina are compressed against this plate during contraction.[5] The contraction is usually a response to increased intraabdominal pressure. In addition, the plate also facilitates emptying of urine and feces by funneling at relaxation.[48]

When the levator is damaged, the support is lost, and the vagina is angled more vertically. An increase in the intrabdominal pressure will then result in protrusion of nearby organs through the levator hiatus resulting in a pelvic organ prolapse (POP).[53]

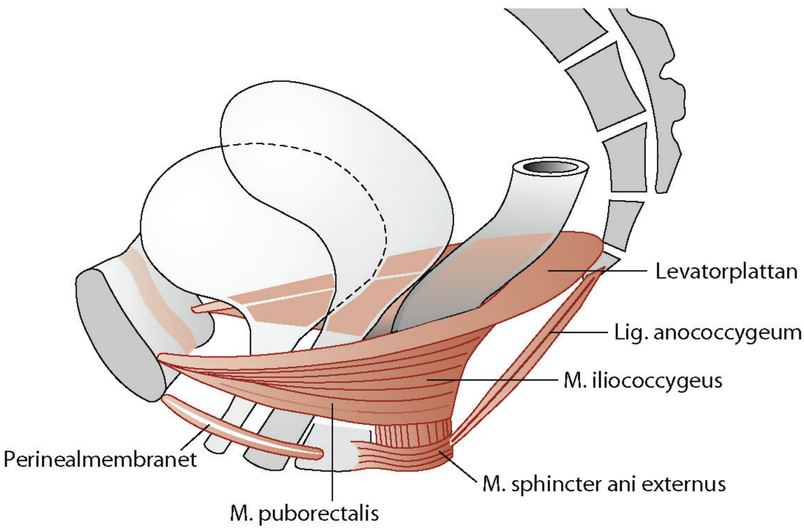


Figure 3 The levator ani muscle. With permission from illustrator Lena Lyons and Studentlitteratur.

2.1.4 Connective tissue

The tissue surrounding the bony pelvis, muscles and viscera is called the endopelvine fascia, anchoring the organs in the pelvic.[48] The fascia is pliable and consists of smooth muscle, elastin, collagen, adipose tissue, nerves and vessels. Included in the endopelvine fascia are structures such as the infundibulopelvicum- and the cardinal ligament, supplying organs with innervation and vessels, as well as the sacrouterine and the pubourethral ligaments, whose main function is to keep the pelvic organ in place.[4]

In the minor pelvis the fascia is formed as a membrane (the urogenital diaphragm) and functions as suspension for the vagina and distal urethra (Figure 4).[48] This membrane includes the bulbocavernosus muscle, ischiocavernosus muscle and the superficial transverse perineal muscles, and supports the anterior portion of the pelvic floor. They insert at the perineal body, an important structure in the pelvic floor, frequently damaged during vaginal delivery.[4, 48]

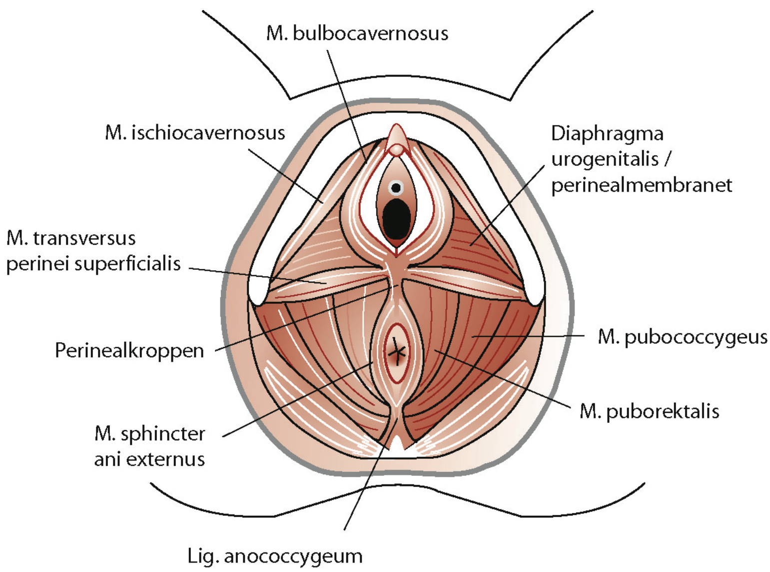


Figure 4 The urogenital diaphragm. With permission from illustrator Lena Lyons and Studentlitteratur.

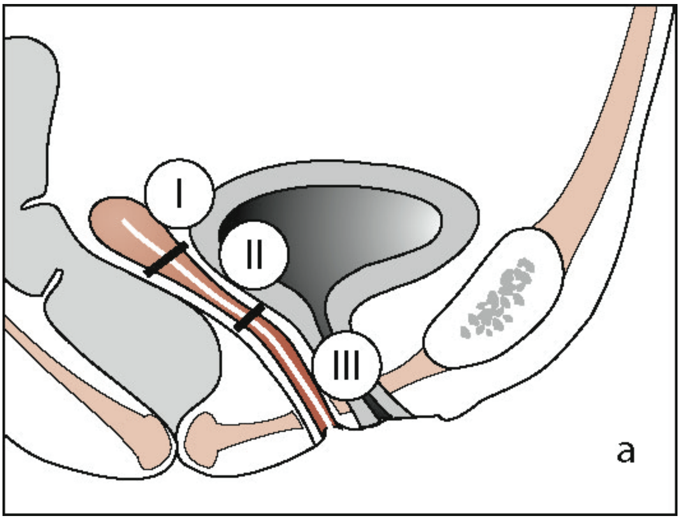
There are three levels of connective tissue support in the pelvis[4, 54, 55] (Figure 5):

I Proximal support of the vagina: sacrouterine and cardinal ligaments

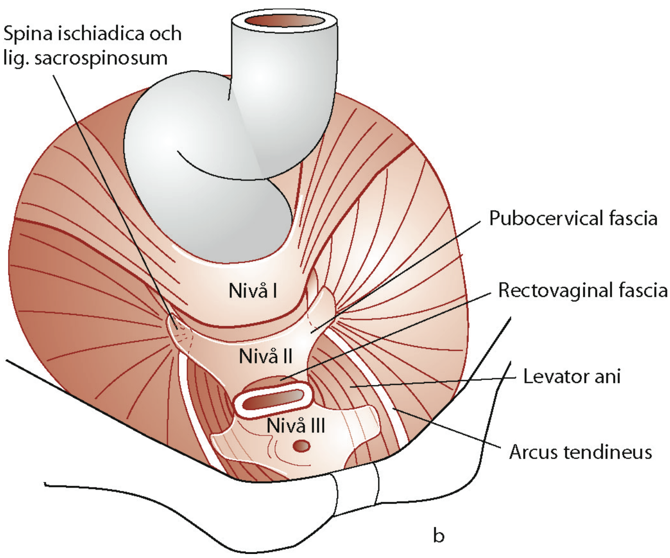
II Middle support of the vagina: arcus tendinous fascia and the fascia of the levator ani muscle

III Distal support of the vagina and urethra: perineal body, urogenital diaphragm and paraurethral connective tissue

Figure 5 The levels of vaginal support after the model of DeLancey. With permission from illustrator Lena Lyons and Studentlitteratur.



a) Levels of support in sagittal view



b) Levels of support seen from above with supportive tissue.

2.1.5 Innervation of the pelvic floor

The pelvic organs and the pelvic floor muscles are innervated by the para-sympathic and sympathic pathways originating from the presacral plexus in addition to somatic nerves. The pudendal nerve contains fibers from all these systems.[48] This nerve innervates the anal sphincter complex, the LAM and the perineal muscles. The sensory fibers are sensitive to tension, pressure and temperature in the vagina and perineum.

2.1.6 Changes to the pelvic floor during pregnancy and delivery

Pregnancy and delivery cause changes in most organ systems including the pelvic floor. During vaginal delivery the muscle fibers can stretch over 130-150% of their original length,[56, 57] which can damage the sarcomeres in the muscle fibrils. Trauma to the LAM are described after delivery and can be detected by ultrasound or palpation.[58] LAM trauma is divided into macro trauma (avulsion) or micro trauma (pathological distention of the levator hiatus). Macro trauma is detected in 10-35% of women after vaginal delivery,[11-13, 59-61] and the prevalence is even higher after forceps delivery.[62] LAM macro trauma is never seen after cesarean section.[62] There is, however, some healing of LAM trauma after delivery.[63] In addition to the increased risk of LAM trauma, there is a risk for a obstetric injury to the anal sphincter complex, which is seen clinically in up to 11% after delivery.[64] Sonographic detected anal sphincter tears are seen in up to 30%.[65]

Vaginal delivery is a known risk factor for developing pelvic floor dysfunction such as urinary incontinence and/or POP.[66, 67] There is, however evidence indicating that the pregnancy itself has an impact on the support of the pelvic organs.[68, 69]

In addition to the muscle, the pudendal nerve is exposed to massive stretch during delivery. It may stretch up to 35 %, and stretching more than 15 %, has been shown to give permanent damage.[70] In addition, the connective tissue structures are damaged.

2.1.7 Ageing of the pelvic floor

Around fifty percent of postmenopausal women experience symptoms of POP or incontinence,[71] and age seems to play a major role in development of POP.[72] With an increasing life expectancy, the burden of pelvic floor disorders on health care systems will increase.[73] Muscle fibers undergo an aging process that can be explained by several factors. Systemic changes in blood flow and innervation to the fibers leads to atrophy and decrease in function of the fibers. Hormonal changes related to old age also leads to atrophy.[74] Local stem cells ("satellite cells") can start regeneration as a response to injury and they are responsible for general maintenance by replacing cells that are damaged due to normal activity. The ability to regenerate damaged tissue, however, decreases over the years, mostly due to structural and biochemical changes.[75] These factors together leads to a general loss of muscle bulk and function, and the striated muscle has reduced strength and contractility in elderly women compared to younger.[75, 76]

Endocrine status, and reduction in levels of estrogen in particular, have been associated with development of pelvic floor dysfunction. Estrogen receptors are identified in connective tissue and smooth muscle cells in the pelvic floor.[77] One suggested mechanism is the decrease in collagen content in the pelvic floor due to a decrease in estrogen levels, as the collagen is estrogen dependent.[78, 79] There is, however, limited evidence on the use of estrogens for prevention and treatment of POP, and further research is needed.[80]

2.2 Clinical examination of the urogynecology patient

2.2.1 General considerations

When assessing an urogynecological patient, the main focus should be on the macro anatomy during a gynecological examination and the clinical decisions should be based on anatomical findings. In the last decades, evaluation of what is hidden behind the prolapse and deeper lying structural abnormalities, have become more defined and important. The joint committee of the International Continence Society (ICS) and the International Urogynecology association (IUGA) has recommend assessment of the pelvic floor muscles as a part of a general examination.[22] There are several methods available for direct and indirect assessment of these muscles i.e. palpation, ultrasound, vaginal manometry and EMG, however, no gold standard exists.[25]

2.2.2 *Pelvic organ prolapse grading*

ICS has published a Pelvic Organ Prolaps Quantification score (POP-Q) for assessment and staging of pelvic floor dysfunction.[81] In this system the distance from the hymen is measured at fixed points in each compartment, as well as the genital hiatus, total vaginal length and the perineal body. Points protruding throug the hymen are positive and points proximal to the hymen are negative (Figure 6).

The staging of prolapse is based on these measurements:

Stage 0: Point above -3 cm, C and D are between TVL and TVL-2

Stage 1: Point above -1 cm

Stage 2: Point between -1 and 1 cm

Stage 3: Point above + 1 cm

Stage 4: Complete eversion, the leading point is the cervix or the vaginal cuff.[81]

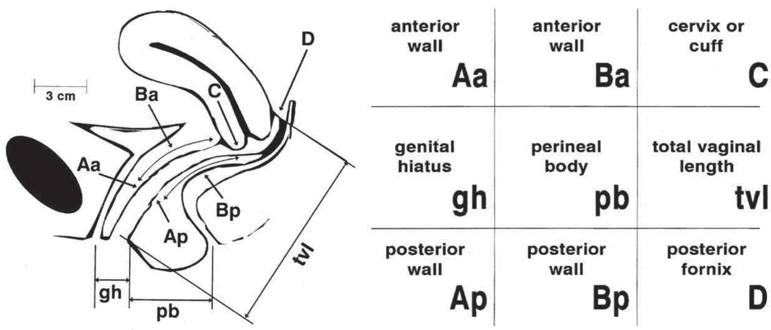


Figure 6. Model of points included in pelvic organ prolapse quantification systems and compartments they represent. In addition to the points for anterior, central and posterior compartments, three lengths are included; measuring the genital hiatus, the perineal body and the total vaginal length. From Bump et al 1996, with permission from Elsevier.

2.2.3 Assessment of contraction

Traditionally the assessment of pelvic floor contraction has been done by palpation. In addition, vaginal manometry and EMG have been used mainly by physiotherapists in research settings. The different methods have their advantages and disadvantages, and there is no gold standard for assessing contraction today, despite international recommendations that it should be done in women with pelvic floor disorders.[22, 25]

Function of the pelvic floor has been described by many different terms in the academic and clinical settings. In this work we have based the terminology on the ICS definitions:

Muscle action characteristics – maximum voluntary contraction (MVC):
"The attempt to recruit as many fibers in a muscle as possible for the purpose of developing force. MVC of the pelvic floor can be assessed by vaginal palpation, manometers, and dynamometers."[26]

Pelvic floor muscle strength:
"Force-generating capacity of a muscle. It is generally expressed as maximal voluntary contraction measurements and as the one repetition maximum (1RM) for dynamic measurements."[82]

Palpation

Intravaginal palpation of the levator ani muscle complex includes assessment of resting tone, integrity, identifying potential tears and evaluation of muscle strength. There are several scales for evaluating contraction. The most widespread scale for evaluating strength by palpation is the 6-point Modified Oxford scale ranging from 0-5 (Tabel 1).[23] .

Grade		Description
0	Absent	Muscle not palpable
1	Flicker	Minimal resistance, flaccid
2	Weak	Some resistance to distension
3	Moderate	Hiatus narrows to some extent
4	Good	Hiatus narrows, musle can be distended
5	Strong	Hiatus very narrow, no distension

Table 1 The Modified Oxford scale, as described by Laycock.

Other scales are the Brink scale and the PERFECT scheme.[83, 84] The Brink scale assess strength, pressure and duration on a 12-point scale and the PERFECT scheme assess strength, endurance, timed repetitions and fast contraction.[23, 83, 84]

Palpation is usually performed with 2 fingers at the level of the LAM aproximately 4 cm into the vagina. If there is an abnormal insertion of the muscle on the pubic bone, this can be detected by palpation. LAM trauma can also be detected with imaging using MRI or transperineal ultrasound. Correlation analysis has shown moderate correlation between palpation and imaging.[58]

Palpation is dependent on the experience of the examiner. Grading is dependent on personal opinion, and studies have showen that the method is poorly reproducible when assessing contraction.[85, 86] When assessing trauma, however, the reproducibility is acceptable, and improves with training.[87, 88]

Palpation also includes assessment of muscle resting tone and tenderness. This is scored on a 6-point scale; 0= not palpable, 1= palpable, wide hiatus and minimal resitance, 2= wide hiatus, but restistace, 3= more narrow hiatus, easy to streach, 4= narrow hiatus, streachable, no pain, 5= very narrow hiatus, pain, not possible to streach.[89]

Vaginal manometry

Vaginal manometry, or perineometry, is a frequently used method to assess strength in the pelvic floor and endurance.[26] A vaginal sensor is placed in the vagina, and the vaginal squeeze pressure is measured in mmHg or cm H_2O. Publications have shown that the method is reliable and valid and correlates moderate to other methods for assessing contraction.[90] There are, however, sources of error,[25] such as the influence of increased abdominal pressure on the pressure measured in the vagina, and contraction of the gluteal muscles and proximal muscles in the under-extremities.

Electromyography

Activity in the pelvic floor muscles can be detected using surface electromyography (sEMG). These electrodes record changes in voltage at contraction (where a high value indicates high activity levels) via vaginal surface probes or deeply placed needles.[91] One study has shown that the method is reliable for assessment of muscle activity in healthy women, [92] but there are sources of error and one of them is the lack of ability to discriminate between muscle groups (for example if the women contracts the gluteal muscles).[25]

2.2.4 Ultrasound

Transperineal ultrasound is performed with a curved array transducer covered with gel and a glove, in the sagittal plane between the labia majora.[31] The acquisition angle should be set as wide as possible, and conventionally at 85° to include all important structures in the image.[32]

The first image for evaluation is the two-dimensional image of the minor pelvis with organs in the mid-sagittal plane (Figure 7) which provides information on the different compartments and functional information regarding displacement of organs during pelvic floor contraction or Valsalva.[33] This examination will reveal the anatomical structures concealed in a prolapse.

For evaluation of the levator hiatus the three/four-dimensional function is used. It provides information on the pelvic floor in sagittal, coronal and axial planes. In addition, the rendered volume provides information on the hiatal dimensions.[93] The real time function of four-dimensional ultrasound gives the opportunity of evaluation functional anatomy in a recorded volume.[32] To assess the levator muscle complex tomographic ultrasound imaging is used (see below).

The plane of minimal hiatal dimensions is where one can find the shortest distance between the symphysis pubis and the medial portion of the puborectalis muscle. This is used as a reference plane in transperineal ultrasound.[93]

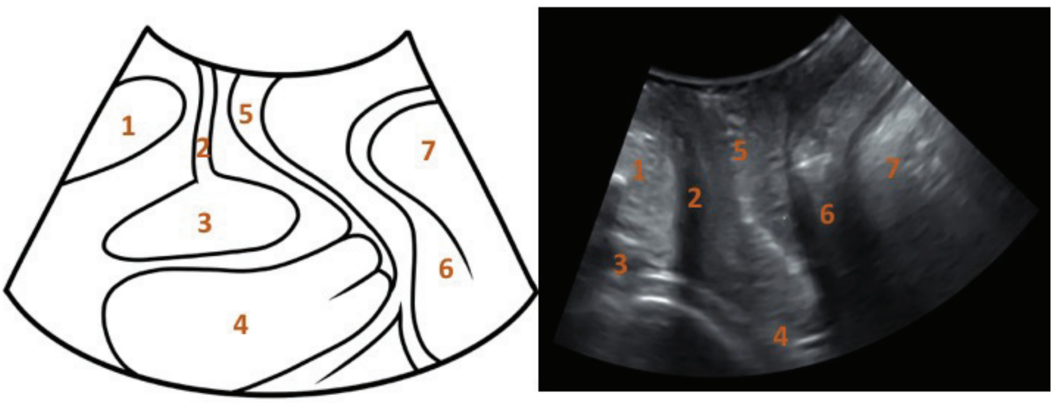


Figure 7. Schematic drawing of the image obtained from 2D transperineal ultrasound in midsagittal view with marked structures and an ultrasound image. 1: symphysis pubis, 2: urethra, 3: bladder, 4: uterus with cervix, 5: vagina, 6 rectum, 7: puborectalis muscle. Illustration: Oda Fredrikke Mebust Øyasæter

Sonographic LAM trauma is divided into two groups:

1. **Micro trauma;** often referred to as ballooning on Valsalva (Figure 8). Micro trauma is an irreversible overdistention of the levator hiatus.[52] The following classification has been suggested: *mild*; 30-34.9 cm^2, *moderate*; 35-39.9, *severe*; $\geq$ 40 cm^2.[94] For proper assessment of the levator area, a woman needs to perform a maximal Valsalva of 6-8 seconds duration.[95]

2. **Macro trauma;** in some publications referred to as avulsion (Figure 9). The volumes are acquired at contraction. After identification of the plane of minimal hiatal dimensions, the TUI mode is used with 2.5 mm inter slice interval. An avulsion is diagnosed when there is a discontinuity between the muscle and the bony pelvis in the three central slices in one or both sides.[58] The trauma can be either uni- or bilateral.

In the last decade several studies have been published regarding sonographic evaluation of pelvic floor muscle function. The reliability of ultrasound and correlation to conventional methods are described as good.[24, 96-102] In these studies different modalities (Two/three-dimensional ultrasound) have been used in addition to different measurements (levator hiatal dimensions, bladder neck descent and vectors). There is no international consensus or standardized ultrasound scale regarding LAM contraction and the terminology is disputed. In this thesis, the term pelvic floor contraction is used.

Ultrasound is an objective evaluation of pelvic floor contraction and is more sensitive in detecting contraction than palpation (Figure 10).[24] A scale for assessment of contraction has been suggested based on the general population, but it is not validated on a patient population.[24] Another advantage of ultrasound is the ability to use the method for teaching and biofeedback as many women perform contraction using accessory muscles or do concomitant Valsalva manouvres.[103]

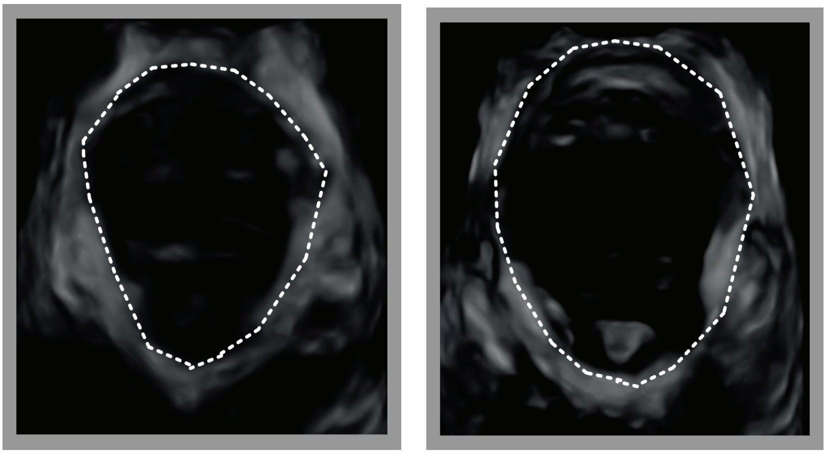


Figure 8 Levator ani micro trauma illustrated in 3D rendered volume. To the left a normal levator hiatus at Valsalva, to the right a pathological distended hiatus at Valsalva. Illustration by M. Ø. Nyhus.

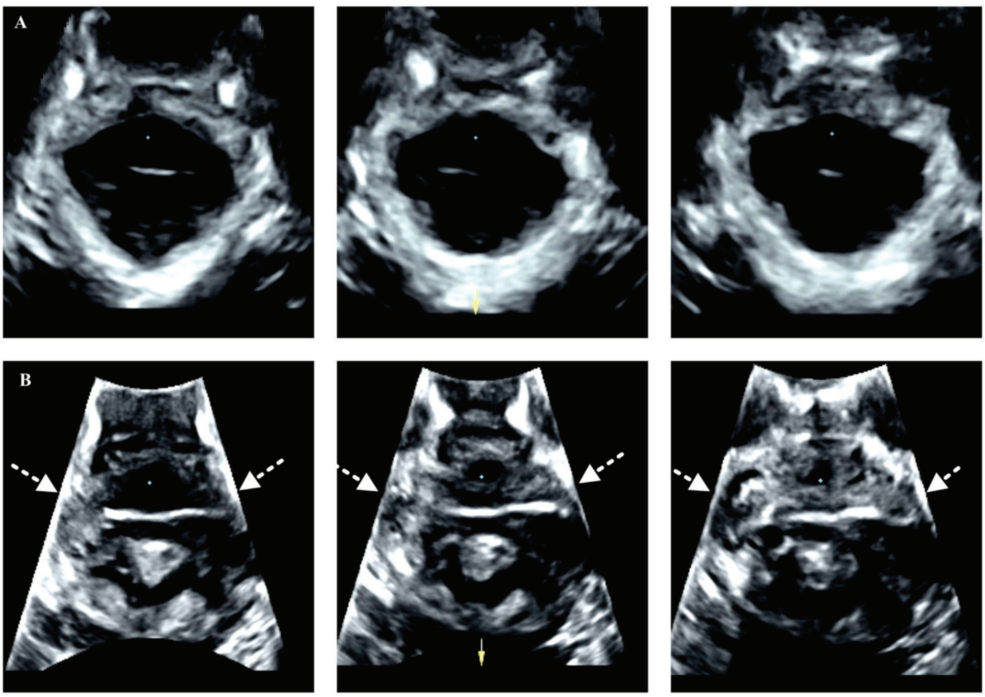


Figure 9 Intact levator ani muscle at the three central slices using tomographic ultrasound imaging: at the level of minimal hiatal dimensions, 2.5 and 5.0 mm above (A).

Bilateral levator ani macro trauma illustrated with arrows in the three central slices (B). With permission from Wiley.

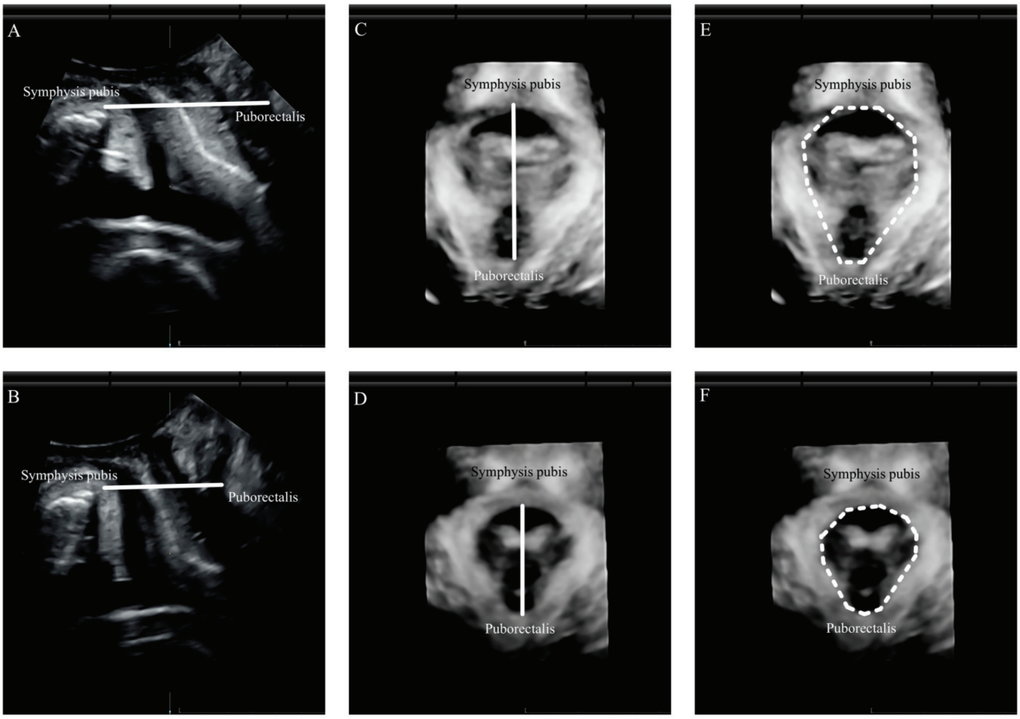


Figure 10. Quantification of pelvic floor contraction using transperineal ultrasound. Measurements of the levator hiatal anteroposterior diameter from the inferior margin of the symphysis pubis to the medial margin of the musculus puborectalis in 2D at rest (A), at contraction (B) and in 3D at rest (C) and contraction (D). Hiatal area at rest (E) and contraction (F). With permission from Wiley.

2.2.5 Magnetic resonance imaging (MRI)

MRI has been used for evaluation of the pelvic floor and is suggested as a tool providing valuable information prior to POP surgery.[104, 105] Correlation analyses for different measures of LAM biometry have shown moderate correlation.[34, 35] Currently it is used mostly in research, due to low availability, time consumption and high costs.

2.3 Pelvic floor dysfunction

2.3.1 Pelvic floor dysfunction in general

Pelvic floor dysfunction is a collective term that includes urinary- and anal incontinence, bladder storing symptoms, voiding difficulties, POP, sexual dysfunctions and pelvic pain.[106] These conditions are associated with taboo and stigmatization. The etiology behind pelvic floor dysfunction is multifactorial, and can be categorized into 4 groups:[55, 107]

1. **Predisposing:** heredity, structural, environment
2. **Inciting:** pregnancy, delivery, muscle trauma, surgery, radiation
3. **Promoting:** chronic increased abdominal pressure due to constipation, heavy lifting, lung disease, obesity
4. **Decompensating:** age, disease, medication

To prevent development of POP and maintain continence, we are dependent on a delicate interaction between structures in the pelvis. In 1993, Norten published “the boat in dry dock” theory, explaining the interaction between these structures (Figure 11).[108]

The boat represents the pelvic organs and the water the pelvic floor muscles. When the support from the water disappears, the boat hangs in the mooring. When a trauma appears in the pelvic floor muscles, the pelvic organs hang in the ligaments and fascia, causing weakening over time.

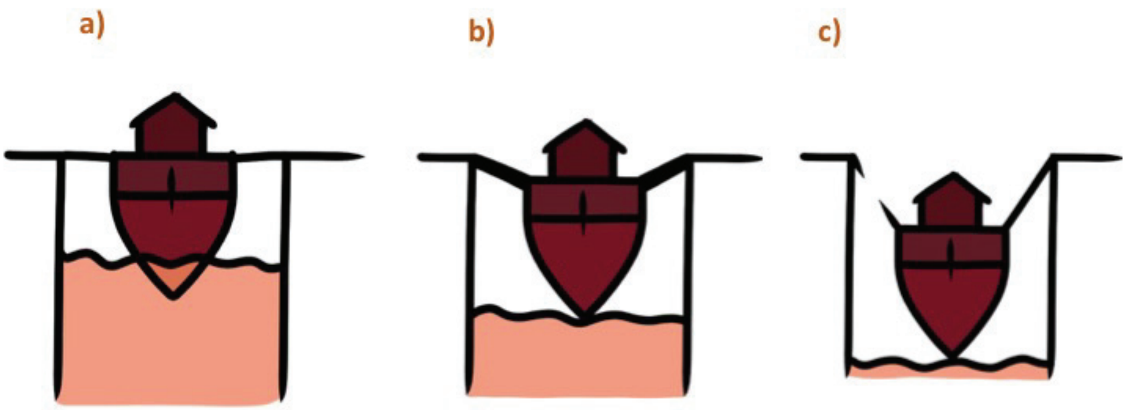


Figure 11. Illustration of “The Boat in dry dock”- theory as described by Norton. a) Good support from the pelvic floor. b) Minimal support from the pelvic floor with stretching of ligaments. c) No support from the pelvic floor and damage to the ligament with further stretching, and descent. Illustration by Oda Fredrikke Mebust Øyasæter

2.3.2 Incontinence, sexual dysfunction and pain

Urinary incontinence is defined as involuntary leakage of urine, which is seen as a social problem by the patient and has an influence on quality of life.[106] Urinary incontinence can be stress related (leakage in relations to physical exertion), urge related (leakage associated with urgency) or a combination of the two, also called mixed urinary incontinence.[106] Urinary incontinence is very common, with a prevalence varying from 25-48%.[109, 110]

Anal incontinence is defined as involuntary leakage of feces or flatus.[106] The prevalence is 4% in the general population,[111] and even higher in women with POP.[112] Anal sphincter injury after vaginal delivery is associated with development of anal incontinence.[65]

Sexual dysfunction is described as a subjective deviation from normal function during sexual activity and the most common symptom is dyspareunia.[106] In addition, sexual dysfunction involves disturbance in drive and desire. Up to 50% of women report sexual problems.[113]

Pelvic pain is a complex condition involving pain located in the urogenital area and involves several conditions, both recurrent and persistent.[106] Over 50% of women report pelvic pain in the last 12 months, but due to the heterogenous nature of the definition and perception of pain the research concerning this phenomenon is difficult to interpret [114]

2.3.3 Pelvic organ prolapse

Anatomic POP is described in the literature as a frequent benign condition, with a prevalence of 50% in routine gynecology examination in general practice.[115, 116] In population based studies up to 10 % report having symptomatic POP.[117, 118] POP is characterized by descent of bladder, rectum, small intestines or uterus which results in symptomatic protrusion of the vagina or uterus downwards and/or through the vaginal orifice.[116] Prolapse is defined according to the involved compartments: anterior, central and posterior. The

POP-Q system, which stages prolapses from 0-4 (see above), is widely used today, both clinically and for research.[81]

Anterior compartment prolapse

Anterior compartment prolapse is protrusion of the anterior vaginal wall, usually involving the bladder (Figure 12). It is the most frequent prolapse reported with prevalence up to 35% in previous publications.[66, 119]

This prolapse usually contains a cystocele with or without an urethracele. More rarely the anterior compartment prolapse may contain an anterior enterocele. Structures behind the prolapse can be detected by transperineal ultrasound. The anterior compartment prolapse might be due to a failure in all three of the support levels and the most common symptom is sensation of bulge, emptying difficulties at micturition with need for double voiding, hesitation, pollakiuria and urinary incontinence.[55]

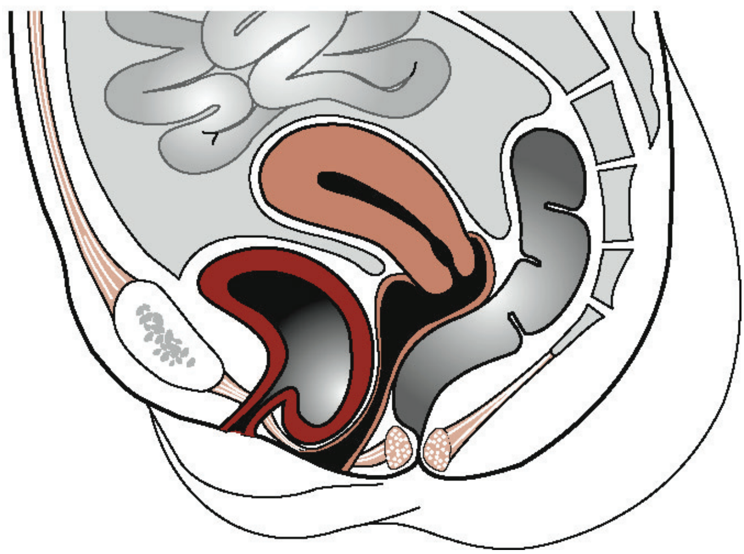


Figure 12 Pelvic organ prolapse in the anterior compartment. With permission from illustrator Lena Lyons and Studentlitteratur.

Central compartment prolapse

Central compartment or apical prolapse refers to protrusion of the vaginal apex involving herniation of the cervix, uterus or post hysterectomy protrusion of the small bowel (Figure 13).

The prevalence of uterine prolapse is up to 15 % and vault prolapse up to 12% post hysterectomy in publications.[66, 119] The most common symptom is bulge sensation. It can be accompanied by difficulties of emptying bladder and bowel due to obstruction. The central compartment prolapse is due to a failure in level one in the connective tissue support levels.[55]

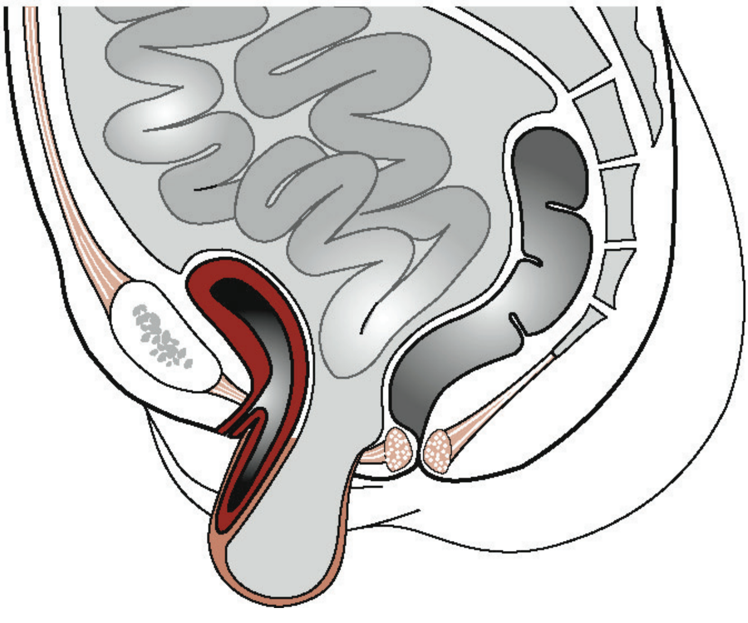


Figure 13 Central compartment prolapse. With permission from illustrator Lena Lyons and Studentlitteratur.

Posterior compartment prolapse

Posterior compartment prolapse is protrusion of the posterior wall of the vagina and the descending organ is usually rectum or small intestines (Figure 14). The enterocele is usually due to a failure in support level two, while a rectocele might be due to a failure in support level two or three. The prevalence is up to 15 % in publications.[66, 119]

The most common symptom is bulge sensation and defecating problems. Preoperative ultrasound assessment of the posterior compartment can be useful to detect enteroceles, entero-rectocele combinations and to exclude rectal intussusception.[33]

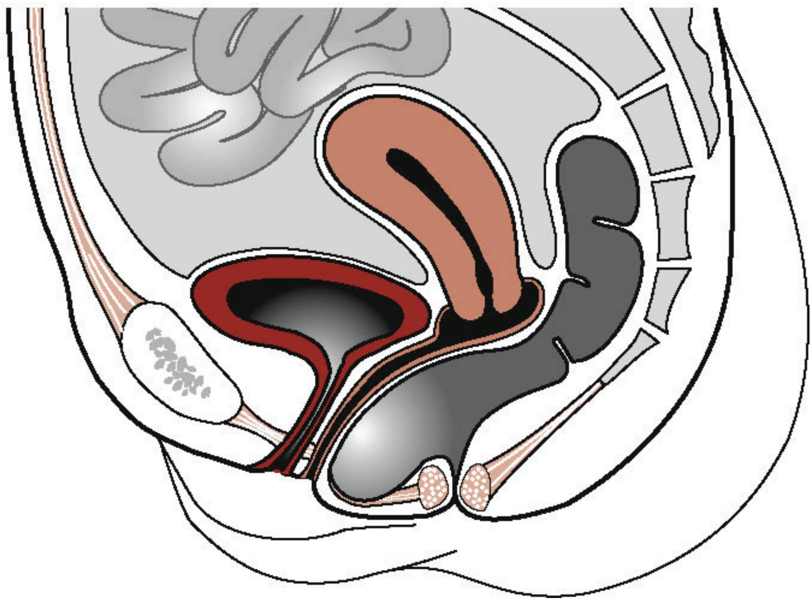


Figure 14 Posterior compartment prolapse. With permission from illustrator Lena Lyons and Studentlitteratur.

2.4 Treatment of pelvic organ prolapse

The indication for treatment is symptomatic POP that can be objectively verified. Treatment options are pelvic floor exercise, pessaries, and surgery.

2.4.1 Conservative treatment

Pessaries

Pessaries come in various sorts and shapes, are made of silicone, and are commonly used by gynecologists as first line treatment for POP.[3, 120] The advantage of pessaries is an immediate treatment without risks associated with surgery. Pessaries help postpone surgery, which is desired in young women, and a pessary is a good treatment option in old and fragile patients. The use is, however, associated with adverse effects such as bleeding, vaginal decubitus and troublesome discharge, which leads to a discontinuation of the treatment.[121] Some women have anatomy making the customization of a pessary difficult, for instance with a missing perineal body or a large introital area.[122]

Pelvic floor exercise

Several studies have shown efficacy of pelvic floor muscle exercise on stress urinary incontinence and therefore intensive pelvic floor exercise is often incorporated in standardized patient care.[123] Publications present evidence of efficacy in treating mild to moderate POP and that it may prevent development of POP.[41] There is no international consensus for the treatment algorithm for pelvic floor muscle training (PFMT).[124] In addition, there is no consensus for different algorithms for incontinence or POP.

The American College of sports medicine has presented progression models for training,[125] and Dumoulin et al used this model in a publication stating a PFMT program.[124] To increase muscle strength, the model recommends repetition of 8-12 contractions in 2-3 sets in the beginning, increasing to 4-5 times per week. Adherence to training program is difficult and previous studies have shown adherence to PFMT in 64% in the short-term and 23% in the long-term.[126] Factors that promote good adherence to home training programs are realistic expectations, follow-up, good feedback and a good routine doing the exercise.[127]

It is common to provide women with lifestyle advice as a supplement to PFMT. This includes information on dietary advice, avoiding straining while defaecating, proper emptying of bladder and bowel and the importance of pelvic floor contraction in specific situations such as heavy lifting. Studies have found an additional effect of lifestyle advice in combination with PFMT.[128-130]

2.4.2 Surgical correction of pelvic organ prolapse

There is a constant quest for the perfect technique for surgical management of POP, with focus on a minimal invasive procedure with low risk for complications and a low risk for recurrence. We have so far not found the solution for this. There is no international consensus for which procedures should be used. The most common procedures used in the Nordic countries are described below, categorized by compartment.

Anterior compartment

The most commonly performed procedure for POP is the anterior vaginal wall repair using native tissue; the anterior colporrhaphy. There is no clear definition of how to perform the procedure, but a midline plication of the fascia is the central component, giving an increase in the support from the connective tissue [131-133]. Also, to create a continuation between the fascia and the cervix is important during this procedure. The anterior colporrhaphy can be accompanied by placing a synthetic mesh, most frequently used for recurrence surgery. Synthetic mesh is used with caution today due to reports of complications.[134] Correction of a lateral cystocele can be done using site-specific repair.[135]

Central compartment

Correction of the central compartment can be divided into procedures with an intact uterus and post hysterectomy procedures. The most common procedure with a large uterus prolapse is a vaginal hysterectomy with a culdoplasty or a sacrospinous fixation.[133]
A sacrospinous hysteropexy can also be performed, in addition to sacrohysteroopexy, either done laparoscopically or abdominally.[136] Post hysterectomy management of the vault often involves sacrospinous colpopexy or sacrocolpopexy.[133] A synthetic mesh is placed when fixating the uterus or the vagina to the promontory sacrum.

Posterior compartment

Posterior compartment procedures are usually native tissue repairs, and the technique can be site-specific with suturing obvious fascial defects (usually transversal) or as a midline plication of the pre-rectal fascia.[133] The posterior correction sometimes involves correction of an enterocele, in addition to a rectocele. Posterior repairs can be accompanied by placement of synthetic meshes, but there is no evidence showing that mesh is superior to native tissue repair.[133]

Combinations of procedures

Due to the complexity of POP, there is often a need for more than one procedure. A common combined procedure in the Nordic countries is a three-step procedure handling the anterior, central- and posterior compartment, sparing the uterus. This procedure is known as the Manchester procedure, however, there is a lack of agreement on whether the procedure involves two or three compartments.[37, 137] The anterior repair usually includes an anterior colporrhaphy and a shortening of the cardinal- and sacrouterine ligaments, displacing the ligaments proximal on the anterior portion of the cervix, leading to an anterior tilt of the uterine body. In addition, a correction of the posterior compartment, usually a posterior colporrhaphy or correction of the perineal body (perineorrhaphy/perineoplasty), is performed.

Recurrence after POP surgery

The recurrence rate after POP is high, and one in three women needs more than one intervention.[36] Despite ambiguous results, several studies have identified age, obesity, vaginal delivery, high parity and prior hysterectomy as risk factors for recurrence.[72, 138] Studies have shown that both LAM ani macro trauma and increased levator hiatal area are associated with recurrence.[139, 140] In addition, absent pelvic floor contraction has been suggested as a risk factor.[44, 141]

3 Knowledge gap and rationale

3.1 The association between levator ani muscle trauma and pelvic floor contraction

The LAM muscle plays an important role for pelvic organ support and maintenance of continence through resting tone and contraction.[4, 51] LAM trauma is seen in up to 20% of women after delivery,[12, 13, 60] and previous publications have demonstrated an association between LAM trauma and altered muscle contraction in patient populations and after delivery.[6, 15-19] There is, however, a lack of studies examining the association between LAM trauma and contraction of the pelvic floor among parous women from a general population.

3.2 Assessment of pelvic floor contraction

There are several different tools available for the assessment of pelvic floor contraction and activity. These include palpation, manometry and electromyography.[24-26] All methods have advantages and disadvantages. The ICS/IUGA recommends that pelvic floor contraction should be assessed in patients with pelvic floor dysfunction, but there is no international consensus regarding method. [22, 25]

Transperineal ultrasound can be used for evaluation of pelvic floor anatomy and function, and previous publications have shown good inter-rater reliability and correlation with conventional methods for 3D/4D ultrasound, when used to assess pelvic floor contraction.[24, 96-102, 142-144] 2D ultrasound is an easy and quick examination.[31, 101, 103] There is no consensus regarding choice of measurement, and there is a need to explore the reliability of 2D ultrasound for assessment of contraction. There is also a need to develop a standardized tool for evaluation of pelvic floor contraction in women to whom we recommend pelvic floor muscle training (PFMT).

3.3 Pelvic floor muscle training as a supplement to pelvic organ prolapse surgery

The recurrence rate after POP surgery is high. [36] The use of synthetic mesh in both primary and recurrent surgery is disputed[39, 40] and there is a need to examine how to improve surgical outcome of POP surgery without use of these meshes. LAM macro trauma is associated with reduced contraction of the pelvic floor and recurrence after surgery.[36, 145] A weak pelvic floor is also associated with recurrent pelvic floor disorders.[44] PFMT is an effective treatment of mild to moderate symptomatic POP[41-43, 129, 130] and several studies have aimed to investigate the effect of perioperative PFMT both on anatomical and symptomatic outcomes, in addition to its effect on contraction of the pelvic floor.[146-151] However, meta-analysis and systematic reviews have concluded that the effect of PFMT as an adjunct to surgery needs further evaluation.[45, 152, 153] In addition, the effect of POP surgery itself on pelvic floor contraction is not properly evaluated.[154]

3.4 The impact of pelvic floor contraction and levator ani muscle trauma on recurrence

LAM macro trauma is associated with the development of POP and with the reduced ability to contract the pelvic floor.[8, 145] Reduced pelvic floor muscle contraction can contribute to prolapse development and is suggested as a risk factor for recurrent pelvic floor disorders.[44] However, the role of the pelvic floor muscle function is not properly evaluated in regards to predicting recurrence after POP surgery. LAM macro trauma is identified as a risk factor for anatomical and symptomatic failure after surgery.[36] This is, however, contradicted in a prospective cohort study on the Manchester procedure.[155] There is a lack of knowledge on the association between LAM macro trauma and contraction of the pelvic floor, and recurrence after surgery.

4 Aim

4.1 Overall aim

The overall aim of this work was to gain more knowledge about the impact of pelvic floor muscle contraction in parous women from both the general population and from a patient population of women with pelvic floor dysfunction and primigravida. The purpose of more knowledge in this field is to improve outcome of treatment and give better advice to women with incontinence and prolapse symptoms.

4.2 Paper I

The aim was to study possible associations between pelvic floor muscle contraction, LAM trauma and/or anatomic POP in parous women from a general population.

4.3 Paper II

The aim of this study was to determine the intra- and interrater reliability and agreement for 2D- and 3D-ultrasound measures of pelvic floor contraction, and to study any correlation between ultrasound and palpation for assessment of muscle contraction in pregnant women and women with pelvic floor disorders. We also aimed to develop an ultrasound scale for measurement of pelvic floor contraction for use in a clinical setting.

4.4 Paper III

The aim of this study was to investigate the effect of pelvic floor exercise as a preoperative supplement to POP surgery in a randomized controlled study, and explore the effects on pelvic floor function, anatomy, symptoms and recurrence rate 6 months after surgery.

4.5 Paper IV

The aim was to determine if there was any association between pelvic floor contraction and LAM macro trauma, and symptoms and anatomical pathology after POP surgery.

5 Material and methods

5.1 Participants and recruitment

Paper I is based on data from the UROPRO study conducted at Norwegian University of science and technology (NTNU) and Trondheim University Hospital, St Olavs hospital, in Trondheim from 2013 to 2016. This study included parous women from the general population. It was originally designed to explore the association between mode of delivery and prevalence of LAM trauma, and symptomatic and anatomic POP.[62, 156] Women who delivered their first child at Trondheim University hospital in the time period January 1990 to December 1997, were identified and invited to participate (Figure 17). They signed an informed consent prior to participation and the study was approved by the Regional Ethics Committee (REK-Midt 2012/666). The women received a questionnaire regarding pelvic floor disorders, and the responders were offered a clinical examination. A total of 608 women met for examination. Exclusion criterion were stillbirth, breach delivery, birthweight < 2000 g at index birth or index birth not in Trondheim. The study was registered in clinicaltrials.gov (NCT01766193).

In papers II-IV, we used data from the CONTRAPOP study, where participants were recruited from Trondheim University Hospital (TUH) during a period of 18 months from January 1st, 2017 to June 29th, 2018. We recruited three groups of women: women scheduled for POP surgery, women scheduled for stress-urinary incontinence surgery and primigravida. Inclusion criteria were age > 18 years, fluency in a Nordic or English language and the ability to consent. The study was registered in clinicaltrials.gov (NCT0364750). Information regarding the UROPRO and CONTRAPOP studies is available at this website: https://www.ntnu.no/ikom/bekkenbunn

In the **POP group,** women were identified when they were referred to surgery from the outpatient clinic or a private gynecologist. They were examined at baseline visit soon after

referral, on the day of surgery (approx. 3-4 months later) and at a postoperative (after approx. 6 months)
Women in the **incontinence group** were identified from the waiting list for tension-free vaginal tape (TVT) surgery, informed of the study by mail and asked to participate and examined on the day of surgery.

Women in the **primigravida** group were informed about the study from a midwife at the routine ultrasound visit at gestational week 18-20. Women interested in participation received a letter with information and an appointment at the outpatient clinic. All women signed an informed consent at the inclusion visit.

In paper II we included 195 women where 65 were scheduled for POP surgery, 65 were scheduled for incontinence surgery and 65 were primigravidas.

In paper III 159 women scheduled for POP surgery were included, and we used data for all three examinations: baseline, the day of surgery and six months after surgery.

In paper IV we included women from paper III and added 41 women who declined randomization.

5.2 Study design

We used different study designs for the four different publications.

1. Paper I: cross-sectional study in a general population of parous women
2. Paper II: cross-sectional study of women scheduled for POP and incontinence surgery and primigravida
3. Paper III: randomized controlled trial with an intervention and a control group
4. Paper IV: prospective, cohort study of women undergoing POP surgery

5.3 Data sources

Paper I

1. Clinical examination
    a. Pelvic floor anatomy; POP-Q (Figure 7)
    b. Pelvic floor muscle anatomy (tomographic ultrasound imaging for assessment of macro trauma and render imaging for assessment of micro trauma)
    c. Pelvic floor muscle contraction (ultrasound measures of levator hiatus, palpation and vaginal manometry)

2. Background variables from medical journals, the Norwegian medical birth registry and questionnaires: possible confounding factors (age, parity, BMI)

Paper II-IV

1. Patient reported outcome and training diary
    a. Symptoms; bulge sensation (VAS) Appendix I
    b. Adherence to intervention Appendix II
2. Clinical examination
    a. Pelvic floor anatomy; POP-Q (Figure 6)
    b. Pelvic floor muscle anatomy; tomographic and render ultrasound imaging
    c. Pelvic floor contraction; ultrasound measures of levator hiatus, palpation, sEMG, vaginal manometry
3. Background variables from the electronic patient journal
    a. Confounding factors; age, parity, BMI, prior hysterectomy, prior POP surgery and POP stage at baseline

5.3.1 Symptoms

For assessment of symptoms we used a visual analogue scale (VAS). The women were asked whether they had a sensation of bulge or not, if yes, they were asked to grade symptoms on a scale from 0 to 100 where 0 equals no bother and 100 equals worst imaginable bother (Appendix III). This method has been used for symptom assessment in previous publications,[157, 158] and there has been good correlation to condition specific standardized patient reported outcome questionnaires.

5.3.2 Anatomy

The participants were instructed to meet for examination with empty bladder and bowel. Prior to examination, they were thourougly instructed in pelvic floor contraction and how to perform a proper Valsalva manouvre. Anatomical prolapse was assessed with a woman in lithotomy posistion at maximal Valsalva.[95] Anatomical assesment for type and stage of POP was performed using POP-Q, measuring the distance from fixed points in the vagina to the hymen (Appendix IV)[81] and POP-Q stage≥ 2 was considered clinically significant. We regisered POP-Q stages for all three compartments, and the highest measurement in the dominating compartment.

POP-Q stage ≥ 2 was regarded as clinically significant at the postoperative visit. We differentiated between any POP classified as POP-Q stage ≥ 2 in any compartment, recurrence of POP defined as POP-Q stage ≥ 2 in the compartment surgically corrected, and new prolapse (defined as POP-Q stage ≥ 2 in a different compartment). To assess symptoms after surgery patients were asked if they had bulge sensation (yes/no), and if yes, they were asked to grade the bother on a VAS.

5.3.3 Pelvic floor contraction

Palpation

Assessment of muscle contraction by palpation was performed with two fingers at the level of the LAM approximately 4 cm into the vagina, and the contraction was assessed using the 6-point Modified Oxford Scale with a range from 0 to 5.[23] Muscle contraction on both sides was evaluated, and the mean value was used in the analysis.

Vaginal manometry

In the UROPRO study the Camtech® (Camtech AS, Sandvika, Norway) equipment was used for vaginal manometry and the Peritron® (CardioDesign, Oakleighm, Australia) with the PFX vaginal sensor was used in the CONTRAPOP study. According to the manual, the sensor was placed in the vagina at the level of the LAM and inflated to standard baseline at 100 mmH_2O. This procedure optimizes contact surface and increase the area to contract against. The device was reset, and women performed series of three contractions of three seconds duration. The peak value in mmH_2O was recorded for use in the analysis.

Surface electromyography

For analysis of muscle activity as an indirect measure of contraction, we performed surface electromyography using a EMG device with the Periform® vaginal surface electrode. The probe has elecrodes on the lateral sides and was placed at the level of the LAM in the vagina. Participants performed contractions in series of three with a duration of 3 seconds, and the mean value was used in the analysis.

5.3.4 Transperineal ultrasound

Transperineal ultrasound was performed after international standards.[31, 32, 94] We used two different machines; Voluson GE S10 or E8 with a RAB 4-8 MHz curved array transducer. The transperineal examination was performed in the midsagital plane at the level of minimal hiatal dimensions with an acquition angel set at 85°. 3D/4D volumes were recorded from rest to maximal contaction or maximal Valsalva. Three volumes of contraction and three volumes at Valsalva were recorded. The women received instuction in how to perform maximal Valsalva and maximal contraction and were corrected if necessary. Offline analysis was performed after 6-12 months using 4D view® (version 14, GE Healthcare), and the examiner (MØN) was blinded for clinical information. For evaltuation of LAM macro trauma and measures of contraction, the volume with the best contraction was chosen for analysis. For evalutation of area at Valsalva and micro trauma, the volume with the best performed maximal Valsalva was chosen.

Macro trauma to the LAM was identified using tomographic ultrasound, where the definition of macro trauma was pathological insertion of the puborectalis muscle to the pubic bone in three central slices, either uni- or bilaterally.[159] Micro trauma was diagnosed based on pathological distended hiatal area on maximal Valsalva $\geq 42\ cm^2$. We used the 75^{th} percentile of the areas on Valsalva to define the upper limit of the normal range, in the population of parous women from the general population and used this cut-off to define micro trauma.

For assessment of contraction we measured the following dimensions of the levator hiatus; area, anteroposterior diameter in the 3D rendered volume and anteroposterior diameter in 2D. The proportional change between rest and contraction was calculated, using the following formula: $100 \times [(\text{measurement}_{rest} - \text{measurement}_{contraction})/\text{measurement}_{rest}]$.[24]

5.4 Randomization

At the inclusion visit, women were randomized to intervention or control by a web-based randomization tool (WebRAND) provided by Unit for Applied Clinical Research, NTNU. The allocation ratio was 1:1, and participants were stratified by POP stage 2 or 3-4 and age over or under 60 years. Group allocation did not interfere with waiting time before surgery. All postmenopausal women received local applied estrogens for strengthening of vaginal mucosa prior to surgery, if there were no contraindications for estrogen use, such as aromatase inhibitors for breast cancer treatment.[160]

Intervention

Intervention consisted of intensive pelvic floor muscle exercise and lifestyle advice regarding diet, physical activity, proper emptying of bladder and bowel and contraction of pelvic floor in situations with increased abdominal pressure (such as coughing, sneezing and heavy lifting). The daily training included three sets of 8 to 12 contractions (Appendix V). Women visited a dedicated pelvic floor physiotherapist at week two and six of the intervention period and were offered to participate in weekly group training.[161,162] Adherence to the intervention program was noted in a training diary, which was collected on the day of the surgery. If the women did not return their diary, they were interviewed by telephone regarding adherence to the intervention program. Adequate adherence to the program was set at 70 % of daily exercise. This cut-off was based on the feasibility to implement the intervention to clinical practice. [126]

Control

Women in the control group waited for surgery with no preoperative intervention. Prior to randomization, they received the same information regarding proper pelvic floor contraction and biofeedback as women allocated to intervention.

5.5 Power and sample size

Paper I

No power analysis was performed a priori for the primary outcomes in paper I. The study sample size was based on power calculations for the primary outcome in the parent study. The UROPRO study aimed to explore associations between mode of delivery, POP and pelvic floor muscle trauma and to identify differences between forceps and vacuum delivery.[62]

Paper II

We aimed to test the correlation between palpation and ultrasound in the prolapse group, incontinence group and group of primigravida. We assumed a bivariate normal distribution with correlation 0.7 for palpation and ultrasound values. Using Pearson correlation coefficient $0.5 < r_s < 0.9$ with 80% power we would need 63 participants in each group. We rounded this up to 65 women in each group.

Paper III

In a previous study we found mean MOS 3.1 (SD 1.3) by palpation among parous women from the general population.[24] We assumed that patients had a lower mean MOS 2.6 (SD 1.3).[15, 102, 163] We assumed that the MOS at 6 months follow up between women randomized to intervention and standard care would be MOS 3.2 vs MOS 2.6, (SD 1.3) with power 80% and level of significance at 0.05, with a sampling ratio 1:1. We would need 74 women in each group, and a total of 150 women undergoing prolapse surgery were considered to be sufficient.

Paper IV

No separate power analysis was done for paper IV.

5.6 Ethical considerations

The studies were approved by the Regional Ethical Committee of Midt-Norge (UROPRO: REK Midt 2012/666, CONTRAPOP: REK Midt 2015/1751), and all women signed an informed consent (see appendix II). Examinations did not involve any risks to the participants, and there was no risk for the fetus of the pregnant women. One disadvantage was the use of extra time for the research examinations and investigations. For women in the CONTRAPOP study baseline examination was performed in combination with the preoperative visit, and the second examination was done at the day of surgery for the participants in the POP group. One extra visit after surgery was seen as a benefit by most participants. One benefit for all women was a thorough examination of pelvic floor function with instructions on how to perform proper pelvic floor contraction.

Women in the intervention group received guidance from a dedicated pelvic floor physiotherapist within 2 weeks of inclusion in the study, which is a service with a long waiting list in our hospital.

5.7 Handling of data

All handling of data was according to the investigator site file. The data was stored without information that could identify the participants. Data from clinical examinations was registered on paper and in a web-based CRF (WebCRF), a data solution delivered from the Unit for Applied Clinical Research at Norwegian University of science and technology, all marked with study id. Ultrasound volumes were marked with study-id and date of examination on the machine, and the volumes were stored on external hard discs in two copies. Results from off-line analysis of ultrasound volumes was registered on paper and entered manually into SPSS, marked with study-id. The source data registrations were filed and stored after local regulations, all described in investigator site file. The link list was stored in a safe area in the hospitals computer system, and only the main investigators had access (MØN, SM, IV). The VAS scores (see appendix) were marked with study-id and scanned into an SPSS-file.

The studies were registered in clinicaltrials.gov (UROPRO: NCT01766193, 11th January 2013, CONTRAPOP: NCT 03064750, 22th February 2017). Changes in the outcomes were done in clinicaltrials.gov in December 2018 due to lack of specifications in the primary aim. Symptoms of pelvic floor disorders were the main indication for POP surgery and change in symptoms was set as a primary outcome at this point. In addition, a clarification of secondary outcomes was needed. Dr. Seema Mathew is currently doing a study on the same data set using other ultrasound volumes collected from the same participants. Outcomes on sphincter ani, pelvic organ mobility, LAM biometry and imaging of implants have been added as secondary outcomes in clinicaltrials.gov.

An external scientific counsellor assisted with the registration in clinical trials.gov. The registration was unfortunately delayed until 22th February 2017. In the meantime, 12 study participants (out of 330) had been recruited. This is the reason for a discrepancy between the study start (17th January) and the date the study was registered in clinical trials.gov (22nd February). The study completion date was set at 26th of June 2019.

We have used STROBE and CONSORT guidelines when reporting our studies.

5.8 Statistics

5.8.1 Statistical analysis in general

In general normal distribution of data was tested with histogram, QQ-plots and Kolmogorov-Smirnov test. The level of statistical significance was set at 0.05. For an overview of the statistical methods, see Table 2.

Paper	Normality	Statistical analysis	Purpose
I	QQ-plots	Independent t-test	Comparing means
	Kolmogorov Smirnov	Mann Whitney	Comparing means
		ANCOVA	Regression analysis, adjusted
II	QQ-plots	Intraclass correlation	Intra- and interrater reliability
	Kolmogorov Smirnov	Spearman rank correlation	Correlation analysis
III	Histograms	Linear mixed models	Testing effect of intervention
	QQ-plots	Chi square	Testing associations in bivariate variables
IV	QQ-plots Histograms	Multivariate logistic regression	Testing associations in bivariate variables

Table 2 Overview of statistical methods.

5.8.2 Paper I

Differences the background variables between women with intact LAM or LAM trauma, and with or without POP were tested using independent samples t-test. To test a possible association between LAM injury and measures of pelvic floor muscle contraction, and between POP-Q ≥2 and contraction, we used the Mann-Whitney U-test as a normal distribution could not be assumed for some of the variables. The chi-squared test was used to test the association between LAM trauma and absent pelvic floor contraction (MOS =0). Analysis of covariance (ANCOVA) was performed for ultrasound measurements, adjusting for confounders with statistically significant difference in distribution between the groups.

5.8.3 Paper II

Reliability analysis

To test correlation and agreement in a test-retest setting for one rater we used intra-rater reliability analysis calculating the Intraclass Correlation Coefficient (ICC) with a two-way mixed effects model and absolute agreement. To determine the correlation and agreement between three raters, we used interrater reliability analysis calculating the ICC with a two-way random effects model and absolute agreement. We reported both the mean of three raters and single measures.[164] For interpretation of the results we used a scale constructed by Altman et al.; ICC< 0.20 = poor reliability, 0.20-0.40 = fair reliability, 0.41-0.60 = moderate reliability, 0.61– 0.80 = good reliability and > 0.80 = excellent reliability.[165]

For determination of agreement, Bland Altman plot with 95 % limits of agreement for means and differences between measurements were constructed. Independent plots for intra-rater agreement and interrater agreement between pairs of raters (MØN/IV and MØN/SO) for the 2D anteroposterior diameter were constructed.[166] We performed a linear regression analysis using the difference between the two raters as outcome and the average of the two raters as explanatory variable to determine that the difference in measurements between the raters was independent of the average of the measurements. In addition, we performed an interrater analysis for MOS score between pairs of raters.

Correlation between methods

To examine the correlation between ultrasound and palpation using MOS for assessment of contraction, we used Spearman's rank correlation, calculating the correlation coefficient; r_s. Higher r_s implies increasing correlation between the tests: r_s=0: no correlation; r_s > 0.3: weak correlation; r_s> 0.5: moderate correlation; r_s> 0.7: strong correlation; r_s=1: perfect correlation.[24]

Development of the ultrasound contraction scale

The ICS has recommended measurement of contraction in four categories; absent, weak, normal, strong.[22] We developed an ultrasound contraction scale for clinical assessment of pelvic floor contraction using proportional change in two-dimensional anteroposterior diameter, as this was the parameter with the highest ICC. We calculated cut-offs for the ultrasound scale, based on the proportion of women allocated to each of the four categories by palpation, using the following definition: MOS 0 = absent, 0.5 – 2.0 = weak, 2.5 – 4.0 = normal and 4.5 – 5.0 = strong contraction. We did additional analysis defining cut-offs when applying the 25 and 75 percentiles within the ultrasound variable without comparison to MOS (weak <25 percentile, normal 25-75 percentile, strong >75 percentile). The proportion of women with LAM macro trauma was calculated and compared between women with absent to weak contraction and moderate to strong contraction using chi-squared test.

5.8.4 Paper III

Analysis was performed on an intention to treat basis. Linear mixed models were used to test the effect of the intervention the continuous outcome variables, with a five-point interaction variable for time and group allocation as fixed factor. The effect of the stratification variables were tested and had no influence on the results, hence they were excluded from the final model. We used restricted maximum likelihood estimation and unstructured covariance in the final model. Due to the randomized controlled setting, no background variables were included as covariates in the model.

5.8.5 Paper IV

To determine associations between LAM trauma, anatomical POP and symptoms after surgery with adjusted odds ratios (OR), we used multivariate logistic regression analysis. A composite outcome was constructed combining any POP ≥ 2 after surgery and presence of bulge sensation as an additional outcome measure. We used the pelvic floor contraction scale from paper II to categorize contraction, scaled in the categories absent, weak, normal or strong. We dichotomized the scale in absent/weak or normal/strong and used the same statistical analysis for examination of associations between contraction and the outcome measures. We selected confounders based on factors associated with POP and POP recurrence in the literature (Table 3).

5.8.6 Statistical tools

For analysis we used SPSS Statistics® version 25 (IBM Corp., Armonk, NY, USA) and R version 2.13.1(Auckland, New Zealand).

Dependent variables	Independent variables	Variables included in multivariate analysis
Any POP ≥ 2 after surgery	LAM macro trauma	Age BMI Parity
POP ≥ 2 in the compartment that underwent surgery	LAM micro trauma	Baseline POP stage ≥ 3 Previous POP surgery Previous hysterectomy
POP ≥ 2 new compartment Composite outcome (any POP ≥ 2 + bulge sensation)	Absent/weak pelvic floor contraction	

Table 3. Dependent and independent variables and confounders included in paper IV.

6 Results

6.1 Participants and background characteristics

6.1.1 UROPRO

Paper I was a secondary analysis of data from the UROPRO study, where the participants were parous women from the general population invited to answer a questionnaire. Non-responders were significantly younger than the responders with (mean age of 46 vs 47 years, p<0.01) and they lived further away from the hospital. The women who met for examination had more POP symptoms than the original group of responders they were recruited from (15% vs 11%, p= 0.01). The flowchart of participants is presented in Figure 15.

Table 4 presents background characteristics for the groups compared in paper 1, based on presences or absence of LAM micro- or macro trauma or clinically significant POP (POP-Q ≥ 2). For complete numbers, see Appendix I, paper I.

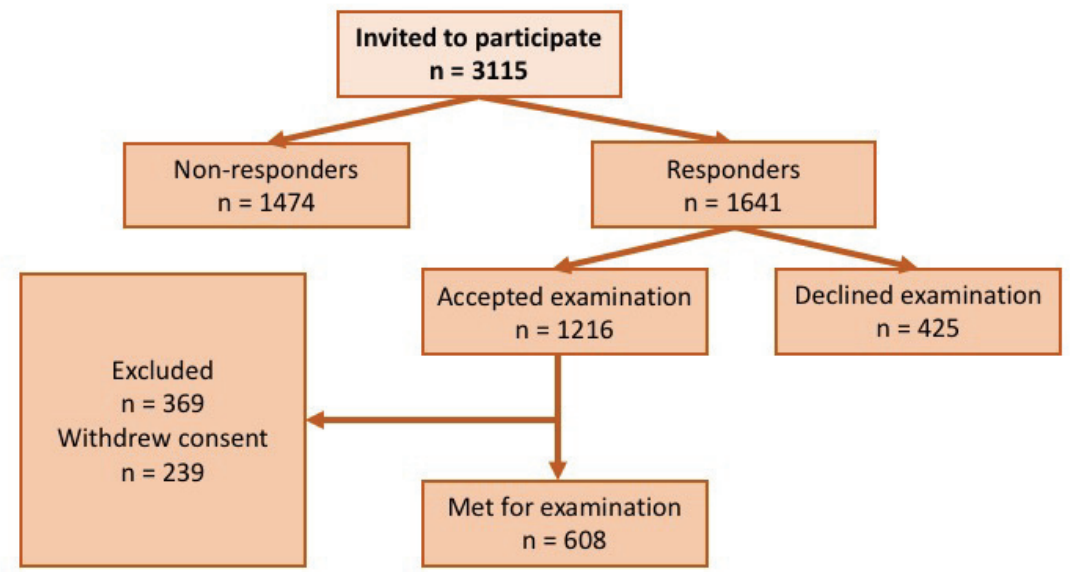


Figure 15 Flowchart of participants in the UROPRO study.

Background variables (mean)	**LAM macro trauma**		***p***	**LAM micro trauma**		***p***	**POP-Q ≥2**		***p***
	No (n=493)	Yes (n=113)		No (n=417)	Yes (n=138)		No (n=333)	Yes (n=275)	
BMI, kg/m^2	25.9	25.4	0.295	25.8	26.6	0.084	25.8	25.8	0.839
Age, years	47.8	48.8	0.038	48.2	47.5	0.140	48.0	47.9	0.951
Parity	2.21	2.19	0.790	2.18	2.3	0.136	2.1	2.3	0.009
Birthweight, g	3854.7	3888.4	0.508	3844.7	3935. 3	0.062	3797.1	3918.5	0.004

Table 4 Background characteristics paper I**.**

6.1.2 CONTRAPOP

In paper II-IV we used data from the CONTRAPOP study, with 330 women (Figure 16). In all, 200 women were scheduled for POP surgery, 65 were scheduled for incontinence surgery and 65 were primigravida. In paper II a total 195 of these women were included, with 65 women from each group. These groups were selected as they represent the groups we recommend pelvic floor exercise. The background characteristics for paper II are outlined in table 5. For complete numbers see Appendix I, paper II.

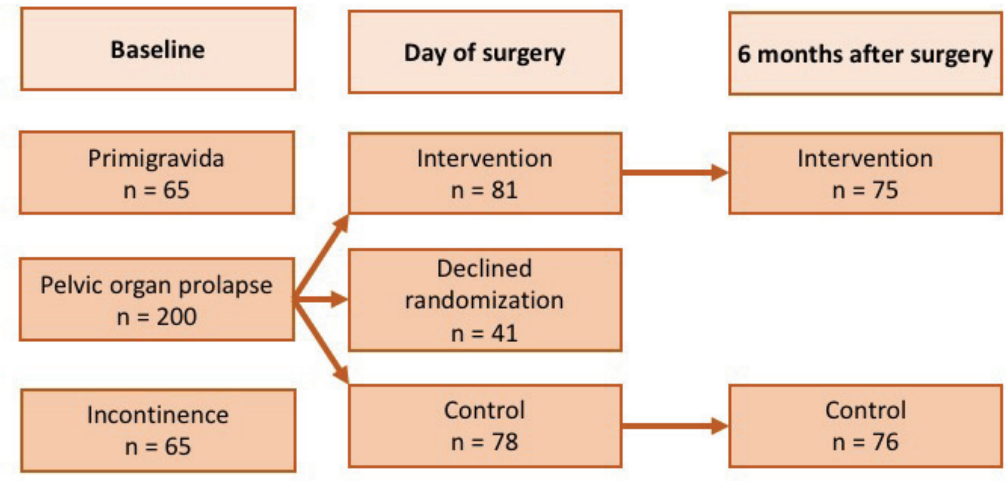


Figure 16 Flowchart of participants in the CONTRAPOP studies.

	Prolapse n=65	Incontinence n=65	Primigravida n=65	Total n= 195
Mean				
Age, years	63.9	50.1	29.1	47.7
Parity	2.5	2.6	0	1.7
Body Mass Index, kg/m^2	25.4	26.3	23.3	25.0
Modified Oxford Scale	2.1	3.5	3.9	3.2
%				
POP-Q stage >2	100	7.7	0	35.9
LAM macro trauma	52.3	15.4	0	22.6

Table 5 Background characteristics paper 2

In all, 159 women accepted participation in the RCT, 81 were allocated to intensive pelvic floor exercise prior to surgery and 78 were allocated to the control group, waiting for surgery with no further intervention (Figure 17). The baseline characteristics are outlined in table 6. For complete numbers, see Appendix I paper III.

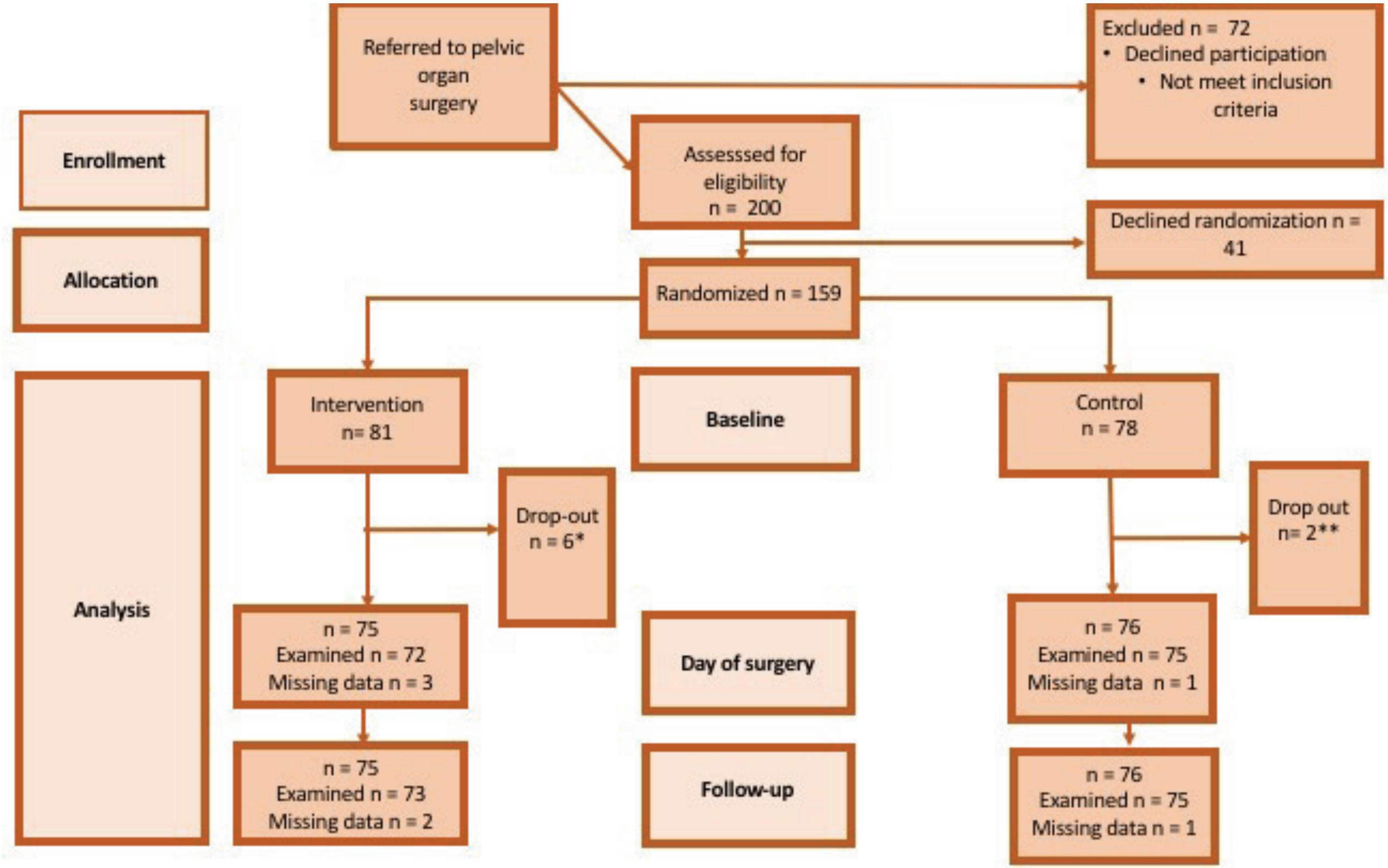


Figure 17 Flowchart of the study population. *Three women withdrew consent and three cancelled surgery ** two women cancelled surgery.

	Intervention n=75	Control n=76
Characteristics		
	Mean	**Mean**
Age (years)	60.1	60.6
Parity	2.3	2.6
Body mass index (kg/m^2)	26.3	25.7
	%	**%**
LAM macro trauma	44	56
Local estrogen therapy	64	63
Previous pelvic floor muscle training	18	18
POP-Q stage ≥3	59	63
Post-menopausal	80	78
Smoking	14	8
Previous pessary treatment	68	79
Previous POP surgery	10	15
Previous hysterectomy	12	10
Outcome variables		
	Mean	**Mean**
Palpation, Modified Oxford Scale (0-5)	2.1	2.1
Ultrasound (% change)*	17.8	17.2
VAS scores (0-100)	60.3	55
Prolapse distance from hymen in dominant compartment (cm)	1.9	1.8

Table 6 Background characteristics and outcome variables at baseline for the intervention and control groups.

* anteroposterior diameter of the levator hiatus in 2D

In study 4 all the women in the CONTRAPOP trial were included as a cohort (Figure 18). The background characteristics and outcomes at baseline are outlined in table 7.

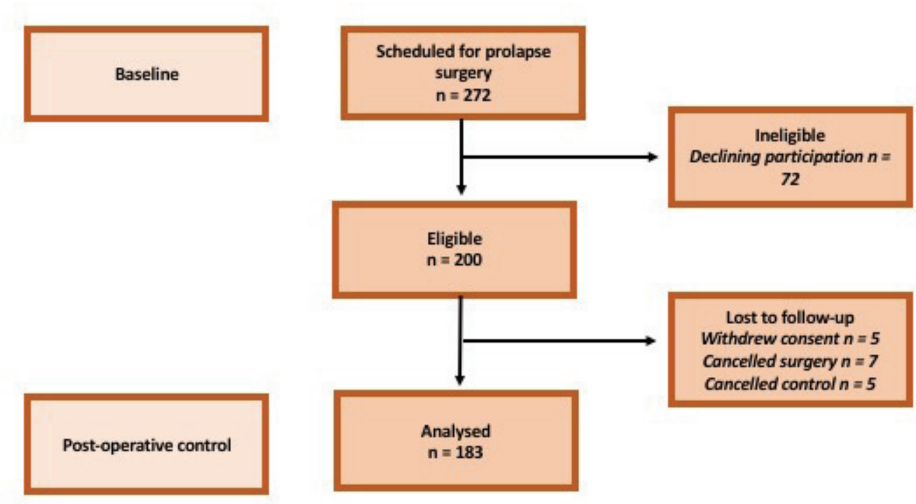


Figure 18 Flowchart of participants in paper IV.

Variables	Levator macro trauma			Levator micro trauma			Pelvic floor contraction		
	No	Yes	*p*	No	Yes	*p*	Normal	Impaired	*p*
Mean age, years	62.2	60.6	0.202	63.4	60.5	0.049	60.5	63.6	0.024
Mean BMI, kg/cm²	26.3	26.0	0.760	25.7	26.4	0.133	26.2	25.9	0.627
Parity	2.6	2.5	0.086	2.5	2.5	0.992	2.6	2.5	0.320
Previous POP surgery	12.1%	16.3%	0.414	10.7%	18.0%	0.177	10.4%	19.7%	0.075
Previous hysterectomy	9.9%	17.4%	0.140	10.7%	17.0 %	0.236	13.2 %	14.5%	0.807
POP-Q stage ≥ 3	56.0%	65.2%	0.204	53.3%	68.0%	0.048	61.3%	60.5%	0.914

Table 7 Background characteristics for women with intact levator ani muscle, macrotrauma or micro trauma, and for women with normal or impaired pelvic floor contraction. Means are given for continuous variables and percentages for categorical variables.

6.1.3 Surgical procedures performed in the CONTRAPOP study

In paper II we included 65 women scheduled for POP surgery and 65 scheduled for incontinence surgery. The surgical procedure for incontinence in this study was tension free vaginal tapes (TVT).

In the RCT 159 women were included. Nineteen percent had an isolated anterior compartment repair (including three synthetic mesh procedures), 18% had an isolated posterior compartment repair, and 25% had isolated central compartment repair. Thirty-eight percent of women had a combination of procedures including more than one compartment.

Two major complications were registered after surgery; one hemorrhage requiring reoperation and one intestovaginal fistula after laparoscopic sacrocolpopexy. In addition, three postoperative infections requiring antibiotics and one woman with persisting residual urine were reported.

In study IV, 41 women were included in addition to the women in study III. In this cohort, 19% native anterior colporrhaphies, 18% posterior colporrhaphies and 15 % Manchester procedures were performed. In addition, vaginal hysterectomy was performed in 12% of women and sacrocolpopexy/uteropexy in 10%. Vaginal mesh was used in 2% of the procedures. A combination of several procedures was performed in 48% of women.

6.2 Qualifications of the examiners

Prior to the study start, I had systematic training with two experienced examiners in transperineal ultrasound (Dr. Ingrid Volløyhaug and Dr. Rodrigo Guzman Rojas). The training included examination and recordings of ultrasound volumes and offline analysis with interrater agreement analysis for the different measurements of contraction, LAM macro trauma and sphincter ani defects. We also did interrater analysis for scoring of Modified

Oxford scale between myself, Dr. Seema Mathew and Dr. Ingrid Volløyhaug. The results of interrater analysis are presented in table 8.

	MOS	MOS	BND	3D AP*	3D AP**	BD	LAM†	Area*
Raters	MØN/SM	MØN/IV	MØN/RGR	MØN/RGR	MØN/RGR	MØN/RGR	MØN/IV	MØN/IV
ICC/κ	0.93	0.92	0.91	0.97	0.89	0.96	0.74	0.97

* at Valsalva

** at rest

† macro trauma

Table 8. Interrater reliability and agreement for ultrasound measures. MØN – Maria Øyasæter Nyhus, SM – Seema Mathew, IV – Ingrid Volløyhaug, RGR – Rodrigo Guzman Rojas, MOS- Modified Oxford Scale, BND – bladder neck descent, 3D AP – three-dimensional anteroposterior diameter, BD – bladder descent, LAM – levator ani muscle. ICC- intraclass correlation coefficient, κ - Cohen's kappa.

6.3 Summary of papers – main results

6.3.1 Association between pelvic floor muscle trauma, pelvic organ prolapse and pelvic floor contraction

A total of 608 women met for clinical examination in the UROPRO study (Figure 15). The background characteristics are outlined in table 4. We found that women with LAM trauma had weaker contraction than women with intact LAM (Table 9). There was no difference in contraction between women with and without LAM micro trauma when we excluded women with macro trauma, indicating that the primary mechanism behind impaired pelvic floor contraction is the macro trauma to the LAM.

We found a significantly weaker pelvic floor muscle contraction in women with POP compared to women with intact anatomy. Sub-analysis for the compartments involved, showed that women with prolapse in the anterior and central compartment had reduced contraction, but not women with posterior compartment prolapse. This suggests a different mechanism behind posterior compartment prolapse (Table 9).

Of the women unable to contract their pelvic floor (4%), 62% were diagnosed with a LAM macro trauma. For women with ability to contract (96%), 17% had a LAM macro trauma, giving an OR of 7.88, (95 % CI of 3.18-19.5) for a MOS score of 0 if you have a LAM macro trauma. Despite the reduced capacity to contract in women with LAM trauma and POP, it is important to realize that most of them still have a detectable contraction, implying that they might benefit from pelvic floor muscle training.

Main results

- **Weak pelvic floor contraction is associated with pelvic organ prolapse and LAM macro and micro trauma**
- **Most women with LAM macro trauma have a detectable contraction**
- **Macro trauma seems to be the major impact factor for reduced contraction in women with injured LAM**

		Palpation	*p*	Manometry	*p*	AP diameter %	*p*	Area %	*p*
Pelvic floor muscle trauma									
LAM macro trauma	No	3.5	<0.001	28.0	<0.001	26.0	<0.001	34.0	<0.001
	Yes	1.5		15.0		16.2		19.9	
LAM micro trauma	No	3.0	<0.001	27.0	<0.001	25.3	<0.001	32.8	<0.001
	Yes	2.5		19.0		19.4		25.1	
LAM micro trauma, no macro trauma	No	3.5	0.561	28.0	0.130	25.7	0.848	33.7	0.541
	Yes	4.0		24.0		27.3		4.7	
Pelvic organ prolapse									
Any POP-Q≥2	No	3.5	<0.001	28.0	<0.001	25.7	<0.001	33.8	<0.001
	Yes	3.0		21.0		22.8		29.6	
Anterior POP-Q≥2	No	3.5	<0.001	28.0	<0.001	25.4	<0.001	32.9	<0.001
	Yes	3.0		19.0		21.3		26.9	
Central POP-Q≥2	No	3.0	<0.001	26.0	0.001	24.5	<0.001	32.3	0.001
	Yes	2.0		15.5		15.5		19.9	
Posterior POP-Q≥2	No	3.0	0.431	26.0	0.994	24.0	0.794	31.8	0.870
	Yes	3.0		24.0		24.7		31.9	

Table 9 Differences in the outcome variables were tested with Mann Whitney U test. The median for each group and p value is outlined in the table. Contraction was assessed with palpation using Modified Oxford scale (0-5), vaginal manometry (cmH_2O) and ultrasound measuring proportional change in anteroposterior diameter of the levator hiatus and area (%) in 3D.

6.3.2 The reliability of transperineal ultrasound for an assessment of pelvic floor contraction

In this study 195 women were included: 65 scheduled for prolapse surgery, 65 scheduled for incontinence surgery and 65 primigravida. The correlation between contraction assessed by the Modified Oxford scale and ultrasound was moderate. Table 10 outlines the results from the correlation analyses (supplementary information, not all published).

A test-retest of 195 volumes was performed for 2D ultrasound measures of contraction, and the results for intrarater reliability and agreement analysis are presented in table 11. These are the numbers for absolute measures at rest, at contraction and the proportional change.

In addition, we performed an interrater reliability analysis including three independent raters evaluating 60 volumes. We found the highest interrater ICC for proportional change in two dimensional measures of the anteroposterior diameter of the levator hiatus. The results from the interrater reliability analysis are outlined in table 12.

Results from the ICC analysis for proportional change in ultrasound parameters from the interrater agreement are outlined in table 12.
Agreement between the raters and at the test-retest is illustrated in the Bland-Altman plots in figure 19. A linear regression analysis demonstrated independent relationship between differences and average of measures between the raters ($p > 0.05$, see appendix I for complete numbers).

Take home message

- **Ultrasound is a reliable method for assessment of pelvic floor contraction**
- **Two-dimensional anteroposterior diameter of the levator hiatus correlates moderately to palpation**

Ultrasound measures	Palpation		Manometry		Electromyography	
proportional change	r_s	*p*	r_s	*p*	r_s	*p*
2D anteroposterior diameter	0.52	< 0.001	0.51	< 0.001	0.46	< 0.001
3D anteroposterior diameter	0.62	< 0.001	0.56	< 0.001	0.44	< 0.001
Area of levator hiatus	0.47	< 0.001	0.40	< 0.001	0.35	< 0.001

Table 10 Spearman rank correlation, r_s (*p*), between different measures for contraction. The ultrasound measures are different ways of measuring the proportional change between rest and contraction as a quantification of contraction. Palpation was assessed by the Modified Oxford scale. r_s= 0 no correlation; r_s >0.3 weak correlation; r_s >0.5 moderate correlation; r_s >0.7 strong correlation; r_s=1 perfect correlation.

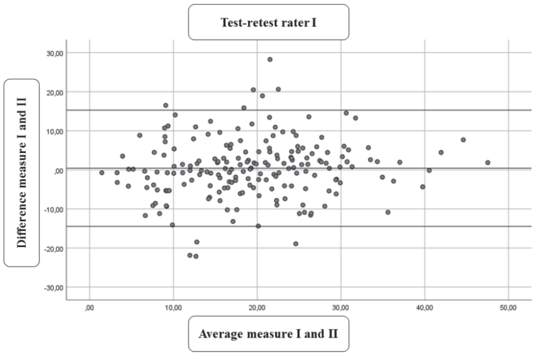
Intrarater analysis two-dimensional ultrasound				
Absolute measures	ICC single rater	95% CI	ICC average	95% CI
Anteroposterior diameter rest	0.87	0.83 - 0.90	0.93	0.91- 0.95
Anteroposterior diameter contraction	0.86	0.82 - 0.89	0.93	0.90 - 0.94
Proportional change				
Anteroposterior diameter	0.67	0.59 - 0.74	0.81	0.74 - 0.85

Table 11 Intrarater analysis for ultrasound measures of contraction in 2D with intraclass correlation coefficient (ICC) and 95 % confidence interval (95% CI).

Interrater analysis ultrasound	ICC single rater	95% CI	ICC average	95% CI
Ultrasound measurements				
2D AP diameter rest	0.83	0.75 - 0.89	0.94	0.90 - 0.96
2D AP diameter contraction	0.82	0.73 - 0.88	0.93	0.89 - 0.96
3D AP diameter rest	0.77	0.54 - 0.88	0.91	0.78 - 0.96
3D AP diameter contraction	0.79	0.60 -0.89	0.92	0.82 - 0.96
Area rest	0.77	0.59 - 0.87	0.91	0.81 - 0.95
Area contraction	0.79	0.62 - 0.88	0.92	0.83 - 0.96
Proportional change				
2D AP diameter	0.61	0.47 - 0.73	0.82	0.72 - 0.89
3D AP diameter	0.57	0.43 - 0.70	0.80	0.69 - 0.88
Area	0.46	0.30 - 0.61	0.72	0.56 - 0.83

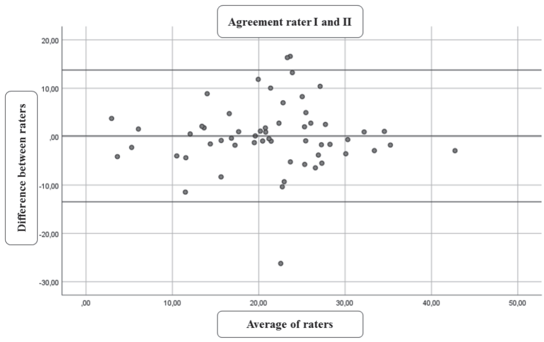
Table 12 Results from the interrater analysis where three independent raters assessed 60 ultrasound volumes measuring pelvic floor contraction. The table outlines the intraclass correlation coefficient (ICC) with 95 % confidence interval (95% CI), both for single rater and average of three raters.

Figure 19



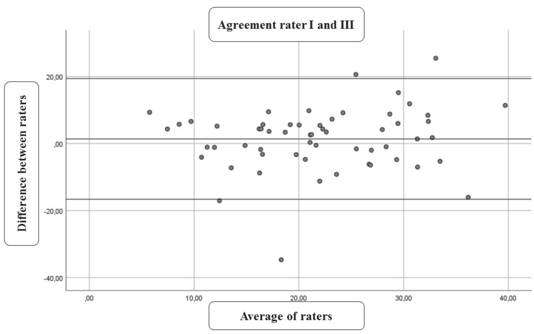
a)

Bland-Altman plot illustrates the intraobserver agreement for the anteroposterior diameter for the levator hiatus, using two-dimensional transperineal ultrasound. The black line is the mean difference and the two gray lines represent the limits of agreement.



b)

Bland- Altman plot illustrates the interobserver agreement between rater I and II for the anteroposterior diameter for the levator hiatus, using two-dimensional transperineal ultrasound. The black line is the mean difference and the two gray lines represent the limits of agreement.



c)

Bland-Altman plot illustrates the interobserver agreement between rater I and III for the anteroposterior diameter for the levator hiatus, using two-dimensional transperineal ultrasound. The black line is the mean difference and the two gray lines represent the limits of agreement.

6.3.3 Development of a pelvic floor ultrasound contraction scale

For development of the pelvic floor ultrasound contraction scale the women were divided into categories according to MOS score; absent, weak, normal, strong. We used the proportional change in 2D anteroposterior diameter of the levator hiatus, and defined cut-offs for each category based on the proportion of women categorized into the four groups. The scale is outlined in table 13.

We did additional analyses of the scale, using percentiles of the anteroposterior diameter of the levator hiatus. We found that the cut-offs did not deviate much from our ultrasound contraction scale (Absent = 0%, Weak =1-13%, Normal = 14-26%, Strong = ≥ 27%). The risk of LAM macro trauma was increased four-fold in the absent/weak contraction group compared to the normal/strong group (OR 4.2, CI 2.1-8.5, $p < 0.001$).

Main results

- **The ultrasound contraction scale can be used in a clinical setting**
- **Absent or weak pelvic floor contraction assessed by the ultrasound contraction scale is associated with LAM macro trauma**

Contraction scale	**Palpation, MOS**	**%**	**Proportional change in 2D AP diameter***
Absent	0	1.5	≤ 1%
Weak	0.5 - 2.0	25.7	2-14%
Normal	2.5 – 4.0	55.4	15-29%
Strong	4.5 – 5.0	17.4	≥ 30%

Table 13 The Ultrasound contraction scale.

6.3.4 The effect of preoperative pelvic floor muscle training as a supplement to pelvic organ prolapse surgery

In paper III we found a statistically significant improvement of pelvic floor contraction assessed with the Modified Oxford scale in the intervention group compared to the control group at the day of the surgery. There were no differences between the groups for other measures of contraction. We found no effect of the intervention on contraction, anatomy or symptoms approximately 28 weeks after surgery (Table 14).

Figure 20 illustrates the results from the mixed model analysis with means and 95 % confidence interval for the two groups respectively.

When comparing the proportion of women with improved contraction, reduction of symptoms and anatomical improvement there was no difference between the groups. Frequencies of bulge sensation or anatomical POP or prolapse in a new compartment were similar (Table 15).

For the overall population including both intervention and control groups, we found an improvement of pelvic floor contraction assessed by palpation and ultrasound, anatomy and symptoms after surgery (Table 16).

Main results

- **Improvement of pelvic floor contraction after POP surgery**
- **No additional effect of pelvic floor muscle training on the outcomes of surgery**

	Baseline	Day of surgery				Postoperative control			
Outcome	**Mean**	**Intervention mean**	**Control mean**	**Difference**	***p***	**Intervention mean**	**Control mean**	**Difference**	***p***
Pelvic floor contraction									
Palpation, Modified Oxford Scale (0-5)	2.1	2.2	1.9	0.3	0.012	2.4	2.2	0.2	0.101
*Ultrasound**(% change)*	17.5	18.2	18.2	0.0	0.999	20.9	19.3	1.6	0.211
Vaginal manometry (cmH_2O)	19.0	17.6	18.1	-0.5	0.664	19.4	19.7	-0.3	0.793
Electromyography (mV)	34.8	32.3	31.3	1.0	0.487	33.5	33.1	0.4	0.815
Sensation of bulge									
Visual analogue scale (0-100)	57.6	55.3	56.5	-1.2	0.761	7.4	6.0	1.5	0.598
Anatomy									
Prolapse distance from hymen (cm)									
Dominant compartment	1.9	1.7	1.9	-0.2	0.394	-1.8	-2.0	0.2	0.556
Anterior compartment	0.8	0.9	0.6	0.3	0.130	-1.3	-1.6	0.3	0.257
Middle compartment	-1.8	-2.3	-1.8	-0.4	0.148	-5.4	-5.3	-0.1	0.870
Posterior compartment	-1.4	-1.5	-1.5	0.0	0.835	-2.5	-2.6	0.1	0.413

Table 14
Mean values and 95% confidence interval (CI) for the groups at baseline, day of surgery and postoperative control. Differences between groups from baseline to day of surgery and postoperative control.
* Proportional change in anteroposterior diameter of the levator hiatus from rest to contraction.

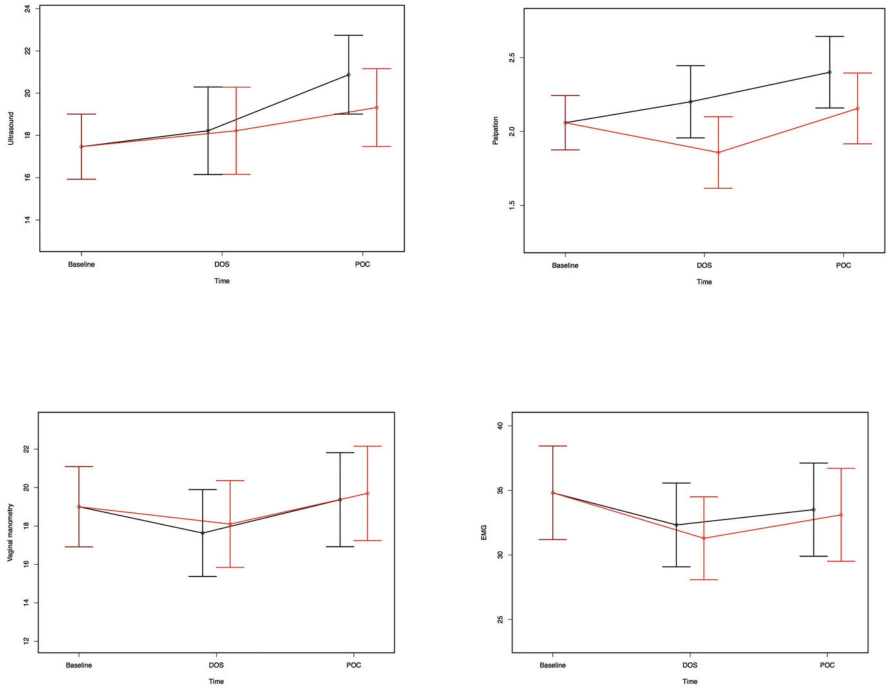
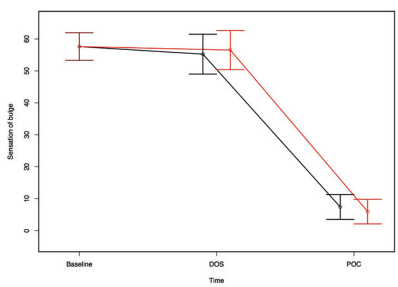
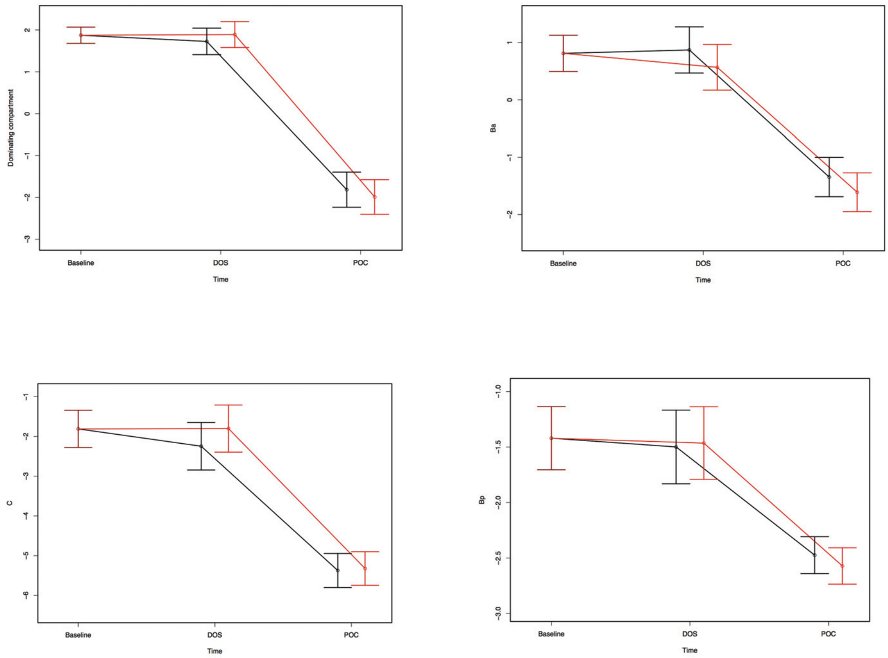


Figure 20 a) Pelvic floor contraction assessed by ultrasound, palpation (MOS), vaginal manometry and surface electromyography at baseline, day of surgery (DOS) and at the postoperative control (POC) with mean and 95 % confidence interval. The intervention group is illustrated by the black line and the control group by the gray line.



b) Bulge sensation assessed by visual analogue scale at baseline, day of surgery (DOS) and at the postoperative control (POC) with mean and 95 % confidence interval. The intervention group is illustrated by the black line and the control group by the gray line.



c) Pelvic organ prolapse measured in centimeters distance from the hymen in the most dominating compartment, and in the anterior-, central and posterior compartment at baseline, day of surgery (DOS) and at the postoperative control (POC) with mean and 95 % confidence interval. The intervention group is illustrated by the black line and the control group by the gray line.

	Total n=148	Intervention n=73	Control n=75	X^2 test
Improvement	%	%	%	*p*
Improved contraction on palpation	44	51	37	0.102
Improved contraction on ultrasound	59	58	59	0.967
Reduction in symptoms	92	90	94	0.310
Reduction in anatomical prolapse in corrected compartment	97	96	99	0.298
Recurrence				
Sensation of vaginal bulge	20	18	22	0.598
Pelvic organ prolapse grade ≥2 in corrected compartment	36	34	37	0.695
Pelvic organ prolapse grade ≥2 in new compartment	5	2	7	0.261

Table 15 Results for improvement or worsening in contraction, symptoms and anatomical findings after surgery.

Outcome	Baseline	Postoperative control	Change	*p*
Pelvic floor contraction				
Palpation, Modified Oxford Scale	2.1	2.3	0.2	0.007
Ultrasound (% change)*	17.5	20.1	2.6	0.001
Vaginal manometry (cmH_2O)	19.0	19.5	0.5	0.420
Electromyography (mV)	34.8	33.3	-1.5	0.126
Sensation of bulge				
Visual analogue scale (0-100)	57.6	6.7	-50.9	< 0.001
Anatomy				
Prolapse distance from hymen (cm)				
Dominant compartment	1.9	-1.9	-3.8	<0.001
Anterior compartment	0.8	-1.5	-2.3	< 0.001
Middle compartment	-1.8	-5.3	-3.5	< 0.001
Posterior compartment	-1.4	-2.5	-1.1	< 0.001

Table 16 Results for mixed model analysis for the overall population including both intervention and control groups for outcome measures after surgery.

* Proportional change in anteroposterior diameter of the levator hiatus from rest to contraction.

6.3.5 Risk factors for recurrence after prolapse surgery

In all, 92% of the women completed the study in paper IV. Anatomical POP after surgery was found in 42%, and anatomical recurrence of prolapse in the compartment that underwent surgery was found in 31% of the participants. In addition, 5% had prolapse in a new compartment, and 7% had a persisting prolapse in a compartment not surgically corrected during the procedure. Nineteen percent of the women reported bulge sensation after surgery. We found an association between LAM macro trauma and overall anatomical POP, but no association with micro trauma. There was no association between recurrence in the same compartment and LAM macro- or micro trauma (Table 17). LAM macro- or micro trauma seemed to increase the risk of POP in a new compartment, but the association was not statistically significant. In addition, LAM macro- or micro trauma had no statistically significant impact on POP in a new compartment. We found no impact of LAM macro-or micro trauma on bulge sensation after surgery.

We found no impact of pelvic floor contraction on any POP ≥ 2 or recurrence. We found a significantly increased risk for reporting bulge sensation in women with normal or strong contraction compared to absent or weak contraction.

We constructed a composite outcome combining clinically significant POP (POP-Q stage ≥ 2) and bulge sensation (yes). We found no associations between the composite outcomes and LAM macro or micro trauma, but we found a borderline significant association between normal/strong contraction and the composite outcome.

The correlation between anatomical POP and bulge sensation was weak, with a Pearson correlation coefficient of 0.31, $p < 0.001$, and only 34% of the women with anatomical POP reported bulge sensation.

Preoperative POP-Q stage ≥ 3 was associated with any POP ≥ 2 (aOR 2.6, CI 1.3-5.2, *p*=0.009) and recurrence in the compartment that underwent surgery (aOR 2.5, 95% CI 1.1-5.5, *p*= 0.025).

Main results

- **Normal pelvic floor contraction is associated with higher risk for bulge sensation after POP surgery**
- **LAM macro trauma is associated with any POP ≥ 2 after surgery**
- **Preoperative POP-Q stage ≥ 3 was associated with both recurrence and any POP ≥ 2 after surgery**

	Levator macro trauma		**aOR**	**Levator micro trauma**		**aOR**	**Pelvic floor contraction**		**aOR**
	Yes (n=92)	***No (n=91)***		***Yes (n=100)***	***No (n=75)***		***Absent -weak (n=76)***	***Normal-strong (n=106)***	
Anatomy n = 183									
Any POP >2	46	30	2.1 (1.1-4.1) *p =0.022**	44	28	1.2 (0.6-2.4) *p =0.532††*	35	41	1.5 (0.8-2.9) *p= 0.233‡‡*
Recurrence in same compartment	33	23	1.7 (0.9-3.4) *p = 0.127***	30	22	1.0 (0.5-2.1) *p =0.962‡*	24	32	1.0 (0.5-2.0) *p = 0.985§*
POP in new compartment	7	2	4.0 (0.8-20.7) *p =0.094*	7	2	3.3 (0.6-17.0) *p = 0.155*	6	3	3.1 (0.7-13.2) *p =0.134*
Symptoms n = 179									
Bulge sensation	19	16	1.1 (0.5-2.4) *p = 0.809*	24	10	1.7 (0.7-4.0) *p =0.231*	9	26	0.4 (0.2-0.9) *p =0.031§§*
Composite n = 179									
Bulge sensation + any POP>2	14	11	1.3 (0.5-3.1) *p =0.612†*	16	8	1.2 (0.5-3.3) *p = 0.656*)	6	19	0.4 (0.1-1.0) *p = 0.058±*

Table 17 Adjusted odds ratios (aOR) and 95 % confidence intervals for anatomical findings and symptoms after surgery. Adjustment was done for preoperative POP stage, previous POP surgery, age, body mass index, parity and prior hysterectomy in a logistic regression analysis.

*	preoperative POP ≥ 3: aOR 2.4 (1.2-4.8), p = 0.010	**	preoperative POP ≥ 3: aOR 2.2 (1.04-4.66), p = 0.038
†	preoperative POP ≥ 3: aOR 3.1 (1.1-9.0), p = 0.039	††	preoperative POP ≥ 3: aOR 2.7 (1.3-5.3), p = 0.006
‡	preoperative POP ≥ 3: aOR 2.6 (1.2-5.8), p = 0.017 age: aOR 1.05 (1.01-1.09), p = 0.012	‡‡	preoperative POP ≥ 3: aOR 2.6 (1.3-5.1), p = 0.005
§	preoperative POP ≥ 3: aOR 2.3 (1.1-4.8), p = 0.030 age: aOR 1.05 (1.01-1.09), p = 0.009	§§	previous POP surgery: aOR 3.7 (1.2-11.9), p = 0.028
±	preoperative POP ≥ 3: aOR 3.1 (1.1-8.9), p = 0.041		

7 Discussion

7.1 Comparison to literature

7.1.1 Prevalence of levator ani muscle trauma

Among parous women from the general population, the prevalence of macro trauma to the LAM was 19% (Paper I), which corresponded well with previous studies.[6, 60, 167] We found no LAM macro trauma among primigravida, whereas among women scheduled for incontinence surgery we found LAM macrotrauma in 15% of women (Paper II), again similar to previous publications.[167] In the population of women scheduled for POP surgery, the prevalence of macrotrauma was 50 % (Paper III), which also corresponds well with previous research in similar populations.[168, 169]

The prevalence of LAM micro trauma was 25% among parous women from the general population, and 57% among women scheduled for POP surgery. Previous publications have included heterogenous patient populations with pelvic floor disorders and found a prevalence of enlarged levator hiatus of 32%.[170]

7.1.2 Pelvic floor muscle trauma and contraction

We found a weaker pelvic floor muscle contraction in women with LAM trauma and POP. Similar results have been documented in previous publications in which palpation, perineometry and different ultrasound measures (absolute measurements of hiatal dimensions, change in AP-diameter, hiatal area, levator plate angle, bladder neck elevation) were used to assess contraction.[6, 15, 17, 19] Other studies have shown a reduction in contraction evaluated by palpation using MOS, but no association between macro trauma and ultrasound measures of contraction.[19] A possible explanation for this difference is that others have used absolute changes while we have used proportional change in ultrasound measures. The advantage of using proportional change is that it takes into account the reduced potential of absolute change in women with small hiatal dimensions at rest.

Another explanation may be that we examined women 15-23 years after delivery whereas Guzman Rojas et al examined participants a few months after delivery. The functional behavior of the connective tissues and muscles soon after delivery and after many years is probably very different.

The association between increasing POP and reduced pelvic floor contraction is also similar to the findings in previous studies, where participants were mostly examined soon after delivery or women recruited from a patient population.[6, 15-17, 19]

7.1.3 Correlation between ultrasound and other diagnostic tools for assessment of pelvic floor contraction

Previous studies have explored the association between change in ultrasound measurements and other measures of pelvic floor contraction.[24, 101, 143] In these studies, some of the ultrasound measurements used were different from ours (absolute change in 3D AP diameter, hiatal area, bladder neck displacement, change in angles), however results from the correlation analysis was moderate and consistent with our findings. We found a moderate correlation between proportional change in anteroposterior diameter in 2D, 3D and hiatal area. The moderate level of correlation between palpation and ultrasound measures can be a result of error due to methodical disadvantages with palpation, as implied by earlier studies.[24, 25]

7.1.4 Reliability of ultrasound for assessment of pelvic floor contraction

Most previous intra- and interrater reliability studies on ultrasound have compared measurements either at rest or contraction,[93, 144, 171-173] and there are only a few that assessed the changes between rest and contraction.[145] ICC was higher for absolute measurements than the proportional changes between rest and contraction, and our ICC values were similar to those found in other studies where primigravida or volunteers were assessed by two raters.[93, 144, 171, 173] Most previous studies do not report the selection in model, type and definition when reporting ICC, which complicates interstudy comparison.

Overall, we found higher ICC for 2D than 3D measurements indicating that 2D measurements are more reliable and reproducible. In addition, 2D ultrasound is available in all gynaecological outpatients clinics and easy to use. For proportional change in 2D AP levator hiatal diameter, the ICC of 0.81 for intrarater reliability indicates excellent reliability. The ICC (average of three raters) of 0.82 implies excellent interexaminer agreement for the measurements in this population,[165] and is higher than the ICC (average of two raters) of 0.77 in another recent publication.[145] The ICC (single measure) of 0.61 is good, providing information on the performance of the test in a clinical setting.

7.1.5 The ultrasound contraction scale

There is no gold standard for assessment of pelvic floor contraction, hence there is no standard to validate a contraction scale against. We constructed the ultrasound scale based on reliability analysis for proportional change in 2D anteroposterior diameter and the correlation to palpation. We used MOS categories for contraction, and the results were quite similar to both the percentiles for proportional change in 2D anteroposterior diameter between rest and contraction, and a previously constructed scale for 3D anteroposterior diameter based on parous women from the general population.[24] There has been a focus on 3D/4D modes for assessment of the pelvic floor, and the devices needed are not readily avaiable. 2D ultrasound is availabel and easy to use. This makes this scale a tool that could be widely used.

7.1.6 Pelvic floor exercise as a supplement to POP surgery

We found no additional effect of preoperative pelvic floor muscle training on contraction, anatomical findings or bulge sensation after surgery. This is in concordance with previous publications on perioperative training and behavioral advice (diet, general exercise, proper emptying of bladder and bowel).[148-150, 174, 175] In these studies contraction was evaluated by palpation or EMG, and other outcomes were anatomical POP and POP symptoms. In contrast to our findings, a study on perioperative PFMT in a randomized controlled setting with 60 participants showed an improvement of contraction assessed by vaginal manometry after three months.[151] The women were scheduled for either incontinence- or prolapse surgery and grade of prolapse was not stated. Other studies have demonstrated effect of PFMT on stress urinary incontinence and smaller prolapses, and this might explain the difference in results. [41, 42, 123, 129]

7.1.7 Intervention and adherence

The effect of PFMT is dependent on the intervention program and the adherence to the program. Our PFMT program is currently in use for urinary incontinence and POP at our hospital, based on international standards and approved by dedicated pelvic floor physiotherapists, who contributed in designing the study.[124] We used a cut-off at 70 % adherence to the PFMT intervention program which consisted of daily exercise. The choice of cut-off was based in the fact that we wanted PFMT to be feasible in a clinical setting. An adherence of 80% to the training program is good, as previous studies have shown a short term adequate adherence in 64% of patients and 23% in the long-term perspective in a clinical setting.[126]

7.1.8 Pelvic floor contraction after POP surgery

Improvement of pelvic floor contraction after surgery regardless of group status (pelvic floor muscle training or control), was somewhat surprising, and not in line with a recently published systematic review.[154] This review stated that there is no clear effect of surgery on pelvic floor muscle morphology and function. However, in the review there was only one study with pelvic floor function as the primary outcome, and this study demonstrated an improvement of contraction assessed by palpation using Modified Oxford Scale, but not for manomerty.[176] In addition, a study of Lone et al, aimed to investigate changes in levator hiatal dimensions after different treatments (surgery, pessary, expectance) for POP.[177] They found a decrease in levator hiatal dimensions 12 months after surgery, not found after expectance or pessary treatment.

7.1.9 The impact of LAM trauma and contraction on recurrence after surgery

The increased risk of any POP $\geq$ 2 after POP surgery coincides with previous studies on risk factors for recurrence after POP surgery.[36, 178] In contrast to this, a recent study of Oversand et al on outcome in the anterior compartment after the Manchester procedure found no impact of LAM trauma.[155] All women underwent the Manchester procedure, whereas women in our study had a variety of procedures. This may explain the differences in results, and our study was not powered to do a sub-analysis on the Manchester procedure alone. We did not find any association between LAM macro trauma and bulge sensation, which is supported by a previous publication showing no association between macro trauma and bother of POP.[179] We found no impact of impaired pelvic floor contraction on anatomical recurrence, and this coincides with previous studies.[180]

We found that an absent or weak contraction was associated with reduced risk for symptoms after surgery which was somewhat surprising. For the composite outcome combining any POP$\geq$ 2 after surgery and bulge sensation, there was as borderline significant reduction in risk with absent/weak contraction. Previous publications have found improved contraction after intensive and supervised PFMT combined with a reduction in symptoms, which is contradictory to our findings.[41, 129] The women in these studies, however, had smaller prolapses, and they did not undergo surgery. An explanation for these differences is that the effect of pelvic floor contraction on bulge sensation might be different in women with smaller prolapses than in women with advanced prolapses scheduled for surgery. The women with normal/strong contraction reporting more symptoms were younger than women with absent- weak contraction. Previous studies have found that younger women are more physically active which may provoke symptoms.[181] In addition, younger women are more likely to report symptoms.[182] A pudendal nerve stretch during delivery can cause reduced motor and sensory pelvic innervation,[183, 184] and women with POP report bulge sensation at higher threshold. POP surgery itself can influence sensation.[185] In our study the results might be influenced by the short follow-up of six months, healing might not be complete and sensation may still be impaired. In addition, the women with absent-weak contraction had borderline significant more previous POP surgery, which may further reduce the sensibility.

7.2 Strengths and limitations

7.2.1 Study size and selection of population

The UROPRO (n=608) and CONTRAPOP (n=330) clinical studies involve large populations, which adds strength to the main findings. In the UROPRO study we included 608 parous women from the general population. The use of women from the general population is one of the major strengths of this study, because most of the available work is based on women either presenting with pelvic floor dysfunction or those selected from a high-risk population (after delivery). There was, however, an oversampling of women with operative vaginal delivery due to the main aim in the parent study. In the CONTRAPOP study we included 330 women from a population of women to whom we consider a good pelvic floor function to be of importance; pregnant women and women with POP and urinary incontinence. We report findings separate for the three groups for background variables and outcomes studied.

7.2.2 Study design

A **cross-sectional study design** (paper I-II) can only show associations and cannot state causality. In addition, findings may be different over time as it is a snapshot. This study design is, however, an inexpensive and fast study to conduct, and it can be used to generate new research ideas.[186]

The randomized controlled trial (paper III) was the main strength of the study. It made it possible to study PFMT as a standard supplement to surgery. A randomized controlled trial can be used to study the effect of an intervention or treatment on a population level and the random allocation to intervention or control groups reduces bias. However, the findings cannot be used to find evidence for individual specific treatment or tailoring of treatment.

Paper IV was a **prospective cohort study** of women scheduled for POP surgery at St Olavs hospital in the time period from January 2017 to June 2018. The findings are relevant for this cohort, but the generalizability of the results can be disputed. The population in this study is close to our clinical population, and we argue that the findings are valid for women undergoing POP surgery in institutions with a population close to ours. The design only allows identification of possible associations and cannot establish causality.

The follow-up time of approximately 28 weeks is a weakness in paper III-IV as long-term reoperation rates and need for further treatment after surgery are important postoperative outcomes that could not be assessed.

7.2.3 Training of examiners

Training of the examiners in ultrasound and off-line analysis, added strength and reduce bias. Raters in the study (Dr. Maria Ø. Nyhus, Dr. Seema Mathew) were validated against experienced raters (Dr. Ingrid Volløyhaug, Dr. Rodrigo Guzman Rojas) with good correlation and agreement. The examiners had long clinical experience in palpation and the use of the POP-Q system prior to study start.

7.2.4 Statistics

In paper I we compare differences between groups using the Mann Whitney U test due to lack of normality some of the variables. The test gives a reduction in statistical power compared to a parametric test, but in this study the high sample size makes up for this reduction. We used Chi square test to test the distribution of categorical variables between the groups and relationship between categorical variables. The test does not allow adjustments for confounding factors, and only crude odds ratios are reported.

In the ICC analysis in Paper II we used two-way mixed as model and absolute agreement as definition, and we reported both single rater and mean of three raters as type, based on the flowchart by Koo et al.[164] We included both intra- and interrater agreement and correlation for ultrasound measures and to other methods assessing pelvic floor muscle contraction. Previous studies have mainly focused on reliability or correlation.[97, 143, 144] The inclusion of three raters made it possible to study reproducibility. In the interrater analysis we included 60 participants, which is a large size for interrater studies.

The mixed model for statistical analysis is a strength in paper III. The mixed model makes it possible to enter all available data in the analysis, including women with missing data. In the longitudinal studies presented in paper III and IV we have only a few women lost to follow up.

In paper IV we used logistic regression for associations between explanatory variables and binominal outcome variables. Performing separate testing on the same data introduces a risk for type I errors, and correction for possible confounding factors is importance. We performed multivariate logistic regression to obtain adjusted odds ratios (aOR) to correct for confounders, both binominal and continuous, reducing the chance for type I errors.[187] The finding of a possible, but not statistically significant association between POP in a new compartment and LAM macro trauma, is interesting, but needs further evaluation in a properly powered study. This finding might represent a possible type 2 error due to small sample size.

In papers I-IV the level of statistical significance was set to 5 %. In situations with borderline statistical significance, the width of the confidence interval was evaluated. When interpreting ICC the confidence interval adds valuable information, hence the ICC is stated with confidence interval.

Confounders are associated both with the explanatory variable and the outcome under study. The choice of confounders adjusted for were based on evidence from the literature. In paper I we adjusted for age, parity and birthweight as risk factors for LAM macro trauma after delivery using ANCOVA,[60, 188] but these potential confounders did not change the results. In paper III, we stratified on preoperative POP stage over or under three and age over and under 60 years. We tested the effect of the stratification variables and found no effect and they were excluded from the analysis. In paper IV we adjusted for age, parity, BMI, previous POP surgery, POP stage under or over 3 at baseline and previous hysterectomy in the logistic regression model. [36, 72, 138]

7.2.5 Bias

Selection bias

For all papers there is a potential selection bias because women accepting participation in a study exploring pelvic floor function may be more interested in pelvic floor exercise and health issues in general. They may be more physically active than women declining to participate. Thus, it is a limitation of this study that we did not collect data on physical activity and work-load. Women with severe symptoms are more likely to participate in studies, and for POP, an active life with situations increasing intraabdominal pressure might reinforce the symptom load.

UROPRO

More women with symptomatic POP met for clinical examination and they were older than the background population they were recruited from. The response rate to questionnaires in the parent study was 53% and 72% of the women invited to clinical examination met for their appointment. [62, 189] In addition, no information was available regarding PFMT, which might have influenced the results regarding contraction.

CONTRAPOP

The women declining randomization were older and had more previous surgery, but POP-Q score and contraction were similar. Furthermore, 72 women declined any participation in the study, and we have no background information on this population, which may represent a selection bias. In the RCT we found no effect of intensive pelvic floor exercise on contraction, anatomy or bulge sensation assessed by VAS. Thus, we found it reasonable to consider the entire group of 159 participants from the RCT and 41 who declined randomization as a heterogenous cohort.

Information bias

In the UROPRO study a possible interrater difference was eliminated using only one experienced examiner, limiting the informational bias. The standardized training of the examiners in the CONTRAPOP study, were done to avoid information bias regarding recording and offline analysis of ultrasound volumes. Validation consisted of evaluation of 20 volumes off-line with calculation of ICC or Cohens kappa to determine correlation and agreement prior to data collection and off-line analysis.

All women who met at the baseline visit were thoroughly instructed in how to properly contract their pelvic floor. If they had difficulties performing a proper contraction they were corrected under sonographic guidance. This gave an increased knowledge and awareness of pelvic floor contraction, also for women in the control group.

A limitation of paper III is the lack of blinding for group status and clinical information when assessing palpation at the day of surgery and the postoperative control. This could only have been avoided if palpation were assessed by another person than the examiner assessing POP and obtaining the ultrasound volumes. On the day of surgery there was a statistically significant difference between the intervention and control group in MOS. This finding has not been emphasized due to lack of blinding, and the effect had disappeared at the postoperative examination. The examiner was, however, blinded at time of analysis of ultrasound volumes limiting possible informational bias.

In paper III we recorded adherence to intervention using a training diary, in which the women marked their exercise sessions. The diary was collected at the day of surgery, and if they had forgotten their diary, they were instructed to send it by mail. If we did not receive a diary, women were interviewed by telephone. This may introduce a recall bias, as there was a delay between the day of surgery and the telephone interview. A total of 37 (49%) delivered their diary, and 33 (44%) were telephone screened. For the missing 5 (7%) we collected information from the electronic physiotherapy journal.

7.2.6 Validity

Internal validity reflects the degree the explanatory variable may affect the outcome, or if some other factor may affect the outcome.[190] External validity refers to the generalizability of the results.[191]

Paper I had a cross-sectional design including a heterogenic population of parous women from the general population, giving the study a high external validity. The internal validity is regarded as good since we could not identify other possible explanatory factors for the association between LAM trauma and reduced contraction.

The population selected for paper II was heterogenic and represented the women to whom health care providers recommend pelvic floor muscle training. This maintains a good external validity. The statistical analysis with correlation and reliability analysis maintained the internal validity to a sufficient level.

An RCT will always have perfect internal validity if the randomization procedure has been properly performed. The selection of participants included was heterogenic and represented a population close to the patient population. Forty-one declined participation in the RCT, but they were included in paper II and paper IV. Analysis showed that the women were statistically significant older and had more previous POP surgery. This may have influenced the external validity in this part of the study.

Paper IV was a cohort study on the possible association between baseline explanatory factors and outcomes after POP surgery. The confounding factors included were known risk factors from the literature. We state the adjusted OR. This leads to a moderate internal validity, despite the cohort design. The external validity is arguably high, and the results are therefore generalizable to women undergoing POP surgery in a population similar to ours.

7.2.7 Quality of tools

In both the UROPRO and CONTRAPOP studies we chose validated tools to assess anatomy, symptoms and contraction.[23, 25, 81, 157] The tools are commonly used in clinical and research settings, and the correlation between the methods and the reliability and reproducibility have been studied.[24, 58, 90, 96-102] Despite the widespread use, there are some issues with the methods that may affect results, interpretations and comparison to other studies.

Vaginal manometry

Vaginal manometry is performed with an intravaginal sensor. There are several different devices on the marked for this purpose, which can make it difficult to compare results. In paper I we used Camtech®, a product mainly used in Norwegian research settings.[20, 24, 192] In paper II-III we used Peritron®, where the sensor is inflated prior to contraction to increase the contact surface. If the sensor is not properly filled, it can influence the result. The sensors cannot distinguish between increased vaginal pressure due to pelvic floor muscle contraction and increased intraabdominal pressure. In additional analysis not included in paper II, we found weak to moderate correlation to ultrasound measures. This correlation can be due to sources of error related to the methods.

EMG

EMG is another indirect method for contraction measuring activity in the muscle. There are two types of sensors available for this purpose; needle and surface EMG.[91] CONTRAPOP study we used a surface electrode EMG. The surface electrode is inferior compared to the needle electrode, but the needle is more painful and less used.[91] We found weak to moderate correlation with ultrasound.

Palpation

Palpation is the most widespread method for assessment of pelvic floor contraction in clinical practice today. There are several different scales for scoring. The Modified Oxford scale was developed by Laycock, who also developed the PERFECT scheme, adding assessment of endurance, timed repetitions and fast contraction to the evaluation[23, 84] The Brink score assesses pressure and duration of contraction together with vertical displacement on a scale from 0-12.[83] Direct comparison of these different scales is challenging. All of these scoring scales are dependent on the examiners experience. In paper I there was one examiner, but for paper II-III there were three examiners assessing palpation. For a selection of participants two examiner (blinded for each other findings) assessed palpation for reliability analysis. We found a good reliability, and this limits the effect of informational bias. In the correlation analysis we found a moderate correlation with ultrasound.

POP-Q

POP-Q was used for assessment of anatomy and staging of POP.[81] The method is widely used today. The system is complex, but it includes all the important aspects of features of anatomical POP. The examiners in these studies were experienced in using POP-Q prior to study start, and the system makes results comparable to other studies.

Ultrasound

The advantage of ultrasound for assessment of pelvic floor contraction is that it is objective, reliable and gives the possibility to correct sources of error throuh biofeedback.[31, 32, 103] There is, however, limitations to this method. There is a need for training in how to obtain and interpret the images. Several studies have found steep learning curves in the use of transperineal ultrasound.[173] We have used standardized methods for diagnosing LAM macro trauma.[58]

VAS

In study III-IV we used visual analogue scale and sensation yes/no for assessment of symptoms of POP. This choice was based on publications showing that bulge sensation correlates well with other clinical findings,[193] and that VAS corresponds well to validated questionnaires.[157] VAS has been used in previous studies on symptoms related to POP.[179, 194] Inclusion of validated questionnaires in this study could have strengthen the results, and will be considered in forthcoming research.

Composite outcome

In paper III and IV we evaluated the outcomes after POP surgery and included symptoms, anatomy and contraction to get a comprehensive view. The construction of composite outcomes combining symptoms and anatomical POP was sensible since a combination of symptoms and anatomical POP is the indication for treatment of POP.

7.3 Clinical and statistical significance

A statistically significant result does not automatically imply a clinically significant finding. Statistical significance states the reliability of the study and clinical significance states the clinical importance of the finding through the effect size.[195]

In the power calculation we used differences of 0.5 in mean MOS score as the expected significant difference between the parous women from the general population and patient populations. This is probably the smallest detectable difference in palpation on a 6-point scale. On the day of surgery we found a statistically significant difference of 0.3 for the intervention group. This difference is hard to detect clinically. We found an improvement of contraction in the overall population after surgery for palpation, again with a small effect size. In these analyses we compared means on a population level. Also for ultrasound measurements, the effect size is small, and the difference statistically significant. Ultrasound is objective and several sources of error can be excluded. Thus, we argue that that the clinical significance is valid.

7.4 Clinical implications

7.4.1 Pelvic floor muscle trauma and contraction

We found an association between LAM macro trauma and reduced contraction of the pelvic floor. We found no association between micro trauma and reduced contraction, indicating that macro trauma has most impact on pelvic floor contraction. In addition, POP in the anterior and central compartment was associated with reduced contraction. The impaired contraction may be a contributor to development of POP. We found no association between posterior compartment prolapse and reduced contraction, which indicated a different mechanism behind development of posterior compartment prolapse. This leads to question that isolated posterior prolapse should be dealt with as a separate condition.

Another important finding was that most women with LAM trauma had a residual function in the muscle, and this suggests that they can benefit from pelvic floor muscle training. The training may improve muscle function and relieve symptoms of pelvic floor disorders,[41] and postpone or prevent the development of POP. [42] It is important to identify these women at an early stage, and we suggest that pelvic floor ultrasound should be a part of a standardized gynecological examination weeks or months after the delivery of their first baby.[196]

Early detection of LAM trauma could be important for initiation of pelvic floor exercise to prevent development of POP or pelvic floor dysfunction.

7.4.2 Assessment of pelvic floor contraction

Pelvic floor ultrasound can be used as a reliable method for quantification of pelvic floor contraction, and we created an ultrasound contraction scale for assessment of pelvic floor contraction. As assessment of pelvic floor contraction should be a part of the examination of the urogynecology population, there is a need for defining how this assessment should be performed, both in research and clinical settings. The reliability of ultrasound for quantification of pelvic floor contraction is good, it correlates moderately to existing methods, and one may argue that the method is more objective and reduces sources of error that are present with palpation and manometry. Thus, the method is suitable for measuring pelvic floor contraction. In addition, two-dimensional ultrasound is available, low-cost and easy to use with little discomfort for women. 2D transperineal ultrasound for assessment of contraction using the ultrasound contraction scale, should be introduced in a clinical setting in the primary evaluation of the urogynecology patient; to teach pelvic floor exercise, to evaluate conservative treatment and to tailor the timing for surgical intervention. The 2D ultrasound contraction scale can also be used in other disciplines, such as urology and colorectal surgery.

7.4.3 Pelvic floor exercise as supplement to POP surgery

We found no evidence supporting the introduction of pelvic floor muscle training as a standard adjunct to POP surgery. However, we found an improvement in contraction of the pelvic floor in the entire population after surgery, which most likely can be explained by the anatomical corrections. The majority of women in this study had a POP stage 3 or 4. The advanced stage of POP in this population makes it reasonable to believe that the size of the prolapse matters and makes it difficult to perform proper pelvic floor contraction.

7.4.4 The impact of pelvic floor muscle trauma and contraction on anatomy and bulge sensation after surgery

This research adds knowledge about the impact of LAM trauma and contraction on anatomical and symptomatic surgical outcome. Women with LAM trauma were younger at the time of surgery, and we suggest focus that early detection of trauma in gynecological examinations can be of importance. With early identification of women with LAM macro trauma, prior to development of POP, these women can be recommended PFMT to prevent and postpone development of POP. In addition, preoperative knowledge can contribute to the choice of procedure and follow-up after surgery.

8 Conclusions

- LAM macro trauma was associated with weaker pelvic floor muscle contraction
- Women with POP had weaker contraction than women without prolapse
- Ultrasound is an objective and reliable method for evaluation of pelvic floor contraction
- The ultrasound contraction scale based on proportional change between rest and contraction in 2D anteroposterior diameter can be used in a clinical setting
- Pelvic floor contraction improved after POP surgery
- There was no additional effect of preoperative PFMT on contraction, anatomy or bulge sensation after surgery
- LAM macro trauma was associated with increased risk of anatomic failure six months after POP surgery
- Normal pelvic floor muscle contraction was associated with increased risk for reporting bulge sensation after surgery

9 Future perspectives

9.1 Follow up of the UROPRO and CONTRAPOP populations

We plan a follow-up of the women from the UROPRO study in five to ten years to look at the natural course of POP development and pelvic floor contraction among parous women from the general population.

For the women in the CONTRAPOP study, we plan a long-term follow-up of in three to five years after surgery to look at anatomy and symptoms of POP. In addition, we aim to explore rates of recurrence, reoperation, and to identify risk factors for recurrence in the long term. We would also like to examine how many of these women maintain PFMT over time. For pelvic floor function it would be interesting to look at contraction in the long-term perspective.

9.2 New research

The ultrasound contraction scale developed in paper II needs further validation in clinical setting. It can be used together with other tools for measuring contraction. In addition, it would be interesting to explore the correlation between on-line and off-line analysis of ultrasound volumes, as the evaluation of ultrasound is performed on-line in a clinical setting, and off-line in a research setting. In the off-line setting, there are several functions in the 4D view program that gives opportunities to optimize the volume, but this is time consuming. Most functions are also available in the ultrasound machines, but in the clinical setting time is limited. It would be interesting to explore if examination time influence the methods quality and leads to over- or underestimations.

In paper III we found no additional effect of PFMT on the outcome after POP surgery. More studies are needed on the effect of pelvic floor muscle training as a supplement to surgery and to focus on the exercise, timing of exercise and duration. In research on pelvic floor muscle training, the attention should be pointed towards how to maintain a good adherence to the intervention program and data collection. Collaborations with other academic communities exploring innovation of effective online patient reported outcomes and other ways of collecting objective clinical data should be prioritized. It may also be of interest to do targeted research to explore if there are differences in effect of PFMT as an adjunct to surgery depending on compartment affected.

The findings in paper IV have raised several questions regarding age, muscle function, sensation and symptoms of POP. It would be of interest to examine the association between age and symptoms of POP. Does age influence bulge sensation? Further evaluation of the relationship between function in sensory nerves, sensation and symptom load are of interest as well as the effect of vaginal surgery on sensation.

LAM macro trauma is a risk factor for any POP$\geq$ 2 after surgery, and our findings suggest that it has an impact on POP in a new compartment. However, our study design was not optimal for confirming this statement. A properly powered study is needed.
There is a need for further investigation on what is the optimal treatment of women at risk of experiencing a recurrence or new POP.

9.3 Is it time to redefine the term recurrence?

It is clear that there remain problems with how to define recurrences and estimating what is the best result possible for each individual case. The definition of an anatomical stage 2 prolapse as a significant POP leads to a prevalence of recurrence after surgery between 38-45% in different publications, supported by our findings of 36% in the present study.[134, 197] However, only 20% report symptoms after POP surgery and the correlation between symptoms and anatomy is poor. A recent systematic review concluded that the most commonly used definition of anatomical success after surgery was based on anatomical findings alone, despite knowledge about the importance of symptoms, rates of reoperation and need for conservative treatment.[198] The use of a composite outcome measure based on symptoms, anatomy and need for treatment would be more suitable for this purpose as the main indication for intervention is symptomatic POP. This assertion is supported by other publications.[198]

9.4 Future treatment of pelvic organ prolapse

The future of POP treatment is still in dispute.[199-201] Synthetic meshes for use in surgical treatment of stress-urinary incontinence and POP were introduced in the early 2000. The entrance of the tension free tapes revolutionized surgery for stress incontinence but not only has further progress stopped with synthetic mesh use deemed controversial, there is now skepticism towards use of incontinence tapes. [202, 203] Their use is prohibited in Scotland and "on hold" in England, leaving the surgeon with no other choice than using old and more comprehensive procedures.[204]

The use of synthetic mesh in POP surgery has been disputed for a longer time. In the Nordic countries it has had a place in recurrence surgery, but in recent years it has been used less frequently.[39, 40] Today the treatment is reserved for hand-picked patients. The most common complaints after vaginal mesh surgery is mesh erosion, infection, pain, dyspareunia, shrinkage of the mesh with a shortened vagina and fistula formation requiring multiple surgeries.[205, 206] In the last years the industry have been withdrawn most mesh products the market.[39, 40, 202]

A multicenter parallel group study with 1350 women, including native repair, synthetic mesh and graft augmentation showed no difference in outcomes in terms of effectiveness, quality of life, adverse effects or other outcomes in the short term, but one in ten women experienced mesh related complications within the two years follow-up.[207] The need for new thinking in surgical management of POP is stressed in a commentary to this publication.[208] There is ongoing research using stem cells, [209, 210] and this might be a future solution for managing POP, however, not clinically available at present.

In the Nordic countries the Manchester procedures has been widely used, and recent research has found good short- and long-term outcomes, few complications and low cost compared to other procedures.[37, 211-213] This suggests that we should continue to use the Manchester procedure and keep training urogynecologists in native repair.

9.5 How to avoid recurrence surgery

The most important factor to avoid recurrent surgery is to postpone the primary surgery. There has been a common, erroneous understanding among patient- and physicians that a woman needs early surgery as to avoid distress when she gets older. Today we perform most POP surgery in local anesthesia and sedation, and there is no fixed upper age limit for POP surgery. Thus, the focus on postponing surgery until conservative methods have been tried should be considered standard practice.

We found no effect of stronger pelvic floor contraction on recurrence after surgery in women with advanced POP. Prior studies including mainly POP stage 2 have found an effect on symptoms.[41, 42, 129, 214] This suggests that PFMT is more effective in smaller prolapses. There is an association between LAM macro trauma and development of POP, and if we can identify women with LAM trauma after vaginal delivery as women at risk for developing POP, they could receive intensive PFMT to prevent or postpone the development of POP.

Approximately seven percent of the women had a POP-Q ≥ 2 in a compartment at inclusion that was not corrected during surgery, most often at vaginal hysterectomies and laparoscopic sacrocolpopexy/uteropexy. It is tempting to believe that a central compartment prolapse leads to a traction on the anterior compartment, and that a correction of the central compartment will resolve also the anterior compartment POP. Persisting prolapse after these procedures, however, implies that concomitant surgical correction in the anterior compartment should be considered.

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11 Appendix I Papers

PAPER I

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Association between pelvic floor muscle trauma and contraction in parous women from a general population

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KEYWORDS: 3D/4D ultrasound; levator ani; pelvic floor; pelvic floor disorder; pelvic floor function; pelvic floor muscle contraction; pelvic organ prolapse

ABSTRACT

Objective *To study possible associations between pelvic floor muscle contraction, levator ani muscle (LAM) trauma and/or pelvic organ prolapse (POP) ≥ Stage 2 in parous women recruited from a general population.*

Methods *This was a secondary analysis of data from a cross-sectional study of 608 parous women from a general population examined using the POP quantification system (POP-Q) and three-dimensional/four-dimensional transperineal ultrasound for identification of LAM macrotrauma (avulsion) and microtrauma (distension of levator hiatal area > 75th percentile on Valsalva maneuver). Muscle contraction was assessed using the modified Oxford scale (MOS), perineometry and ultrasound measurement of proportional change of anteroposterior hiatal diameter and levator hiatal area at rest and on pelvic floor muscle contraction. The Mann–Whitney* U*-test was used to study associations between pelvic floor muscle contraction, LAM trauma and POP.*

Results *Women with macrotrauma* ($n = 113$) *had significantly weaker median pelvic floor muscle contraction, as measured using MOS and perineometry, than did women with an intact LAM* ($n = 493$) *(contraction strength was 1.5 (range, 0.0–5.0)* vs *3.5 (range, 0.0–5.0) on MOS, and vaginal squeeze pressure was 15.0 (range, 0.0–78.0) cmH_2O* vs *28.0 (range, 0.0–129.0) cmH_2O on perineometry;* $P < 0.001$*). This was also demonstrated by ultrasound measurement, with a proportional change in hiatal area of 19.9% (range, 4.1–48.0%)* vs *34.0% (range, 0.0–64.0%)* ($P < 0.001$) *and proportional change in anteroposterior diameter of 16.2% (range, −5.7 to 42.6%)* vs *26.0% (range, −3.4 to 49.4%)* ($P < 0.001$)*. No statistically significant difference between women with* ($n = 65$)*, and those without* ($n = 378$)*, microtrauma was found after excluding women with macrotrauma. Women with POP had weaker muscle contraction than those without; in those with POP-Q ≥ 2* ($n = 275$) *compared with those with POP-Q < 2* ($n = 333$)*, muscle contraction strength was 3.0 (range, 0.0–5.0)* vs *3.5 (range, 0.0–5.0) on MOS, vaginal squeeze pressure was 21.0 (range, 0.0–98.0) cmH_2O* vs *28.0 (range, 3.0–129.0) cmH_2O on perineometry, proportional change in hiatal area was 29.6% (range, 0.0–60.9%)* vs *33.8% (range, 0.0–64.4%) and proportional change in anteroposterior diameter was 22.8% (range, −5.7 to 49.4%)* vs *25.7% (range, −3.4 to 49.4%)* ($P < 0.001$ *for all).*

Conclusions *LAM macrotrauma was associated with weaker pelvic floor muscle contraction measured using palpation, perineometry and ultrasound. Women with POP had weaker contraction than did women without POP. Copyright © 2018 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

The levator ani muscle (LAM) plays an important role in the maintenance of continence and support of the pelvic organs[1]. The median part of the LAM surrounding the urethra, vagina and rectum provides resting tone and contraction, giving a narrow closure of the urogenital hiatus that prevents descent of the pelvic organs[2]. LAM trauma is detected in about 13–21% of women after vaginal delivery[3–5]. Macrotrauma is defined as abnormal insertion of the muscle into the pubic bone, with uni- or bilateral loss of muscle attachment[6], while microtrauma is irreversible overdistention of the levator hiatus[7]. Both injuries cause enlargement of the levator hiatus and are therefore associated with an increased risk of pelvic organ prolapse (POP) later in life[8,9].

Impaired muscle contraction is possibly involved in prolapse development[10]. An association between

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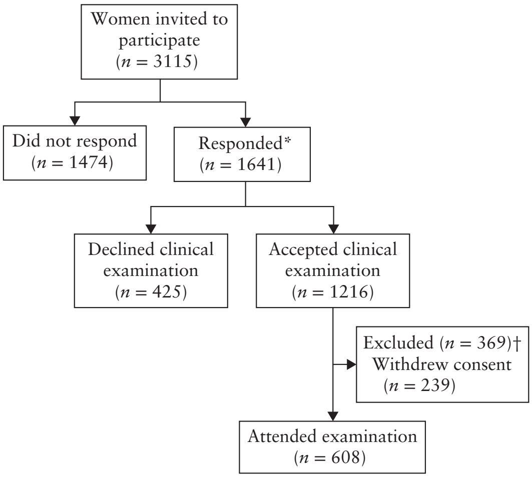

Figure 1 Flowchart of study participants. *Responded to questionnaire about pelvic floor disorders. †Not invited for clinical examination according to protocol of parent study ($n=221$), lived too far away ($n=109$) or was unable to attend during study period ($n=39$)[17].

LAM trauma and altered muscle contraction has been demonstrated in urogynecological patients and women after delivery[11–15]. Different tools have been used to assess pelvic floor muscle contractility, such as digital palpation with the modified Oxford scale (MOS) and vaginal manometry/perineometry. More recently, pelvic floor ultrasound has been shown to be a valuable tool for the assessment of muscle contraction[13]. Studies following women a few months after delivery have shown reduced muscle contraction associated with LAM macrotrauma[13,15]. Moreover, macrotrauma is associated with reduced muscle contraction in women with a pelvic floor disorder[11], and women who are unable to contract their pelvic floor muscles have a high rate of LAM macrotrauma[16]. We were unable to find a study on the association between muscle function, LAM trauma and anatomical POP in parous women from a general population.

The aim of this study was to assess possible associations between pelvic floor muscle contraction, LAM trauma and/or POP ≥ Stage 2 in parous women from a general population.

METHODS

This was a secondary analysis of data from a cross-sectional study in which the primary aim was to investigate the prevalence of pelvic floor muscle trauma after different modes of delivery. Women who delivered their first child at Trondheim University Hospital between January 1st 1990 and December 31st 1997 were identified. All women who had a Cesarean section or operative vaginal delivery, and a similar number of consecutive women with normal vaginal delivery, from January until June each year, were invited to participate (Figure 1). All women signed informed consent prior to inclusion, and the study was approved by the local regional ethics committee (REK Midt 2012/666). The study sample size was based on power calculations for the primary outcome in the parent study[17]. Parity and infant birth weight were obtained from the medical birth registry of Norway and body mass index (BMI) was self-reported.

A total of 608 women attended for clinical examination. They were instructed on how to relax and contract their pelvic floor and perform a Valsalva maneuver with a duration of 6–8 s[18]. The women underwent a gynecological speculum examination with assessment using the International Continence Society pelvic organ prolapse quantification system (POP-Q)[19]; POP-Q Stage ≥ 2 in any compartment was considered clinically significant.

Muscle strength was assessed by digital palpation using the examiner's index and middle fingers intravaginally at the level of the LAM, approximately 4 cm into the vagina. The muscle was assessed at rest and during contraction. Strength on maximum contraction was scored using the MOS, where 0 is no contraction, 1 is flicker, 2 is weak, 3 is moderate, 4 is good and 5 is a strong contraction[20]. The mean MOS score of both sides was used for analysis. Vaginal squeeze pressure was measured using perineometry (Camtec AS, Sandvika, Norway). A balloon connected to a fiber-optic pressure transducer was placed in the vagina, with the middle of the balloon at the level of the levator ani[21]. Each woman performed three pelvic floor contractions, and the best contraction was used in the analysis.

Finally, a three/four-dimensional (3D/4D) transperineal ultrasound scan of the pelvic floor was performed at rest, on pelvic floor contraction and on Valsalva maneuver using a Voluson S6 ultrasound machine (GE Medical Systems, Zipf, Austria) and abdominal 3D probe (RAB 4–8 MHz). The acquisition angle was set to 85° with recording in the midsagittal plane. One examiner (I.V.), who was blinded to the clinical examination and identity of the women, performed offline analysis using 4D-View software version 14 (GE Medical Systems). The ultrasound volumes obtained during the strongest of three contractions and those in which Valsalva maneuver caused the most distal displacement of the pelvic organs were selected for analysis. LAM macrotrauma was defined as abnormal muscle insertion to the pubic bone in the three central slices on tomographic ultrasound imaging (Figure 2)[22]. Poor image quality or significant artifact led to exclusion from the analysis.

For the definition of overdistended hiatal area on Valsalva (microtrauma), the 75th percentile was used to define the upper limit of the normal range, as this gave group sizes appropriate for comparison. This gave an upper cut-off of normal hiatal area on Valsalva of 42 cm^2. A smaller hiatal area on Valsalva than at rest, indicating pelvic floor coactivation, led to exclusion from the analysis.

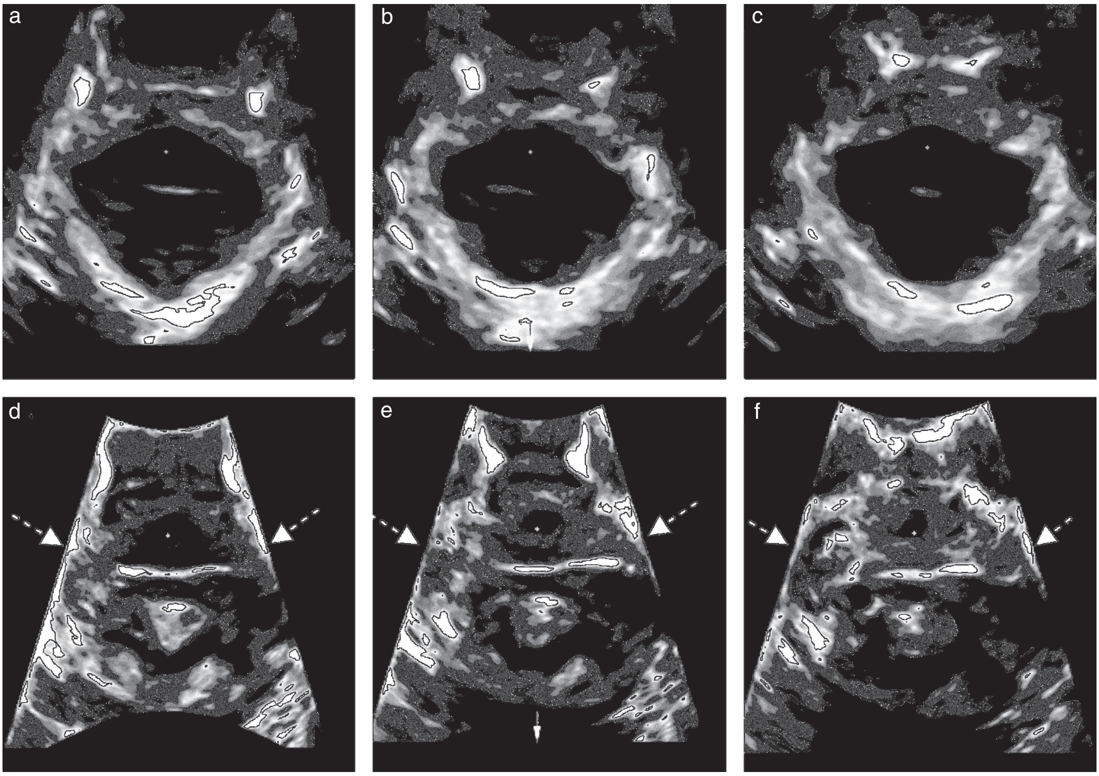

Figure 2 Tomographic ultrasound images of intact levator ani muscle (LAM) (a–c) and bilateral LAM macrotrauma (d–f) (arrows) in plane of minimal hiatal dimensions (a,d) and slices 2.5 mm (b,e) and 5.0 mm (c,f) cranial to this.

We measured the anteroposterior (AP) diameter (from the distal point of the symphysis to the proximal point of the puborectalis muscle) and hiatal area at rest and on contraction, in a rendered volume of 1–2 cm thickness (Figures 3 and 4). The proportional differences in AP diameter and hiatal area were used as ultrasound measures of contraction, and were calculated using the formula: $100 \times ((\text{measurement}_{\text{rest}} - \text{measurement}_{\text{contraction}})/\text{measurement}_{\text{rest}})$[23,24].

Statistical analysis was performed using SPSS version 24 (IBM Corp., Armonk, NY, USA). Normal distribution was tested for using the Kolmogorov–Smirnov test and Q–Q plots. All background variables (BMI, age, infant birth weight and parity) and ultrasound measurements of contraction were normally distributed, but perineometry and MOS were not. Difference in background variables was tested using independent samples *t*-test between women with intact and those with injured LAM and between women with, and those without, POP-Q $\geq$ 2. The Mann–Whitney *U*-test was used to explore associations of LAM injury and POP-Q $\geq$ 2 with measures of pelvic floor muscle contraction, and the chi-square test was used to test the association between LAM injury and being unable to contract (MOS score = 0). In addition, for normally distributed variables (ultrasound measurements), analysis of covariance (ANCOVA) was performed, adjusting for variables that were significantly different between the groups; statistical significance was set at $P < 0.05$.

RESULTS

In total, 608 women were examined using POP-Q and palpation (MOS) and were included in the analysis (Figure 1). LAM macrotrauma was not possible to determine for two women because of artifacts, and hiatal area on Valsalva was measured in 555 women. Vaginal perineometry was performed in 559 women.

Mean BMI at the time of inclusion was 25.6 (range, 15.9–47.3) kg/m^2, mean age was 47.9 (range, 35–64) years and 126 of the 541 (23.3%) women for whom this information was available were postmenopausal. Mean ± SD birth weight of the heaviest infant was 3862 ± 475 (range, 2350–5550) g and parity was 2.2 ± 0.8 (range, 1–5). Background variables and differences between the groups are outlined in Table 1. Mode of delivery was normal vaginal for 217/608 (35.7%) women, forceps for 159/608 (26.2%), vacuum for 131/608 (21.5%) and Cesarean section for

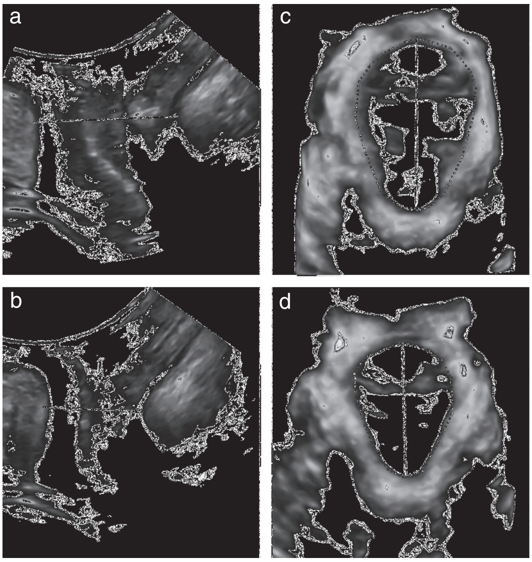

Figure 3 Sonographic images of intact levator ani muscle. (a,b) Two-dimensional images in midsagittal view in plane of minimal hiatal dimensions, showing anteroposterior levator hiatal diameter from distal border of pubic symphysis to puborectalis muscle (lines) at rest (a) and on contraction (b). (c,d) Three-dimensional images showing anteroposterior hiatal diameter and area (solid lines and dotted lines, respectively) at rest (c) and on contraction (d).

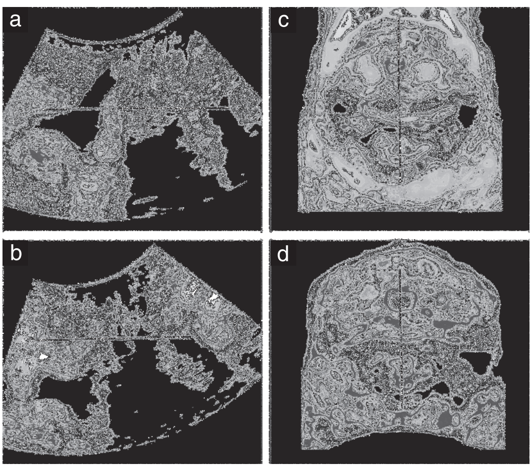

Figure 4 Sonographic images of levator ani muscle macrotrauma. (a,b) Two-dimensional images in midsagittal view in plane of minimal hiatal dimensions, showing anteroposterior levator hiatal diameter from distal border of pubic symphysis to puborectalis muscle (lines) at rest (a) and on contraction (b). (c,d) Three-dimensional images showing anteroposterior diameter and hiatal area (solid lines and dotted lines, respectively) at rest (c) and on contraction (d).

101/608 (16.6%). LAM macrotrauma was diagnosed in 113 (18.6%) women, overdistended levator hiatus on Valsalva in 138 (22.7%) and POP-Q ≥ 2 in 275 (45.2%). The overall median change in AP diameter was 24.3% (range, −5.7 to 49.4%) and median change in hiatal area was 31.9% (range, 0.0–64.0%). On maximum contraction, the overall median strength was 3.0 (range, 0.0–5.0) on MOS, and vaginal squeeze pressure was 25.0 (range, 0.0–129.0) cmH_2O on vaginal perineometry.

The proportion of women unable to contract (MOS score = 0) was 21/606 (3.5%), of whom 13/21 (61.9%) had LAM macrotrauma. In contrast, the proportion of women able to contract (MOS score > 0) was 585/606 (96.5%), of whom 100/585 (17.1%) had LAM macrotrauma, giving an odds ratio of 7.88 (95% CI, 3.18–19.51) ($P < 0.001$) for MOS score = 0 in women with macrotrauma. The median values for the different measures of pelvic floor muscle contraction (palpation, perineometry and ultrasound) for women with, and those without, levator injury and women with, and those without, POP-Q ≥ 2, with comparisons between the groups, are shown in Tables 2 and 3, respectively. All measures demonstrated weaker contraction among women with LAM trauma ($P < 0.001$). For women with an overdistended hiatal area, the difference was not significant after excluding women with macrotrauma. Women with POP-Q ≥ 2 in any compartment had weaker contraction than those with POP-Q < 2. Statistically significant differences were found in the anterior and central compartments, but not in the posterior compartment. For ultrasound measurements, ANCOVA was used to adjust for age, parity and birth weight, but these potential confounders had a small effect size and did not change the results (partial eta squared value < 0.004 and $P > 0.14$ for all potential confounders).

DISCUSSION

We found significantly weaker pelvic floor muscle contraction in women with LAM macrotrauma. No difference in contraction between women with large and those with normal levator hiatal area on Valsalva was found after excluding women with macrotrauma. We also found weaker muscle contraction in women with POP.

Our findings are in line with those of previous studies in women with a pelvic floor disorder and women examined soon after delivery, in which MOS-evaluated palpation, perineometry and different ultrasound measures were used to assess contraction[11–13,15]. In contrast to our results, Guzman Rojas *et al.*[13] found an association between microtrauma and a weaker contraction assessed by MOS and ultrasound in primiparae, even after eliminating women with macrotrauma. However, they found no association between LAM macrotrauma and ultrasound measurements of contraction. A possible explanation is that they used absolute change in ultrasound measurements, whereas we used proportional change. We believe it is more appropriate to use proportional change, as this takes into account the

Table 1 Background characteristics of parous women with and those without levator ani muscle trauma and pelvic organ prolapse quantification system (POP-Q) score ≥ 2

	Levator macrotrauma (n = *606)*			*Hiatal area > 42 cm²* (n = *555)*			*POP-Q ≥ 2* (n = *608)*		
Characteristic	*No*	*Yes*	P	*No*	*Yes*	P	*No*	*Yes*	P
n	493	113		417	138		333	275	
BMI (kg/m²)	25.9 ± 4.6	25.4 ± 4.2	0.295	25.8 ± 4.5	26.6 ± 4.8	0.084	25.8 ± 4.6	25.8 ± 4.4	0.839
Age (years)	47.8 ± 5.0	48.8 ± 4.4	0.038	48.2 ± 5.0	47.5 ± 4.4	0.140	48.0 ± 1.8	47.9 ± 4.9	0.951
Parity	2.21 ± 0.83	2.19 ± 0.74	0.790	2.18 ± 0.83	2.3 ± 0.77	0.136	2.1 ± 0.8	2.3 ± 0.8	0.009
BW, heaviest infant (g)	3854.7 ± 473.2	3888.4 ± 487.6	0.508	3844.7 ± 468.8	3935.3 ± 482.6	0.062	3797.1 ± 461.0	3918.5 ± 481.6	0.004

Data are given as mean ± SD. Data compared using *t*-test. BMI, body mass index; BW, birth weight.

Table 2 Measurements of pelvic floor muscle contraction in parous women with and those without pelvic floor muscle trauma

	Levator macrotrauma (n = *606)*			*Hiatal area > 42 cm²* (n = *555)*			*Hiatal area > 42 cm², women with macrotrauma excluded* (n = *443)*		
Parameter	*No*	*Yes*	P	*No*	*Yes*	P	*No*	*Yes*	P
n	493	113		417	138		378	65	
MOS	3.5 (0.0 to 5.0)	1.5 (0.0 to 5.0)	< 0.001	3.0 (0.0 to 5.0)	2.5 (0.0 to 5.0)	< 0.001	3.5 (0.0 to 5.0)	4.0 (0.0 to 5.0)	0.561
Perineometry (cmH_2O)	28.0 (0.0 to 129.0)	15.0 (0.0 to 78.0)	< 0.001	27.0 (2.0 to 129.0)	19.0 (0.0 to 95.0)	< 0.001	28.0 (2.0 to 129.0)	24.0 (0.0 to 95.0)	0.130
Δ hiatal AP diameter (%)	26.0 (−3.43 to 49.4)	16.2 (−5.7 to 42.6)	< 0.001	25.3 (−4.4 to 49.4)	19.4 (−5.67 to 46.7)	< 0.001	25.7 (−3.4 to 49.4)	27.3 (4.8 to 46.7)	0.848
Δ hiatal area (%)	34.0 (0.0 to 64.0)	19.9 (4.1 to 48.0)	< 0.001	32.8 (0.0 to 64.0)	25.1 (4.1 to 56.7)	< 0.001	33.7 (0.0 to 64.0)	34.7 (9.2 to 56.7)	0.541

Data presented as median (range). Comparisons made using Mann–Whitney *U*-test. AP, anteroposterior; MOS, modified Oxford scale.

reduced potential for absolute change in women with a smaller hiatal area at rest. Furthermore, they examined a population of primiparous women a few months after delivery, whereas we examined women 15–23 years after their first delivery. The supportive tissues and muscles can behave differently soon after being exposed to strain during delivery than they do when examined many years after delivery. In contrast to our results, Nygaard *et al.*[25] found no reduction in strength in women with POP, but this conclusion has been contradicted in a more recent study[10]. It should be noted that measures of contraction differ between these studies. We used the 75th percentile for the definition of overdistended levator hiatal area on Valsalva, which gave a cut-off of 42 cm^2. This is similar to that of Dietz *et al.*[26], who defined a cut-off of 40 cm^2 using receiver–operating characteristics curves to test hiatal area against prolapse symptoms.

A strength of the present study was the use of three different and well-established techniques for the measurement of pelvic floor muscle contraction (digital palpation, perineometry and ultrasound). Additionally, validated methods for diagnosing macrotrauma were used. Since all the examinations were performed by one experienced investigator, inter-rater difference was eliminated. This study included a large number of subjects compared with previous studies[12–15], and we found no previous studies exploring the association between muscle function, LAM trauma and anatomical POP in parous women from a general population.

A limitation of the study is that participants were mainly Caucasian women from Norway, and studies in different ethnic populations are needed. Another limitation is the cross-sectional design. We describe associations between LAM trauma and muscle function and cannot infer causality. In addition, women with symptoms of a pelvic floor disorder might be over-represented, as they are more likely to respond to questionnaires and attend an examination. In the parent study, 53% of women responded to the questionnaire and 72% of women invited to an examination turned up for their appointment[17]. Furthermore, we have no information about the use of pelvic floor exercise in this population, which might affect a woman's ability to contract her pelvic floor muscles.

We found a statistically significant and clinically relevant association between impaired pelvic floor muscle contraction, LAM trauma and POP. This implies that reduced muscle contraction could be a contributor to the development of POP, as noted in previous studies[10,27]. No difference in contraction between women with a large and those with a normal hiatal area was found after excluding women with macrotrauma, which implies that the primary mechanism behind impaired contraction of the pelvic floor may be macrotrauma. This confirms the findings of Dietz and Shek[11] in a patient population, in which macrotrauma was associated with a reduction in MOS. Despite our finding that macrotrauma is associated with an almost eight-times higher risk of not being able to contract, most women with LAM trauma still have the ability to contract the pelvic floor muscles; this implies that these women

Table 3 Measurements of pelvic floor muscle contraction in parous women with and those without pelvic organ prolapse quantification system (POP-Q) score ≥ 2, according to compartment

Parameter	*Any* (n = 608)			*Anterior* (n = 608)			*Central* (n = 608)			*Posterior* (n = 608)		
	No	*Yes*	P	*No*	*Yes*	P	*No*	*Yes*	P	*No*	*Yes*	P
n	333	275		436	172		579	29		454	154	
MOS	3.5 (0.0 to 5.0)	3.0 (0.0 to 5.0)	< 0.001	3.5 (0.0 to 5.0)	3.0 (0.0 to 5.0)	< 0.001	3.0 (0.0 to 5.0)	2.0 (0.0 to 5.0)	< 0.001	3.0 (0.0 to 5.0)	3.0 (0.0 to 5.0)	0.431
Perineometry (cmH_2O)	28.0 (3.0 to 129.0)	21.0 (0.0 to 98.0)	< 0.001	28.0 (3.0 to 129.0)	19.0 (0.0 to 95.0)	< 0.001	26.0 (0.0 to 129.0)	15.5 (0.0 to 61.0)	0.001	26.0 (0.0 to 129.0)	24.0 (4.0 to 98.0)	0.994
Δ hiatal AP diameter (%)	25.7 (−3.4 to 49.4)	22.8 (−5.7 to 49.4)	< 0.001	25.4 (−3.4 to 49.4)	21.3 (−5.7 to 49.4)	< 0.001	24.5 (−5.7 to 49.4)	15.5 (0.0 to 49.4)	< 0.001	24.0 (−3.4 to 49.4)	24.7 (−5.7 to 46.7)	0.794
Δ hiatal area (%)	33.8 (0.0 to 64.4)	29.6 (0.0 to 60.9)	< 0.001	32.9 (0.0 to 64.0)	26.9 (0.0 to 60.9)	< 0.001	32.3 (0.0 to 64.0)	19.9 (0.0 to 60.9)	0.001	31.8 (0.0 to 64.0)	31.9 (4.1 to 55.9)	0.870

Data presented as median (range). Comparisons made using Mann–Whitney *U*-test. AP, anteroposterior; MOS, modified Oxford scale.

may benefit from pelvic floor muscle exercise, which could improve muscle function and relieve symptoms of pelvic floor disorders[28], and postpone or prevent the development of POP[29]. Identification of such women at an early stage may be important. We suggest that pelvic floor ultrasound should be a part of standardized gynecological examination a few weeks or months after the delivery of their firstborn[30]. The clinical implication of early detection of LAM trauma is early initiation of pelvic floor exercise, before development of POP or pelvic floor dysfunction. We found a different strength of pelvic floor muscle contraction in women with, compared to those without, prolapse of the anterior or central compartment, but not in those with prolapse of the posterior compartment. This suggests a different mechanism behind the development of posterior compartment prolapse, as also suggested by previous work[31].

More research is needed to investigate the importance of pelvic floor function in women with LAM trauma. Studies have investigated the effect of pelvic floor muscle exercise on POP symptoms[28,29]. There is a need to ascertain if women with LAM trauma can benefit from pelvic floor muscle exercise. In addition, long-term follow-up of women with muscle trauma is needed to assess how muscle contraction and anatomical POP develop over time.

In conclusion, pelvic floor muscle trauma was associated with reduced pelvic floor muscle contraction, but most women with muscle trauma were still able to contract. Macrotrauma was the main contributor to impaired contraction. We found weaker contraction in women with clinically significant POP, and reduced contraction may contribute to increased risk for POP in women with LAM trauma.

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PAPER II

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Ultrasound assessment of pelvic floor muscle contraction: reliability and development of an ultrasound-based contraction scale

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KEYWORDS: levator ani muscle; observer variation; pelvic organ prolapse; reproducibility of results; transperineal ultrasound; urinary incontinence

CONTRIBUTION

What are the novel findings of this work?
Ultrasound is a reliable method for assessment of pelvic floor muscle contraction. The best results were for measurement of two-dimensional anteroposterior diameter of the levator hiatus, which had a moderate correlation with contraction assessed by palpation. We created an ultrasound contraction scale based on this measurement.

What are the clinical implications of this work?
Ultrasound can be used in a clinical setting to assess pelvic floor muscle contraction. The ultrasound contraction scale can be used as a tool for its assessment in the investigation of pelvic floor disorders and to evaluate the effect of conservative treatment of urinary incontinence or pelvic organ prolapse.

ABSTRACT

Objectives *To determine intra- and interrater reliability and agreement for ultrasound measurements of pelvic floor muscle contraction and to assess the correlation between ultrasound and vaginal palpation. We also aimed to develop an ultrasound scale for assessment of pelvic floor muscle contraction.*

Methods *This was a cross-sectional study of 195 women scheduled for stress urinary incontinence (n = 65) or prolapse (n = 65) surgery or who were primigravid (n = 65). Pelvic floor muscle contraction was assessed by vaginal palpation using the Modified Oxford Scale (MOS) and by two- and three-dimensional (2D/3D) transperineal ultrasound. Proportional change in 2D and 3D levator hiatal anteroposterior (AP) diameter and 3D levator hiatal area between rest and contraction were used as measures of pelvic floor muscle contraction. One rater repeated all ultrasound measurements on stored volumes, which were used for intrarater reliability and agreement analysis, and three independent raters analyzed 60 ultrasound volumes for interrater reliability and agreement analysis. Reliability was assessed using the intraclass correlation coefficient (ICC) and agreement using Bland–Altman analysis. Tomographic ultrasound was used to identify women with major levator injury. Spearman's rank correlation coefficient (r_S) was used to assess the correlation between ultrasound measurements of pelvic floor muscle contraction and MOS score. The proportion of women allocated to each category of muscle contraction (absent, weak, moderate or strong) by palpation was used to determine the cut-offs for the ultrasound scale.*

Results *Intrarater ICC was 0.81 (95% CI, 0.74–0.85) for proportional change in 2D levator hiatal AP diameter. Interrater ICC was 0.82 (95% CI, 0.72–0.89) for proportional change in 2D AP diameter, 0.80 (95% CI, 0.69–0.88) for proportional change in 3D AP diameter and 0.72 (95% CI, 0.56–0.83) for proportional change in hiatal area. The prevalence of major levator injury was 22.6%. The strength of correlation (r_S) between ultrasound measurements and MOS score was 0.52 for 2D AP diameter, 0.62 for 3D AP diameter and 0.47 for hiatal area (P < 0.001 for all). On the ultrasound contraction scale, proportional change in 2D levator*

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hiatal AP diameter of < 1% corresponds to absent, 2–14% to weak, 15–29% to normal and > 30% to strong contraction.

Conclusions *Ultrasound seems to be an objective and reliable method for evaluation of pelvic floor muscle contraction. Proportional change in 2D levator hiatal AP diameter had the highest ICC and moderate correlation with MOS score assessed by vaginal palpation, and we constructed an ultrasound scale for assessment of pelvic floor muscle contraction based on this measure.*

INTRODUCTION

The levator ani muscle surrounds the urethra, vagina and rectum. It provides resting tone and contraction and a narrow closure of the levator hiatus, which prevents pelvic organ prolapse[1,2]. Obstetric levator trauma is a risk factor for prolapse later in life[3–5]. Although women with levator trauma have impaired muscle function, they still have the ability to contract and can benefit from pelvic floor exercise[6], which is effective for prevention and treatment of stress urinary incontinence and prolapse[7–9]. Different tools can be used to investigate pelvic floor muscle contraction and activity, such as digital palpation, vaginal manometry and surface-electromyography[10–12]. All methods have disadvantages, and there is no gold standard for assessment of pelvic floor muscle contraction despite recommendations that it should be performed in women with pelvic floor dysfunction[2,11].

Three- and four-dimensional (3D/4D) transperineal ultrasound has become a method for evaluation of pelvic floor anatomy and function, and some studies have suggested that ultrasound can be used for assessment of contraction with good interrater reliability and correlation with conventional methods[13–18]. A previous study suggested a contraction scale for 3D levator hiatal anteroposterior (AP) diameter based on data from parous women from the general population[10]. Two-dimensional (2D) ultrasound, however, is easier and less time-consuming[16,19,20]. Measures of levator hiatal AP diameter and bladder neck displacement have been shown to have a weak to moderate correlation with the Modified Oxford Scale (MOS) assessed by palpation[15,17]. There is a lack of studies regarding the intra- and interrater reliability of 2D levator hiatal AP diameter as a measure of contraction and, to our knowledge, there is no existing ultrasound scale for the assessment of contraction that has been validated in patient populations.

The objective of this study was to determine intra- and interrater reliability and agreement for 2D- and 3D-ultrasound measurements of pelvic floor muscle contraction, and to assess the correlation between ultrasound and vaginal palpation for assessment of muscle contraction in primigravidae and women with a pelvic floor disorder. We also aimed to develop an ultrasound scale for measurement of pelvic floor contraction for use in a clinical setting, based on data from these women.

METHODS

This was a cross-sectional study based on baseline data from a randomized controlled trial exploring the effect of pelvic floor exercise on pelvic floor function in women scheduled for pelvic organ prolapse surgery at Trondheim University Hospital, Norway, from January 2017 to June 2018 (clinicaltrials.gov, NCT03064750). In addition, we included women undergoing stress urinary incontinence surgery and primigravidae, as pelvic floor exercise is routinely recommended to these groups.

Power calculation was based on the assumption that the correlation between ultrasound and palpation in each of the three study groups (women with prolapse, those with incontinence and primigravidae) would be the same as in the general population of parous women, as assessed by Spearman's rank correlation coefficient ($r_S = 0.7$)[10]. We assumed a bivariate normal distribution with Pearson's correlation coefficient (r) of 0.7 for palpation and ultrasound measurements and needed 63 participants in each group to identify $0.5 < r < 0.9$ with 80% power and a significance level of 0.05. This was rounded up to 65 women in each group.

Women with prolapse were recruited from the outpatient clinic at Trondheim University Hospital and examined at the time of referral for surgery. Women with incontinence were identified in the operation planner program (OP-Plan Pluss, Helse Midt-Norge, Trondheim, Norway) and examined on the day of surgery. Primigravidae were recruited at the time of their routine ultrasound examination at 17–21 weeks' gestation and were examined within a few weeks. Eligibility criteria were age over 18 years, ability to consent and fluency in the Norwegian or English language. Informed consent was obtained from all participants and the study was approved by the Regional Committee for Medical and Health Research Ethics (REK midt 2015/1751).

Women were examined in the supine position with hips and knees semi-flexed and with an empty bladder and bowel. Pelvic organ prolapse was measured according to the Pelvic Organ Prolapse Quantification (POP-Q) system and prolapse stage ≥ 2 was recorded as significant[21]. Muscle contraction was assessed using palpation and 3D/4D transperineal ultrasound. Women were thoroughly instructed on how to contract their pelvic floor prior to the examination. Palpation was performed by one of three experienced examiners (M.Ø.N., S.M., I.V.). For reliability analysis, 57 women were assessed by two examiners blinded to each other's findings. The examination was performed using two fingers at the level of the levator ani muscle, approximately 4 cm into the vagina. Pelvic floor muscle contraction was evaluated by the MOS, where 0 = no contraction and 5 = maximum contraction, and the mean of both sides was used for analysis.

Ultrasound examination was performed using a Voluson S10 or E8 ultrasound machine (GE Healthcare, Zipf, Austria) with a RAB 4–8-MHz curved array transducer placed in the midsagittal plane at 85° acquisition angle. Ultrasound volumes were recorded at rest and on maximum contraction in a series of three contractions.

Offline analysis was performed by M.Ø.N. (Rater 1) 6–12 months later using 4D View version 14 (GE Healthcare) and was repeated after a further 3–6 months. Sixty volumes selected randomly were analyzed by two additional investigators (I.V. (Rater 2) and S.H.O. (Rater 3)) and all investigators were blinded to clinical information. First, levator hiatal AP diameter was measured on the 2D image in the midsagittal plane from the most inferior margin of the pubic symphysis to the most medial margin of the puborectalis muscle (Figure 1). Levator hiatal AP diameter and area were then measured in the 3D rendered volume in the plane of minimal hiatal dimensions (Figure 1)[22]. All measurements were performed at rest and on maximum contraction. The proportional change in contraction from at rest to on maximum contraction was calculated for all ultrasound measurements using the formula: $100 \times [(\text{measurement}_{\text{rest}} - \text{measurement}_{\text{contraction}})/\text{measurement}_{\text{rest}}]$[10]. Major levator trauma was diagnosed using tomographic ultrasound imaging, and was defined as abnormal insertion of the levator ani muscle on the pubic bone in all three central slices on one or both sides[23].

Statistical analysis

Statistical analysis was performed using SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA). Normality of distributions was assessed using Q–Q plots and the Kolmogorov–Smirnov test.

For analysis of intrarater reliability for ultrasound measurements, we used the intraclass correlation coefficient (ICC) two-way mixed effects, absolute agreement model. To determine interrater reliability, we used the ICC two-way random effects, absolute agreement model, applying both the mean of three raters and single measurements[24]. The following ICC cut-offs were applied: < 0.20 = poor reliability, 0.20–0.40 = fair reliability, 0.41–0.60 = moderate reliability, 0.61–0.80 = good reliability and > 0.80 = excellent reliability[25]. Bland–Altman plots with 95% limits of agreement for means and differences between measurements of proportional change in 2D levator hiatal AP diameter were constructed for analysis of intrarater agreement and interrater agreement between pairs of raters (Raters 1 and 2 and Raters 1 and 3)[26]. Linear regression analysis was performed using the difference in measurements between the two raters as the outcome and the average of the two raters as an explanatory variable to determine

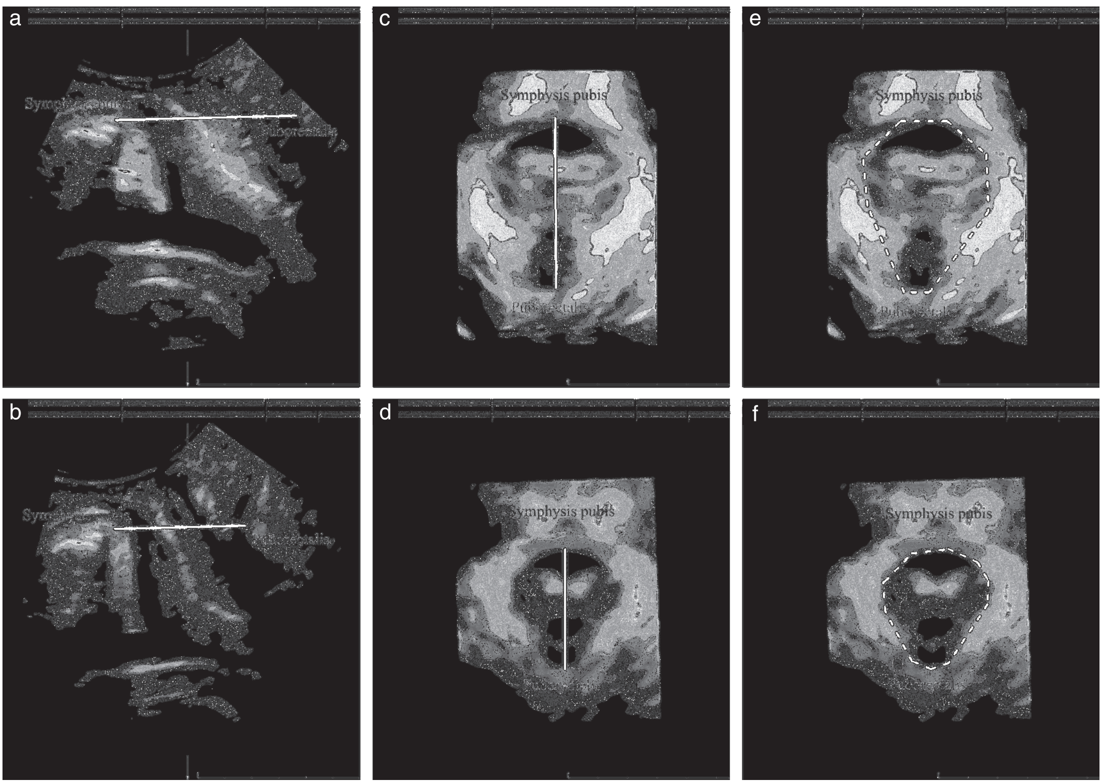

Figure 1 2D (a,b) and 3D (c–f) ultrasound images of pelvic floor, showing measurements of levator hiatal anteroposterior diameter (——) from inferior margin of pubic symphysis to medial margin of puborectalis muscle at rest (a,c) and on contraction (b,d), and levator hiatal area (– – –) at rest (e) and on contraction (f).

if the difference in measurements is independent of the average. Interrater analysis was performed for MOS score between pairs of raters.

Spearman's rank correlation was used for analysis of the correlation between MOS score assessed by palpation and ultrasound measurements of contraction. A higher r_S value indicates a stronger correlation: 0 = no correlation; > 0.3 = weak correlation; > 0.5 = moderate correlation; > 0.7 = strong correlation; 1 = perfect correlation[10].

For development of the ultrasound contraction scale, the ultrasound measure with the highest ICC value was used. The International Continence Society (ICS) has recommended categorization of pelvic floor muscle contraction as absent, weak, normal or strong[2]. Women were categorized based on MOS score assessed by vaginal palpation, using the following definitions: 0 = absent, 0.5–2.0 = weak, 2.5–4.0 = normal and 4.5–5.0 = strong contraction. For development of the ultrasound contraction scale, cut-offs of the ultrasound variable were determined based on the proportion of women categorized into each of the four groups. Using the chi-square test, the proportion of women with major levator injury was calculated and compared between women with absent to weak contraction and those with moderate to strong contraction. Additional analysis was performed in which cut-offs were instead based on percentiles of the ultrasound variable (0% change = absent, < 25th percentile = weak, 25–75th percentile = normal and > 75th percentile = strong contraction). The level of statistical significance was set at 0.05.

RESULTS

A total of 195 women were included in this study, of whom 65 were scheduled for pelvic organ prolapse surgery, 65 were scheduled for stress urinary incontinence surgery and 65 were primigravid. Background characteristics and clinical findings in each group are presented in Table 1. All women scheduled for prolapse surgery had POP-Q stage ≥ 2, 52 (80%) of whom had anterior compartment prolapse, 24 (37%) had central compartment prolapse and 17 (26%) had posterior compartment prolapse. Twenty-eight (43%) women had significant prolapse involving two compartments.

When considering proportional change in ultrasound measures of pelvic floor muscle contraction between rest and maximum contraction, 2D levator hiatal AP diameter had the highest interrater ICC value (Table 2). Intrarater ICC values for proportional change in 2D AP diameter are presented in Table 3 and intra- and interrater agreement are shown in Bland–Altman plots (Figure 2). Linear regression analysis showed that the difference in measurements of proportional change in 2D levator hiatal AP diameter between raters was independent of the average of the measurements for both Raters 1 and 2 ($P = 0.87$) and Raters 1 and 3 ($P = 0.33$). The ICC for MOS score was 0.93 for Raters 1 and 2 and 0.92 for Raters 1 and 3.

Table 1 Background characteristics of women scheduled for pelvic organ prolapse or stress urinary incontinence surgery and primigravidae

Characteristic	*Prolapse* (n = 65)	*Stress urinary incontinence* (n = 65)	*Primigravid* (n = 65)	*Total* (n = 195)
Age (years)	63.9 ± 11.4 (34–83)	50.1 ± 9.3 (32–76)	29.1 ± 4.0 (19–39)	47.7 ± 16.8 (19–83)
Parity	2.5 ± 0.7 (1–4)	2.6 ± 0.93 (1–5)	0 ± 0 (0–0)	1.7 ± 1.4 (0–5)
Body mass index (kg/m^2)	25.4 ± 3.6 (19.8–33.2)	26.3 ± 4.5 (18.5–37.2)	23.3 ± 3.5 (17.8–35.4)	25.0 ± 4.1 (17.8–37.2)
MOS score*	2.1 ± 1.2 (0–5)	3.5 ± 1.2 (0–5)	3.9 ± 0.9 (1–5)	3.2 ± 1.3 (0–5)
POP-Q stage ≥ 2	65 (100)	5 (7.7)	0 (0)	70 (35.9)
Major levator trauma	34 (52.3)	10 (15.4)	0 (0)	44 (22.6)

Data are given as mean ± SD (range) or *n* (%). *Score can range from 0 to 5. MOS, Modified Oxford Scale; POP-Q, Pelvic Organ Prolapse Quantification.

Table 2 Interrater reliability of measurements of levator hiatal anteroposterior (AP) diameter and area in 57 ultrasound volumes*

	Rater			*ICC (95% CI)*	
Measurement	*1*	*2*	*3*	*Single rater*	*Average of raters*
AP diameter on 2D US (cm)					
At rest	5.9 ± 1.0	5.9 ± 0.9	5.7 ± 0.9	0.83 (0.75–0.89)	0.94 (0.90–0.96)
On contraction	4.6 ± 0.9	4.7 ± 0.9	4.5 ± 0.9	0.82 (0.73–0.88)	0.93 (0.89–0.96)
Proportional change (%)	21.1 ± 8.5	21.4 ± 8.7	22.5 ± 9.5	0.61 (0.47–0.73)	0.82 (0.72–0.89)
AP diameter on 3D US (cm)					
At rest	6.3 ± 0.9	6.3 ± 0.9	5.8 ± 0.9	0.77 (0.54–0.88)	0.91 (0.78–0.96)
On contraction	5.0 ± 1.0	5.0 ± 1.0	4.6 ± 0.9	0.79 (0.60–0.89)	0.92 (0.82–0.96)
Proportional change (%)	19.6 ± 9.0	21.0 ± 9.0	20.5 ± 8.7	0.57 (0.43–0.70)	0.80 (0.69–0.88)
Area on 3D US (cm^2)					
At rest	21.8 ± 7.2	22.0 ± 6.4	18.9 ± 5.5	0.77 (0.59–0.87)	0.91 (0.81–0.95)
On contraction	16.0 ± 5.7	16.5 ± 6.2	13.4 ± 4.7	0.79 (0.62–0.88)	0.92 (0.83–0.96)
Proportional change (%)	26.2 ± 11.4	26.0 ± 12.5	26.7 ± 12.3	0.46 (0.30–0.61)	0.72 (0.56–0.83)

Measurements given as mean ± SD. *Three volumes excluded due to poor quality. ICC, intraclass correlation coefficient; US, ultrasound.

Table 3 Intrarater reliability of measurements of levator hiatal anteroposterior (AP) diameter measured by Rater 1 in 192 two-dimensional ultrasound images*

			ICC (95% CI)	
Measurement	*Test*	*Retest*	*Single measurement*	*Average of measurements*
AP diameter (cm)				
At rest	6.0 ± 1.0	6.0 ± 0.9	0.87 (0.83–0.90)	0.93 (0.91–0.95)
On contraction	4.8 ± 0.9	4.8 ± 1.0	0.86 (0.82–0.89)	0.93 (0.90–0.94)
Proportional change (%)	19.7 ± 9.8	19.1 ± 9.0	0.67 (0.59–0.74)	0.81 (0.74–0.85)

Measurements given as mean ± SD. *Three volumes excluded due to poor quality. ICC, intraclass correlation coefficient.

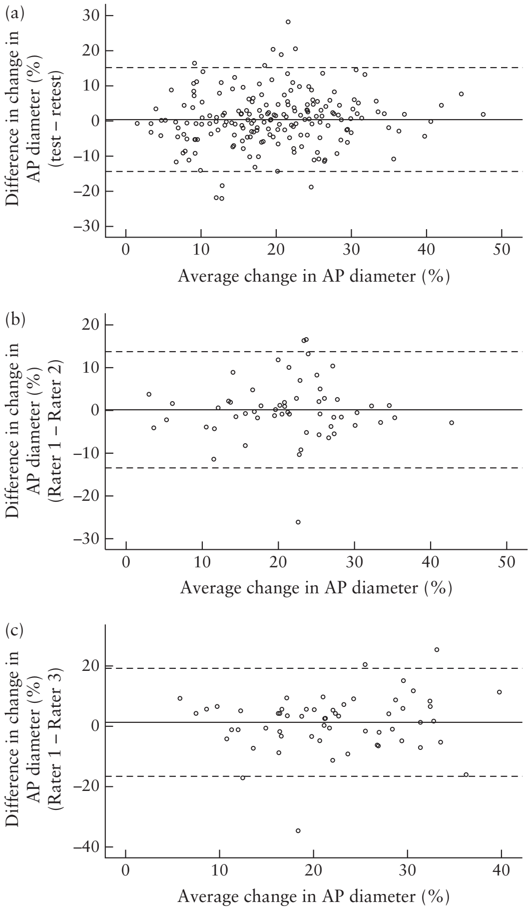

Figure 2 Bland–Altman plots of proportional change in levator hiatal anteroposterior (AP) diameter measured using two-dimensional ultrasound, showing intraobserver agreement (a) and interobserver agreement between Raters 1 and 2 (b) and Raters 1 and 3 (c). Solid lines represent mean difference and dashed lines represent 95% limits of agreement.

Spearman's rank test showed a weak to moderate correlation between MOS score and proportional change in hiatal area ($r_S = 0.47$, $P < 0.001$) and 3D AP diameter ($r_S = 0.62$, $P < 0.001$). The correlation was moderate between MOS score and proportional change in 2D levator hiatal AP diameter ($r_S = 0.52$, $P < 0.001$).

Table 4 Ultrasound scale for assessment of pelvic floor muscle contraction based on proportional change in levator hiatal anteroposterior (AP) diameter between rest and maximum contraction, measured using two-dimensional ultrasound

Contraction scale	*MOS score*	n *(%)*	*Proportional change in AP diameter (%)**
Absent	0	3 (1.5)	≤ 1
Weak	0.5–2.0	50 (25.7)	2–14
Normal	2.5–4.0	108 (55.4)	15–29
Strong	4.5–5.0	34 (17.4)	≥ 30

*Cut-offs of proportional change in AP diameter based on proportion of women allocated to each category of contraction according to Modified Oxford Scale score assessed by vaginal palpation.

The ultrasound contraction scale for proportional change in 2D levator hiatal AP diameter based on the proportion of women allocated to each category of pelvic floor muscle contraction according to MOS score is presented in Table 4. Using percentiles of proportional change in 2D AP diameter to determine cut-offs, the ultrasound contraction scale was as follows: absent = 0; weak (< 25^{th} percentile) = 1–13%; normal (25^{th}–75^{th} percentile) = 14–26%; strong (> 75^{th} percentile) = ≥ 27%. The prevalence of major levator trauma in the overall study population was 22.6% (44/195), and was 52.3% in the prolapse group. In women with absent to weak contraction, levator trauma was significantly higher (41%; 24/59) than in those with moderate to strong contraction (14%; 19/135) (OR, 4.2; 95% CI, 2.1–8.5; $P < 0.001$).

DISCUSSION

This study found good intra- and interrater reliability and agreement for ultrasound measurements of pelvic floor muscle contraction, with proportional change in 2D levator hiatal AP diameter having the highest ICC. Weak to moderate correlation was found between ultrasound measurements of contraction and MOS score assessed by palpation. We used proportional change in 2D levator hiatal AP diameter to construct an ultrasound contraction scale.

The prevalence of major levator trauma in the overall study population was 22.6%, and was 52.3% in the prolapse group. This high prevalence is in agreement with that in previous publications in women with pelvic organ prolapse scheduled for surgery[27,28]. Previous publications have found that women with major levator trauma had reduced pelvic floor contraction compared with those without trauma[6,29]. Additionally, in the present study, we found a 3-fold increased prevalence of major levator trauma among women with absent to weak contraction compared with those with moderate to strong contraction.

Most previous intra- and interrater reliability studies on ultrasound assessment of pelvic floor muscle contraction have compared measurements taken either at rest or on contraction[22,30–33], and only a few have compared the change between rest and contraction[29]. In the present study, the ICC was also found to be higher for absolute measurements than the proportional change between rest and contraction. The ICC values were similar to those found in other studies in which primigravidae or volunteers were assessed by two raters[22,30,31,33]. Most previous studies do not indicate which type of ICC was used and include only two raters, which complicates comparison with other studies. A strength of this study is that ICC was calculated for both the average measurements of three raters and single measurements.

Overall, we found a higher ICC for 2D than for 3D measurements, indicating that 2D measurements are easier to perform. For proportional change in 2D levator hiatal AP diameter, the ICC of 0.81 for intrarater reliability indicates excellent reliability. The ICC (average of the three raters) of 0.82 implies excellent agreement between the raters in this population[25], and is higher than the ICC (average of two raters) of 0.77 found in another recent publication[29]. The ICC (single measurement) of 0.61, providing information on the performance of the test in a clinical setting in which one examiner assesses one woman, is good, and the method is acceptable to use in such settings.

Previous studies have explored the association between change in ultrasound measurements and other measures of pelvic floor contraction[10,16,34]. There is no gold standard for assessment of pelvic floor contraction, and hence there is no standard against which to validate a contraction scale. The moderate level of correlation between MOS score assessed by palpation and ultrasound measurements could be a result of error due to methodological disadvantages of palpation, as implied by earlier studies[10,11]. The examiner's experience and subjective interpretation during palpation might affect the results. Ultrasound reduces such sources of error, making ultrasound assessment more objective.

Furthermore, a live scan can be used as biofeedback to teach proper pelvic floor contraction and identify sources of error, allowing correction of co-activation or Valsalva during contraction[19,20].

The combination of analysis of intra- and interrater reliability and agreement of ultrasound measures and analysis of the correlation between ultrasound and palpation add strength to this study.

Women with prolapse or incontinence and primigravidae selected for this study represent groups of women for whom healthcare providers recommend intensive pelvic floor muscle training. This makes the results transferable to the clinical setting in urogynecology and obstetrics. The study design and study population provide high internal and external validity. Women scheduled for prolapse surgery were invited to participate regardless of age, prolapse stage and the affected compartment or surgical technique planned. The population is heterogeneous, and the results can be generalized to a similarly diverse population in a clinical setting.

The ultrasound contraction scale suggested in this study has the potential to become the standard for assessment of pelvic floor contraction in a clinical setting as ultrasound machines with a 2D abdominal probe are readily available in most gynecological and obstetric units. The method has low costs, is easy to learn, is not time-consuming, is non-intrusive to the woman, and can be used for biofeedback and teaching pelvic floor exercise. The cut-offs coincide with a previously published scale using proportional change in 3D levator hiatal AP diameter, constructed using data from a general population of parous women[10]. When applying the 25th and 75th percentiles of proportional change in 2D levator hiatal AP diameter without comparison to MOS, we found almost identical cut-offs, strengthening their clinical applicability. Still, we recognize that further studies are needed to standardize and validate the clinical use of ultrasound for assessing pelvic floor muscle function.

One limitation of this study is the possibility of selection bias. Women interested in health issues and those with severe symptoms are more likely to participate in studies[35]. Women interested in pelvic floor exercise are also more likely to participate, while those who have trained their pelvic floor without experiencing any effect are more likely to decline participation. The examiners were blinded to medical history and anatomical findings, but the ultrasound volumes reveal important information about the women. The fetus in pregnant women and bulking agents or tension-free vaginal tapes might be visible in the ultrasound volumes. In women with prolapse, the anatomical changes are obvious in some volumes.

In conclusion, ultrasound seems to be an objective and reliable method for evaluation of pelvic floor contraction with good ICC. The highest ICC was found for proportional change in 2D levator hiatal AP diameter. 2D ultrasound is readily available and constitutes a low-cost examination with minimal discomfort for the woman. Proportional change in 2D levator hiatal AP diameter can be used as a new, more objective measure of pelvic floor muscle contraction. The proposed contraction scale may be useful for the decision-making process in a clinical setting, to evaluate conservative treatment, or to individualize timing of surgical intervention for women with pelvic floor dysfunction.

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PAPER III

The effect of preoperative pelvic floor muscle training on pelvic floor contraction, symptomatic and anatomical pelvic organ prolapse after surgery – a randomized controlled trial

Short title:

Preoperative pelvic floor muscle training

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Conflict of interest for all authors: none.

Contribution:

What are the novel findings?

We found no additional effect of preoperative pelvic floor muscle training on contraction, symptomatic or anatomical prolapse after surgery, but overall, contraction, anatomical findings and symptoms improved over time.

What are the clinical implications?

We found no evidence to support the introduction of pelvic floor muscle training as a standard supplement to pelvic organ prolapse surgery. Contraction of the pelvic floor improved after surgery, most likely due to the anatomical correction of the prolapse.

Key words:

Randomized controlled trial, pelvic organ prolapse, pelvic floor, muscle contraction, physical therapy, ultrasonography, gynecologic surgical procedures

Abstract

Objective To evaluate the effect of preoperative pelvic floor muscle training (PFMT) on pelvic floor contraction, symptoms and anatomical pelvic organ prolapse (POP) six months after surgery and to study overall changes in contraction, symptoms and anatomy after surgery.

Methods Randomized controlled trial. Women scheduled for POP surgery (n=159) were randomized to intervention including daily PFMT from inclusion to surgery (n= 81) or control (n=78). Participants were examined at inclusion, day of surgery and after six months. Pelvic floor muscle contraction was assessed with palpation using the Modified Oxford Scale (MOS) (0-5), vaginal manometry, surface-EMG, and transperineal ultrasound measuring proportional change in levator hiatal anteroposterior diameter from rest to contraction. POP distance from hymen in most dominant compartment was measured, and sensation of vaginal bulge was graded using a visual analogue scale (VAS) (0-100). Mixed models were used for statistics.

Results 151 women completed the study. Mean waiting time for surgery was 22 weeks and follow-up was 28 weeks after surgery. No difference between intervention vs control group was found for palpation (MOS): 2.4 vs 2.2, p= 0.101, manometry (cmH_2O): 19.4 vs 19.7, p= 0.793, surface-EMG (mV): 33.5 vs 33.1, p= 0.793, ultrasound (% change): 20.9 vs 19.3, p=0.211, POP distance from hymen (cm): -1.8 vs -2.0, p = 0.556 or bulge sensation (VAS): 7.4 vs 6.0, p = 0.598. Overall, contraction improved after surgery: palpation (MOS) 2.1 vs 2.3, p = 0.007 and ultrasound (% change) 17.5 vs 20.1, p = 0.001. POP distance from hymen (cm) 1.9 vs -1.9, p< 0.001 and bulge sensation (VAS) 57.6 vs 6.7, p < 0.001 were reduced.

Conclusion We found no effect of preoperative PFMT on contraction, symptomatic or anatomical prolapse after surgery. Over all, contraction and symptoms improved over time, most likely explained by the anatomical correction of POP after surgery.

Introduction

Pelvic organ prolapse (POP) is a common condition which represents an economical burden for the society and has great impact on quality of life for the women affected.[1] Anatomical prolapse is diagnosed in up to 50 % of parous women, of which 20% report symptoms.[2] Up to 20% of women undergo POP surgery during lifetime,[3, 4] however the recurrence rate after primary surgery is high.[5] A weak pelvic floor is associated with recurrence after surgery.[6] Major levator ani muscle trauma is a risk factor for weaker muscle contraction, [7, 8] and for recurrence of prolapse after primary surgery.[5] Synthetic mesh has been popular in recurrence surgery, but is less used today due to complications.[9-11] There is a need to improve surgical outcome of POP surgery without use of synthetic mesh.

Pelvic floor muscle training (PFMT) is effective for prevention and treatment of mild to moderate prolapse,[12-15] and previous studies have aimed to investigate effects of perioperative PFMT combined with lifestyle advice on symptoms, anatomical success and muscle contraction after surgery.[3, 16-22] Despite these findings, reviews and meta-analysis conclude that the effect of PFMT as a supplement to prolapse surgery needs further investigation[3, 21, 23]. Furthermore, previous publications have focused on peri-operative and not pre-operative PFMT, and there is a lack of studies evaluating the impact on pelvic floor muscle contraction assessed by ultrasound. In addition, a possible effect of POP surgery on measures of pelvic floor muscle contraction needs further evaluation, as the evidence is unclear.[24]

The aim of this study was to evaluate the effect of preoperative PFMT on pelvic floor contraction, symptoms and anatomical POP six months after surgery and to study overall changes in symptoms, anatomy and contraction after surgery.

Method

We conducted a randomized controlled trial including women scheduled for POP surgery at Trondheim University Hospital, Norway, from January 2017 to March 2019. Eligibility criteria were indication for POP surgery defined as symptomatic POP stage two or larger, age over 18 years, ability to consent, and understanding Norwegian or English language. Women were invited to participate when they were referred to surgery by one of the hospital´s urogynecologists. The study was approved by the Regional Ethics Committee (REK midt 2015/1751), and the women signed an informed consent at the inclusion visit. The study was registered in clinicaltrials.gov with the identifier NTC0364750.

At the inclusion visit, women were randomized to intervention or control by a web-based randomization tool (WebRAND) provided by Unit for Applied Clinical Research, Norwegian University of Science and Technology, NTNU. The allocation ratio was 1:1 and participants were stratified by POP stage two or three to four and age over and under 60 years. The data was entered into a web-based case report form (WebCRF). Surgery was planned three months after inclusion. This was the expected waiting time for surgery at Trondheim University Hospital during the study period. Time to surgery was not influenced by group allocation. A postoperative follow-up was planned six months after surgery. Primary outcomes were pelvic floor contraction assessed by palpation, ultrasound, vaginal manometry and surface electromyography (EMG), and symptomatic POP assessed by a visual analogue scale (VAS). A secondary outcome was anatomical POP.[25-27]

The intervention consisted of intensive PFMT in the period between inclusion and surgery. Women in the intervention group received an information leaflet and were encouraged to perform daily training with 8-12 contractions with duration 6-8 seconds in 3 sets.[28] They received information of prevention and treatment of obstipation and proper emptying of bladder and bowel.[29] They were also instructed to perform pelvic floor contraction in situations leading to increased intraabdominal pressure (sneeze, lifting, coughing) and to avoid straining when defecating. They had personal visits with a dedicated pelvic floor physiotherapist after two and six weeks where a vaginal examination was done to ensure proper contraction of the pelvic floor muscles. Women were offered optional weekly PFMT in groups with the dedicated physiotherapist. Training adherence was recorded in a training diary collected on the day of surgery. Women who failed to deliver a diary were interviewed by telephone. Adequate adherence to the intervention program was defined as 70 % fulfilment of the scheduled training program.[30] Women in the control group waited for surgery with no intervention. Postmenopausal women in both groups started local estrogen therapy if not contraindicated (e.g. ongoing treatment with aromatase inhibitor for breast cancer).

Choice of surgical procedure was made according to the department´s practice, based on type and grade of prolapse, compartments involved and whether prior surgery had been done. Possible procedures for anterior and posterior compartments were colporrhaphy, perineorrhaphy and correction of enterocele. For the central compartment shortening and displacement of cardinal and sacrouterine ligaments followed by cervical amputation, vaginal hysterectomy, sacrospinous ligament fixation, laparoscopic sacrouteropexy or -colpopexy were possible. Type of procedure and frequency of peri- and postoperative complications were registered.

All women were examined by one of three investigators (MØN/SM/IV) at the inclusion, the day of surgery and the post-operative follow-up. The examiner was not blinded for group allocation on the day of surgery or post-operative visit. Women were instructed in emptying bladder and bowel and they were thoroughly instructed in pelvic floor contraction and how to perform proper Valsalva.

Assessment of muscle contraction by palpation was performed with two fingers at the level of the levator ani muscle muscle aproximately 4 cm into the vagina, and the contraction was assessed using the 6-point Modified Oxford Scale with a range from 0 to 5.[31] Muscle contraction on both sides were evaluated, and the mean value was used in the analysis. We used Peritron® manometer with a vaginal probe for manometry. The probe with a sensor was placed in the vagina at the level of the levator ani muscle and the woman performed series of three contractions of three seconds duration. The peak value of the strongest contraction was used in the analysis. The electromyography (EMG) device Neurotrac ETS® with the Periform® vaginal surface electrode was used to collect the electromyographic data. The probe with electrodes on the lateral sides was placed in the vagina with the electrodes at the level of the levator ani muscle aproximately 4 cm into the vagina. Women were instructed to contract in series of three contractions with a duration of three seconds. We used the mean value in the analysis.

Ultrasound examination was performed using a Voluson GE S10 or E8 device with a RAB 4-8 MHz curved array transducer. The transperineal examination was performed in the midsagital plane with an acquition angle set at 85°. Three 3D/4D volumes were recorded from rest to maximal contaction and three volumes at Valsalva. Offline analyses were performed 6-12 months after recording using 4D view. One examiner (MØN) analysed the volumes blinded to clinical information. Major levator trauma was diagnosed using tomographic ultrasound and defined as an abnormal insertion of the levator ani muscle to the pubic bone in the three central slices, either uni- or bilateral.[32] Contraction was measured using the proportional change in levator hiatal anteroposterior diameter between rest and contraction as described previously: $100 \text{ x } [(\text{measurement}_{rest} - \text{measurement}_{contraction})/\text{measurement}_{rest}]$.[33, 34]

The women answered yes/no to a question of whether they experienced a sensation of vaginal bulge, and if yes, they marked the grade of bother on a VAS ranging from 0 to 100 mm.[27] A positive response at the postoperative visit was registered as symptomatic recurrence.

POP was assessed in lithotomy position using the pelvic organ prolapse quantification system (POP-Q) at maximal Valsalva.[35] We included measurements from the anterior (Ba), central (C) and posterior (Bp) compartments in the analysis. The value from the most dominent compartment was recorded as a separat variable. Postoperativ POP stage ≥ 2 in the compartment undergoing surgery was interpreted as recurrence, and POP stage ≥ 2 in a different compartment was interpreted as new POP.

Power calculation was performed based on data from previous studies on parous women from the general population where contraction assessed by MOS was 3.1, SD 1.3, [33] and women with pelvic floor dysfunction with MOS between 2.2 and 2.6.[36-38] We anticipated that women scheduled for POP surgery had MOS 2.6, SD 1.3, and assumed that a clinically relevant change in MOS at six months follow up was MOS 3.2, SD 1.3. With power 80%, p= 0.05 and sampling ratio1:1, a study sample of 74 women in each group would be sufficient.

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 25. Analysis was performed according to the intention-to-treat principle. Normality was assessed using histograms and QQ plots. Level of statistical significance was set at 5%.

Differences between women accepting and declining randomization were compared with t-test (age, contraction evaluated by palpation and ultrasound) and Chi square test (previous POP surgery).

We used linear mixed models to test the effect of the intervention on continuous outcome variables with a five-point combined variable for time and group status as fixed effects (baseline: entire study population, day of surgery: intervention and control, postoperative control: intervention and control). The model included restricted maximum likelihood estimation and unstructured covariance. The effect of the stratification variables (age and POP stage) was tested and no effect was found. Hence, these variables were excluded from the analysis. Any need to include other background variables as covariates was excluded since these were similar across the groups at baseline. We also examined a possible change in the total study population, with time as fixed effect

Finally, the proportion of women with improved contraction, symptomatic and anatomical improvement, symptomatic and anatomical recurrence and POP >2 in a new compartment was calculated and compared between the intervention and control groups at the postoperative control using Chi square test.

Results

In all, 272 women were referred to surgery between January 2017 and June 2018. Seventy-two women did not meet inclusion criteria or did not want to participate. Forty-one women declined randomization at the inclusion visit leaving 159 women included in the trial, see Figure 1. Women declining randomization were significantly older (67 years vs 62 years, p=0.002) and had more prior POP-surgery; (11/41 (27%) vs. 29/159 (12%) p = 0.015), but similar muscle contraction assessed by palpation (MOS of 2.0 vs 2.1, p=0.639) and ultrasound (15.9 % vs 17.5 %, p=0.346).

One hundred fifty-one (95%) women completed the study (see Figure 1). In the intervention group, three women did not want further examinations after inclusion and three cancelled surgery (one due to other medical condition, two because of improvement of symptoms). In the control group two women cancelled surgery due to improvement of symptoms. The intervention and control groups were similar for background characteristics and outcome variables at baseline, see Table 1. The mean (SD) waiting time before surgery was 22 (9.7) weeks, similar for the intervention and control group (22 vs 23) and they were examined on average 28 (7.8) weeks after surgery (28 vs 28). In the intervention group 80% reached an adherence level of 70%.

Twenty-eight (19%) women had isolated anterior compartment repair (including three synthetic mesh procedures), 27 (18%) had isolated posterior compartment repair, and 38 (25%) had isolated central compartment repair. Fifty-eight (38%) women had a combination of procedures including several compartments. We registered two major complications after surgery; an intestovaginal fistula after laparoscopic sacrocolpopexy and one hemorrhage requiring reoperation. Other complications reported were three postoperative infections requiring antibiotics and one woman had persisting residual urine.

On the day of surgery there was a statistically significant difference in contraction assessed by palpation in favor of the intervention group ($p = 0.015$), but not for other outcome variables (Table 2). We found no statistically significant difference between the groups at the postoperative follow-up (Table 2). For the total study population, a significant change over time was found for all outcome variables except vaginal manometry and surface EMG (Table 3). The proportion of women with improved contraction, symptomatic and anatomical improvement, symptomatic and anatomical recurrence and prolapse in a new compartment is presented in Table 4, and no difference between the groups was found.

Discussion

We found no statistically significant effect of preoperative PFMT on pelvic floor contraction, symptoms or anatomical POP at mean follow-up of 28 weeks after surgery. However, we found an overall improvement after surgery for contraction evaluated by ultrasound and palpation, symptoms and anatomical POP.

Our findings are consistent with results from previous randomized controlled trials on PFMT as an adjunct to surgery, showing no effect on contraction evaluated by palpation or

EMG, POP symptoms or anatomical outcome.[18-20, 22] These studies included women scheduled for POP surgery alone or in combination with procedures for urinary incontinence[19] or hysterectomy.[22] In contrast, other studies have shown effect of pelvic floor exercise on pelvic floor function, anatomical- and symptomatic prolapse.[12, 13] Braekken et al included women who were younger, had a lower POP-Q stage (mainly stage 2) compared to our study population of women scheduled for POP surgery with mainly POP-Q stage 3 and 4) [12] Also Jarvis et al found an improvement of pelvic floor muscle contraction assessed by vaginal manometry after perioperative PFMT in an RCT with 60 participants evaluated after three months.[39] This study included women scheduled for either incontinence or POP surgery and grade of POP was not stated. It is possible that PFMT is more effective in women with stress urinary incontinence and smaller prolapses.[12, 40]

The overall reduction of symptomatic and anatomical POP was expected after surgery, but the improved pelvic floor contraction was somewhat surprising and not in line with results from a recently published systematic review.[24] This review concludes that there is no clear effect of POP surgery on pelvic floor muscle morphology or function. However, only one of the studies in this review had pelvic floor function as primary outcome, and the findings of this study are in concordance with our findings. [41] They found an improvement in contraction assessed by palpation (MOS), but no effect using manometry at 40 days follow-up. Another study investigated levator hiatal dimensions with 3D endovaginal ultrasound after different treatment approaches to POP; expectance, pessary and surgery.[42] They found a decrease in levator hiatal dimensions 12 months after POP surgery which was not found for women treated with pessaries or expectance.[42] Our findings together with these previous studies implicate that the size of the prolapse can make it difficult to perform PFMT, and when the prolapse is surgically reduced contraction and strength increases. A long-term follow-up may help clarify if there are unrevealed effects of PFMT in addition to surgery over time.

The frequencies for recurrence of anatomical POP and symptoms correspond well with frequencies published after native tissue repair in two reviews of recent literature, which report 38-45% for anatomical recurrence and 19-20% for symptomatic recurrence.[43, 44]

We chose a somewhat arbitrary cut-off at 70 % adherence to the PFMT intervention program consisting of daily exercise. We wanted PFMT to be feasible for women in normal everyday life and make the results generalizable to a clinical setting. 80% adherence to the program is very good, since previous studies have shown adherence in 64% of patients in a short term perspective and 23% in the long term in a clinical setting.[30]

The main strength of our study was the randomized controlled setting. We evaluated the effect of preoperative PFMT on both anatomical findings and symptoms, and measured contraction with off-line analysis of ultrasound volumes. Ultrasound is an objective and reproducible method, and the experience of the examiner plays a minor role when assessing contraction by ultrasound compared to palpation. Possible bias such as knowing group allocation (problem with palpation) or co-activation of other muscle groups (problem with perineometry and sEMG) was eliminated for off-line analysis of ultrasound volumes.[45] Furthermore, we used validated tools to evaluate the outcomes. The mixed model made it possible to enter all available data in the analysis, including women with missing data at the day of surgery or postoperative follow-up.

One limitation of this study is the lack of blinding of the examiner. Thus, the results for palpation should be interpreted with caution. However, blinding was ensured when evaluating the ultrasound volumes for contraction after 6-12 months. Another limitation is the heterogenicity regarding compartment, surgical technique and primary or recurrent POP. Previous studies have shown that POP in anterior and middle compartments are related to pelvic floor muscle trauma, whereas posterior compartment POP has a different etiology.[46] A larger study aiming at specific compartments could clarify if subgroups of women would benefit from PFMT. The control group received a thorough examination of the pelvic floor and instruction in how to contract as part of the clinical assessment, and this may mask a possible effect of PFMT. Women declining randomization were older and had more previous POP surgery, and this may have influenced the external validity of the trial. Most study participants were white European, and the effect of PFMT could theoretically be different in other ethnic groups.

In conclusion, we found that pelvic floor contraction improved after POP surgery, most likely explained by the anatomical correction of POP. No additional effect of PFMT was found. Altogether, we did not find evidence to support the introduction of PFMT as a standard adjunct to surgery in women with symptomatic POP ≥ grade 2 scheduled for surgery.

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Registration

The study is registered in clinicaltrials.gov, NCT0364750

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Legends

Figure 1 Flowchart of the study population.

*Three women withdrew consent and three cancelled surgery ** two women cancelled surgery

Figure 2 Results from linear mixed model analysis for comparison between the groups. Time on the x-axis. The participants were examined at baseline, day of surgery (DOS) (mean 22 weeks after inclusion) and postoperative control (POC) (mean 28 weeks after surgery).

Pelvic floor muscle contraction assessed by a) palpation using the Modified Oxford Scale (MOS), b) vaginal manometry, c) ultrasound measuring proportional change in levator hiatal anteroposterior diameter from rest to contraction and d) surface electromyography.

Sensation of vaginal bulge assessed by e) visual analogue scale. Prolapse distance from the hymen in f) dominating compartment, g) anterior compartment (Ba), h) central compartment (C) and i) posterior compartment (Bp).

Table 1 Background characteristics and outcome variables for the intervention and control group. Continuous variables with mean and standard deviation (SD), and categorical variables with number (%).

	Intervention n=75	Control n=76
Background characteristics		
	Mean ± SD	**Mean± SD**
Age (years)	60.1± 11.2	60.6 ± 10.9
Parity (number)	2.3 ± 0.8	2.6 ± 0.9
Body mass index (kg/m^2)	26.3 ± 4.4	25.7 ± 4.1
	n (%)	**n (%)**
Major levator trauma	33 (44)	42 (56)
Local estrogen therapy	47 (64)	48 (63)
Previous pelvic floor muscle training	13 (18)	14 (18)
Pelvic organ prolapse ≥grade 3	44 (59)	48 (63)
Postmenopausal	59 (80)	59 (78)
Smoking	10 (14)	6 (8)
Previous pessary treatment	50 (68)	60 (79)
Previous pelvic organ prolapse surgery	7 (10)	11 (15)
Previous hysterectomy	9 (12)	8 (10)
Outcome variables		
	Mean (SD)	**Mean (SD)**
Palpation, Modified Oxford Scale (0-5)	2.1 ± 1.1	2.1 ± 1.2
Ultrasound (% change)*	17.8 ± 9.6	17.2 ± 9.8
Visual analogue scale (0-100)	60.3 ±27.2	55.4 ± 26.4
Prolapse distance from hymen in dominant compartment (cm)	1.9 ± 1.4	1.8 ± 1.1

*Proportional change in anteroposterior diameter of the levator hiatus from rest to contraction.

Table 2 Mean values and 95% confidence interval (CI) for the groups at baseline, day of surgery and postoperative control. Differences between groups from baseline to day of surgery and postoperative control.

	Baseline	Day of surgery				Postoperative control			
Outcome	**Mean (95% CI)**	**Intervention mean (95% CI)**	**Control mean (95% CI)**	**Difference (95% CI)**	***p***	**Intervention mean (95% CI)**	**Control mean (95%CI)**	**Difference (95% CI)**	***p***
Pelvic floor contraction									
Palpation, Modified Oxford Scale (0-5)	2.1 (1.9-2.2)	2.2 (2.0-2.4)	1.9 (1.6-2.1)	0.3 (0.1-0.6)	0.012	2.4 (2.2-2.6)	2.2 (1.9-2.4)	0.2 (-0.1-0.5)	0.101
Ultrasound(% change)*	17.5 (15.9-19.0)	18.2 (16.2-20.3)	18.2 (16.2-20.3)	0.0 (-2.7- 2.7)	0.999	20.9 (19.0-22.7)	19.3 (17.5-21.2)	1.6 (-0.9-4.0)	0.211
Vaginal manometry (cmH_2O)	19.0 (16.9-21.1)	17.6 (15.4-19.9)	18.1 (15.9-20.4)	-0.5 (-2.6- 1.6)	0.664	19.4 (16.9-21.8)	19.7 (17.3-22.2)	-0.3 (-2.8-2.1)	0.793
Electromyography (mV)	34.8 (31.2-38.4)	32.3 (29.1-35.6)	31.3 (28.1-35.6)	1.0 (-1.9-3.9)	0.487	33.5 (29.9-37.1)	33.1 (29.5-36.7)	0.4 (-3.0-3.8)	0.815
Sensation of bulge									
Visual analogue scale (0-100)	57.6 (53.3-62.0)	55.3 (49.0-61.5)	56.5 (50.4; 62.7)	-1.2 (-9.5- 7.0)	0.761	7.4 (3.5-11.3)	6.0 (2.1- 9.8)	1.5 (-4.0- 6.9)	0.598
Anatomy									
Prolapse distance from hymen (cm)									
Dominant compartment	1.9 (1.7-2.1)	1.7 (1.4-2.0)	1.9 (1.6- 2.2)	-0.2 (-0.5- 0.2)	0.394	-1.8 (-2.2- -1.4)	-2.0 (-2.4- -1.6)	0.2 (-0.4- 0.8)	0.556
Anterior compartment	0.8 (0.5-1.1)	0.9 (0.5-1.3)	0.6 (0.2- 1.0)	0.3 (-0.1- 0.7)	0.130	-1.3 (-1.7- -1.0)	-1.6 (-2.0- -1.3)	0.3 (-0.2- 0.7)	0.257
Middle compartment	-1.8 (-2.3--1.3)	-2.3 (-2.8--1.6)	-1.8 (-2.4- -1.2)	-0.4 (-1.0- 0.2)	0.148	-5.4 (-5.8- -4.9)	-5.3 (-5.7- -4.9)	-0.1 (-0.6- 0.5)	0.870
Posterior compartment	-1.4 (-1.7--1.1)	-1.5 (-1.8- -1.2)	-1.5 (-1.8--1.1)	0.0 (-0.4- 0.3)	0.835	-2.5 (-2.6--2.3)	-2.6 (-2.7- -2.4)	0.1 (-0.1- 0.3)	0.413

* Proportional change in anteroposterior diameter of the levator hiatus from rest to contraction.

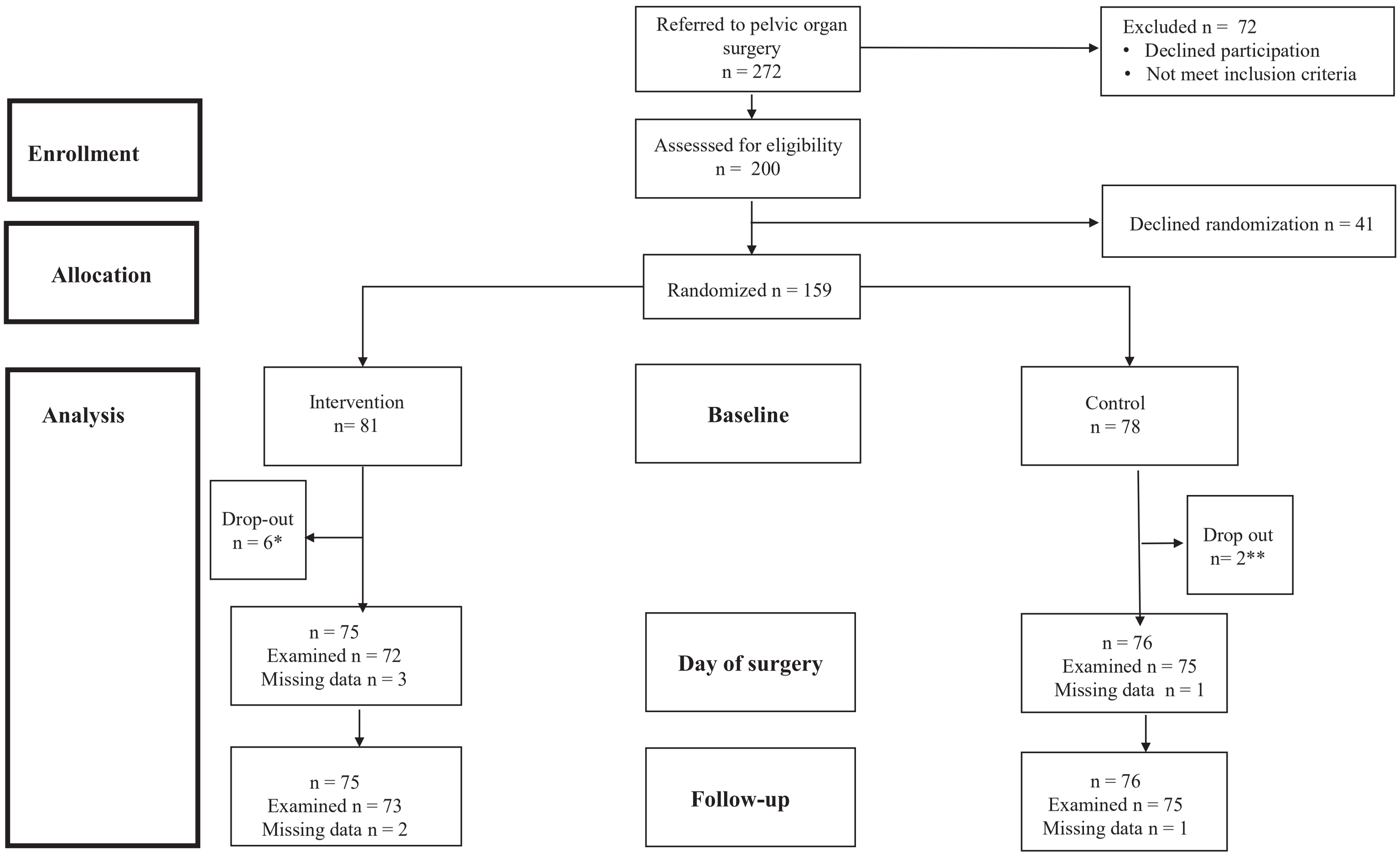
Table 3 Over all change between baseline and postoperative control

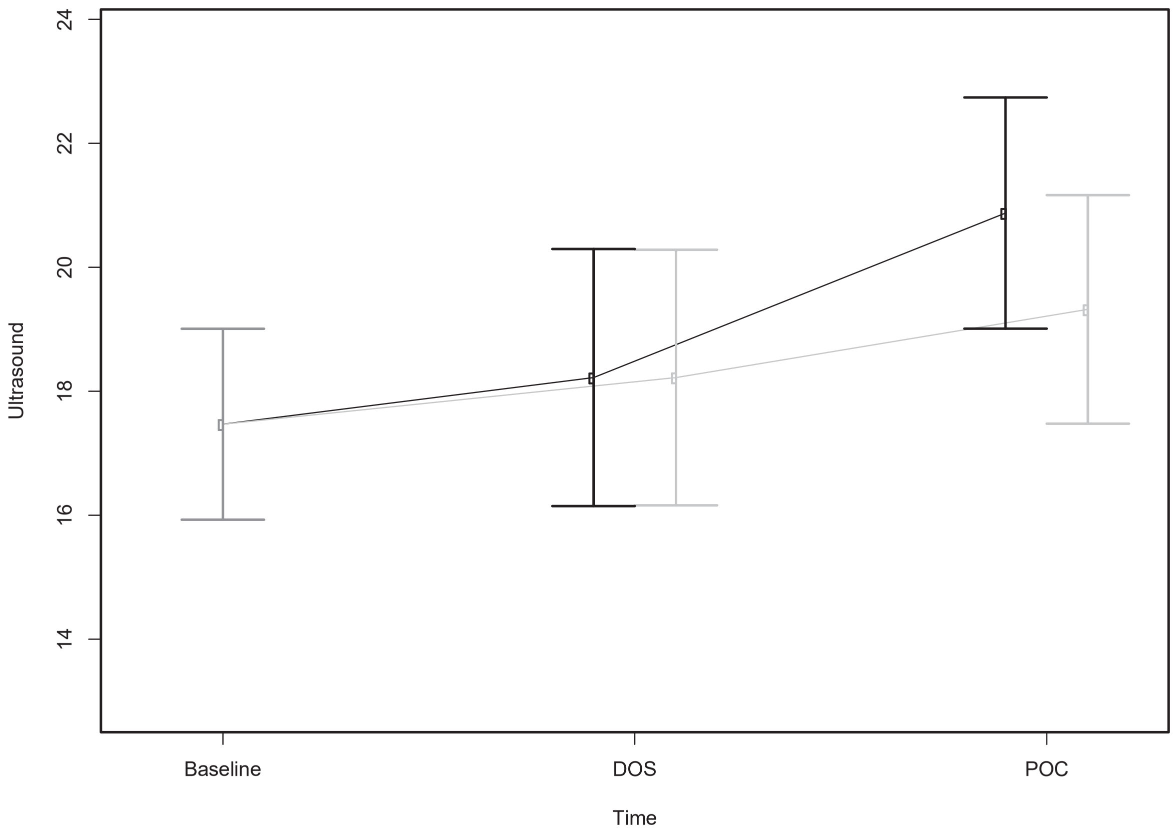
Outcome	**Baseline**	**Postoperative control**	**Change (95 %CI)**	***p***
		Pelvic floor contraction		
Palpation, Modified Oxford Scale (0-5)	2.1 (1.9- 2.2)	2.3 (2.1- 2.5)	0.2 (0.1- 0.4)	0.007
Ultrasound (% change)*	17.5 (15.9- 19.0)	20.1 (18.7- 21.5)	2.6 (1.1- 4.1)	0.001
Vaginal manometry (cmH₂O)	19.0 (16.9- 21.1)	19.5 (17.4- 21.6)	0.5 (-0.8- 1.8)	0.420
Electromyography (mV)	34.8 (31.2- 38.4)	33.3 (30.1- 36.5)	-1.5 (-3.4- 0.4)	0.126
Sensation of bulge				
Visual analogue scale (0-100)	57.6 (53.3- 62.0)	6.7 (3.9- 9.4)	-50.9 (-55.8- -46.1)	< 0.001
Anatomy				
Prolapse distance from hymen (cm)				
Dominant compartment	1.9 (1.7- 2.1)	-1.9 (-2.2- -1.6)	-3.8 (-4.1- -3.5)	<0.001
Anterior compartment	0.8 (0.5- 1.1)	-1.5 (-1.7- -1.2)	-2.3 (-2.6- -2.0)	< 0.001
Middle compartment	-1.8 (-2.3- -1.3)	-5.3 (-5.7- -5.0)	-3.5 (-4.0- -3.0)	< 0.001
Posterior compartment	-1.4 (-1.7- -1.1)	-2.5 (-2.6- -2.4)	-1.1 (-1.4- -0.8)	< 0.001

* Proportional change in anteroposterior diameter of the levator hiatus from rest to contraction.

Table 4 Proportion of women with improved contraction, reduced symptoms and anatomical prolapse, prolapse recurrence and prolapse in a new compartment with comparison between the groups at postoperative follow-up.

	Total n=148	**Intervention n=73**	**Control n=75**	**X^2 test**
Improvement	n (%)	n (%)	n (%)	*p*
Improved contraction on palpation	65 (44)	37 (51)	28 (37)	0.102
Improved contraction on ultrasound	86 (59)	42 (58)	44 (59)	0.967
Reduction in symptoms	130 (92)	62 (90)	68 (94)	0.310
Reduction in anatomical prolapse in operated compartment	144 (97)	70 (96)	74 (99)	0.298
Recurrence				
Sensation of vaginal bulge	29 (20)	13 (18)	16 (22)	0.598
Pelvic organ prolapse grade ≥2 in operated compartment	53 (36)	25 (34)	28 (37)	0.695
Pelvic organ prolapse grade ≥2 in new compartment	7 (5)	2 (2)	5 (7)	0.261


Enrollment
Allocation
Analysis
Referred to pelvic organ surgery n = 272
Excluded n = 72
• Declined participation
• Not meet inclusion criteria
Assesssed for eligibility n = 200
Declined randomization n = 41
Randomized n = 159
Intervention n= 81
Baseline
Control n = 78
Drop-out n = 6*
Drop out n= 2**
n = 75
Examined n = 72
Missing data n = 3
Day of surgery
n = 76
Examined n = 75
Missing data n = 1
n = 75
Examined n = 73
Missing data n = 2
Follow-up
n = 76
Examined n = 75
Missing data n = 1


Ultrasound
24
22
20
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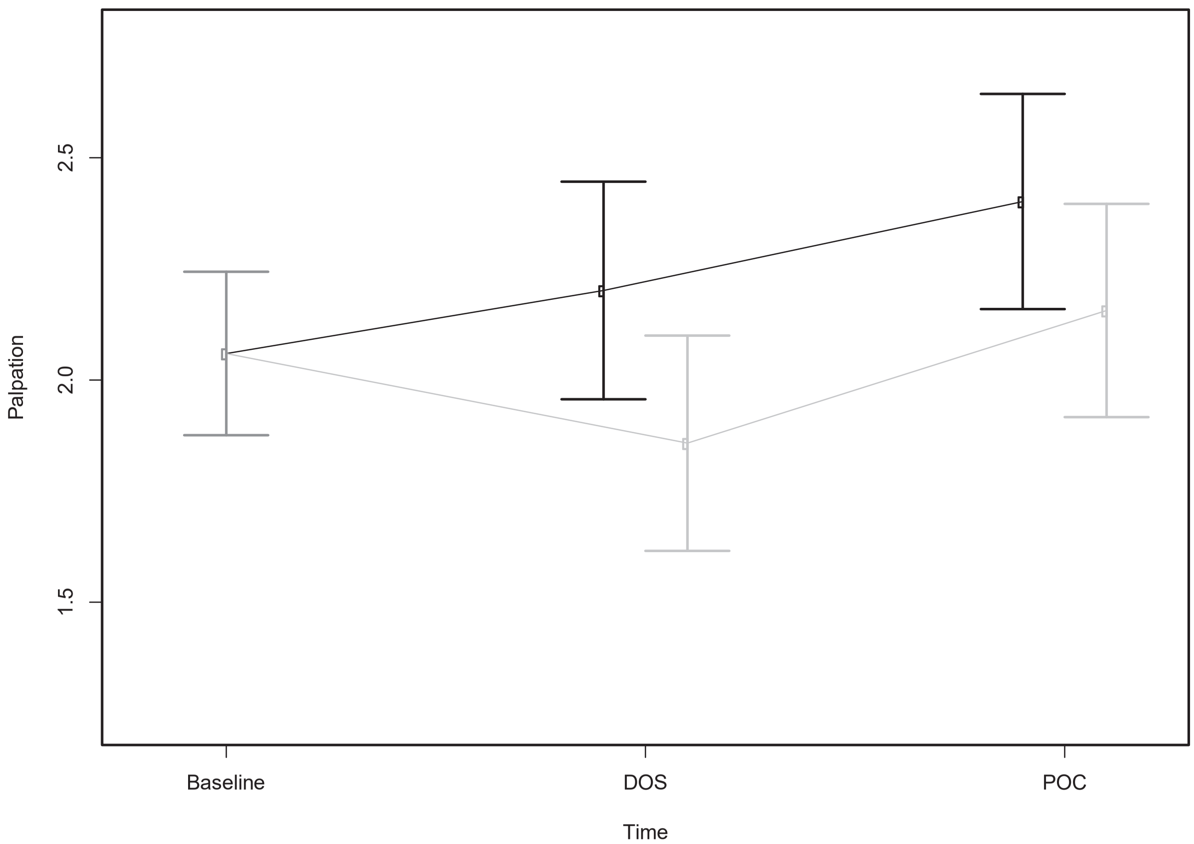
Baseline
DOS
POC
Time



Palpation
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1.5
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DOS
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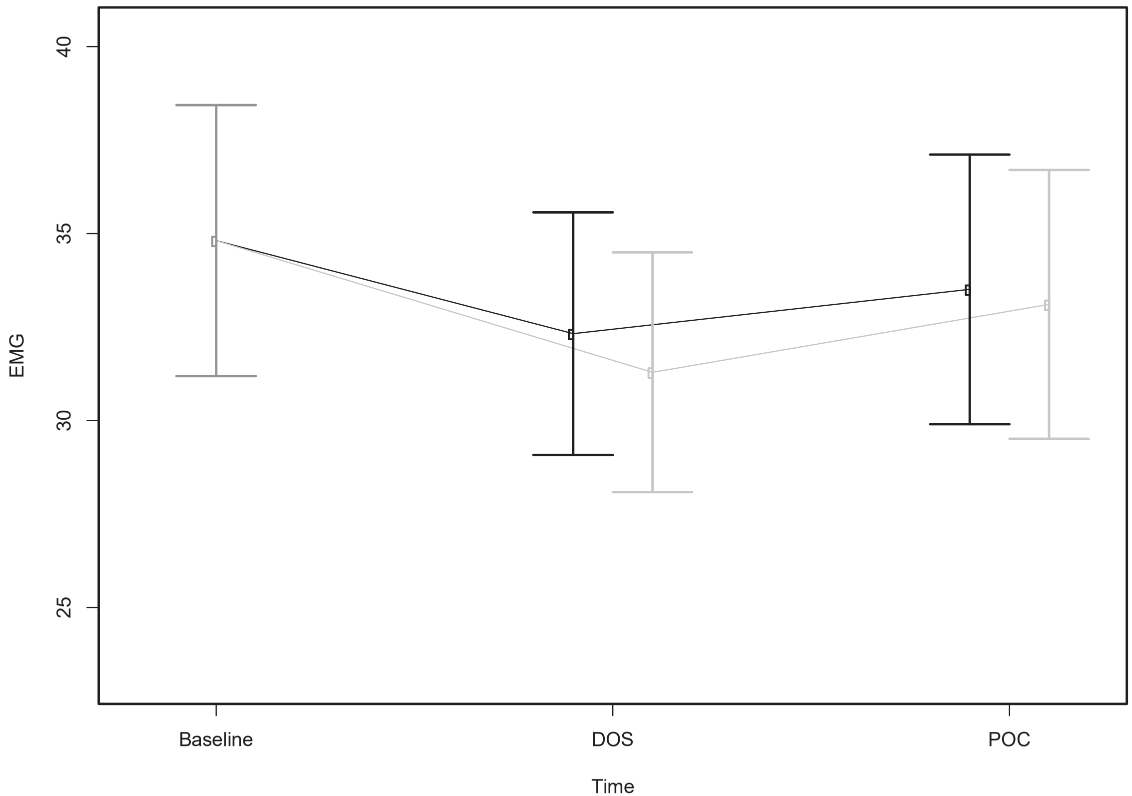
Time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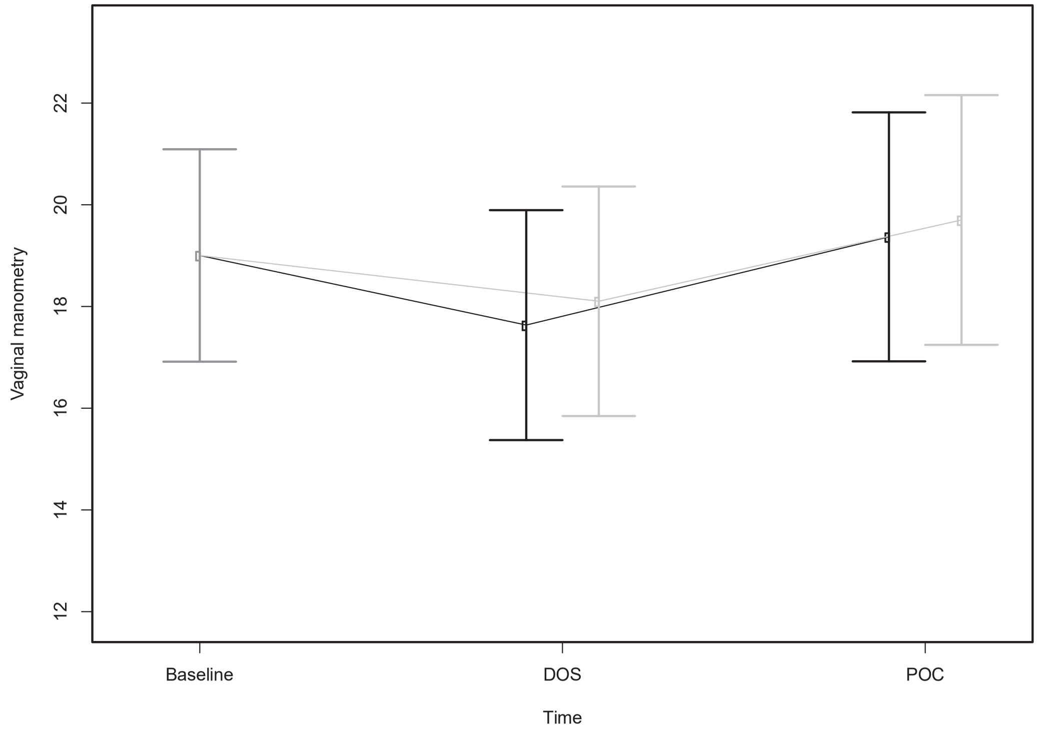
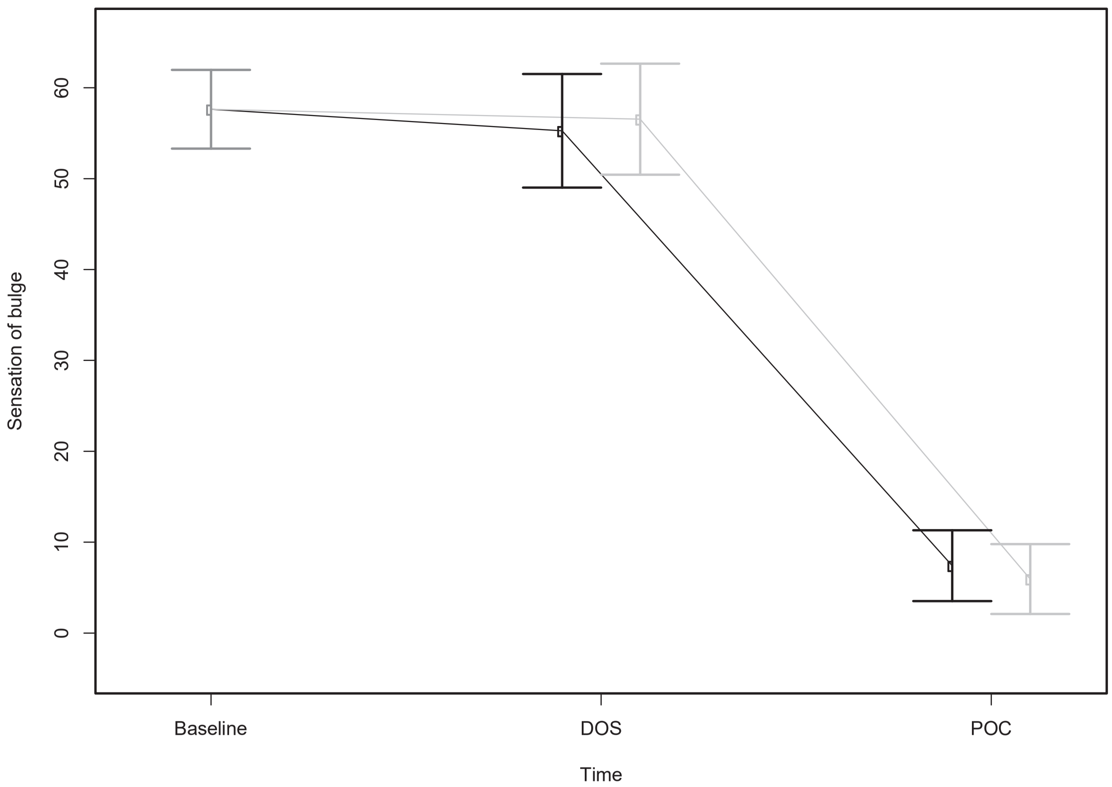
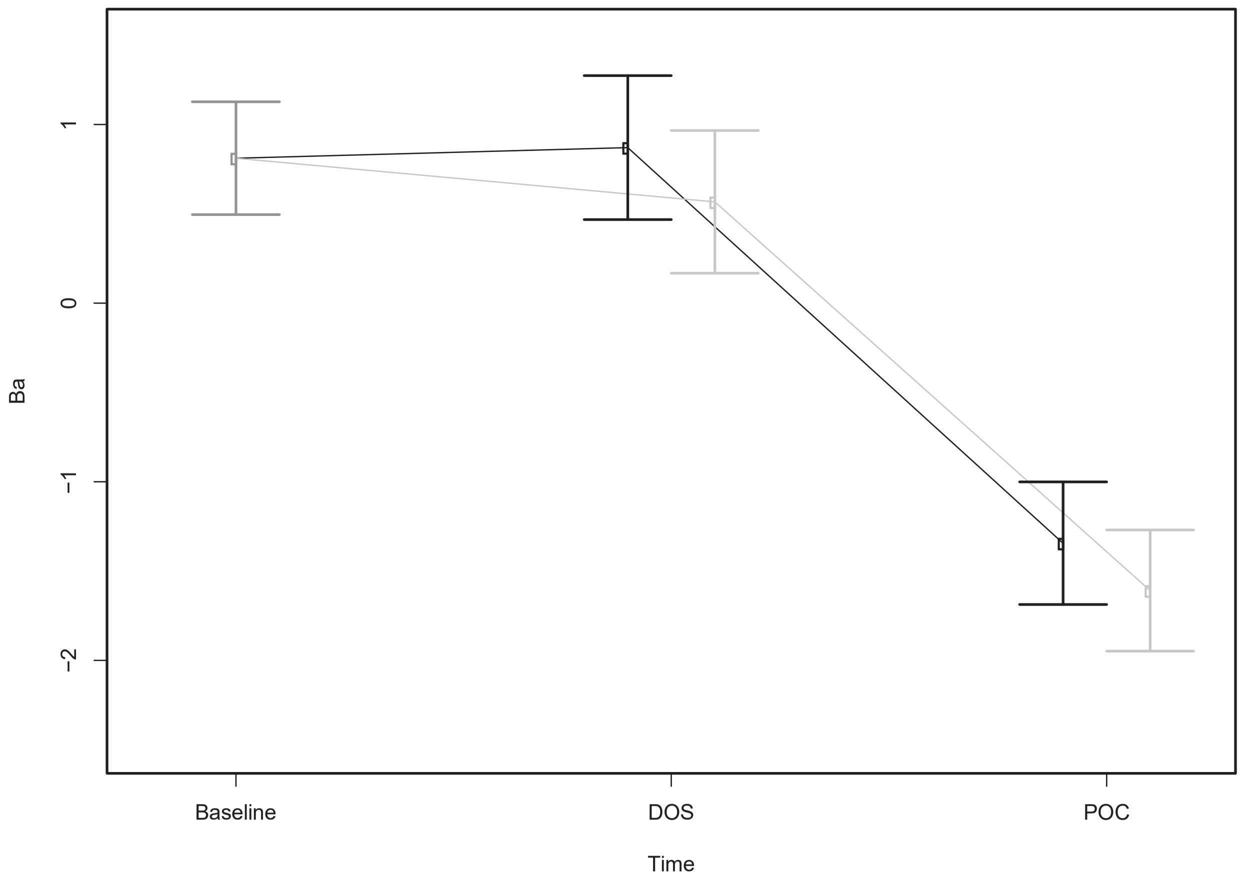
25
EMG
Baseline
DOS
POC
Time



Vaginal manometry
22
20
18
16
14
12
Baseline
DOS
POC
Time



Sensation of bulge
0
10
20
30
40
50
60
Baseline
DOS
POC
Time



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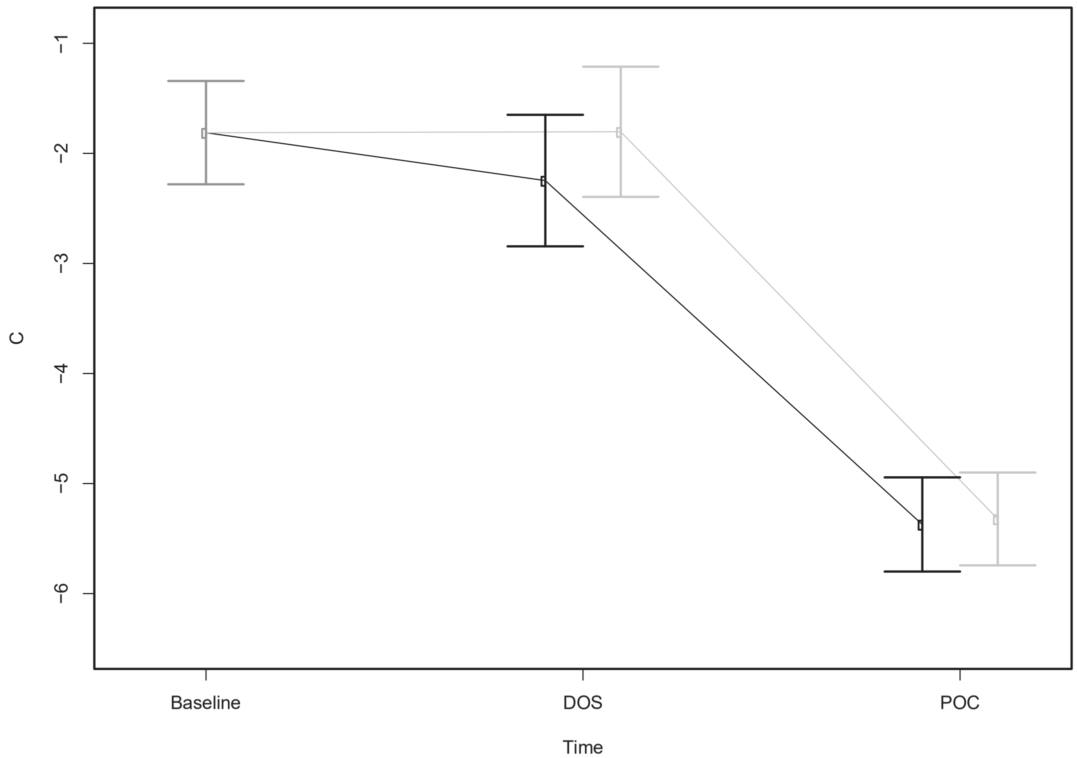
C
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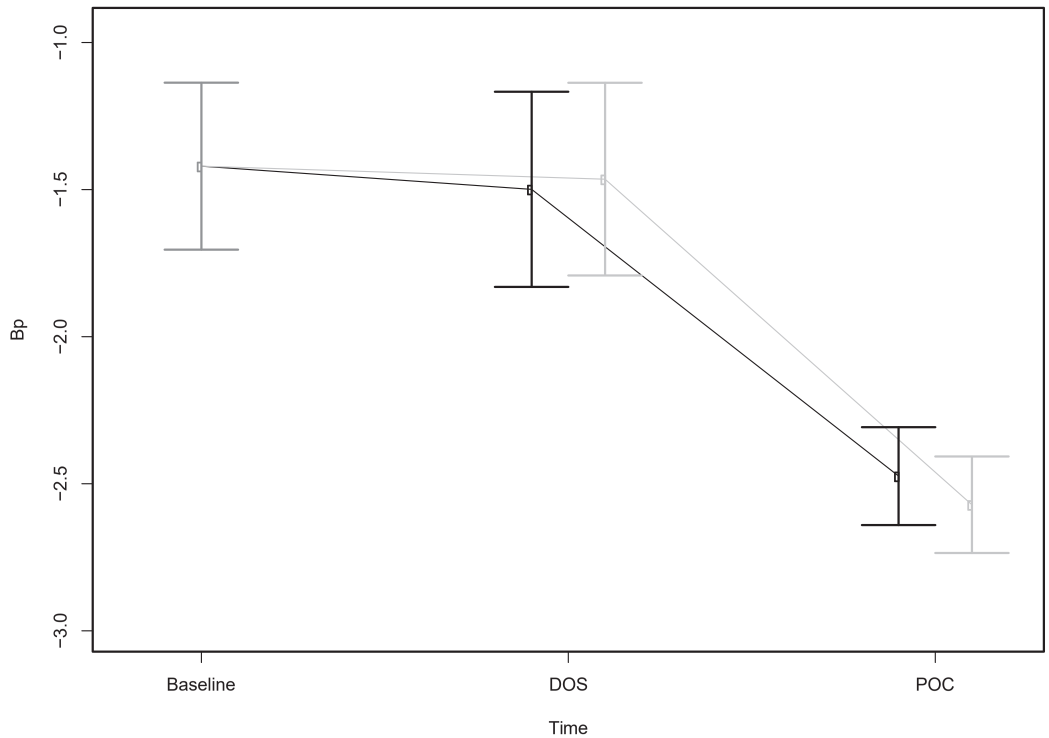
Baseline
DOS
POC
Time



Bp
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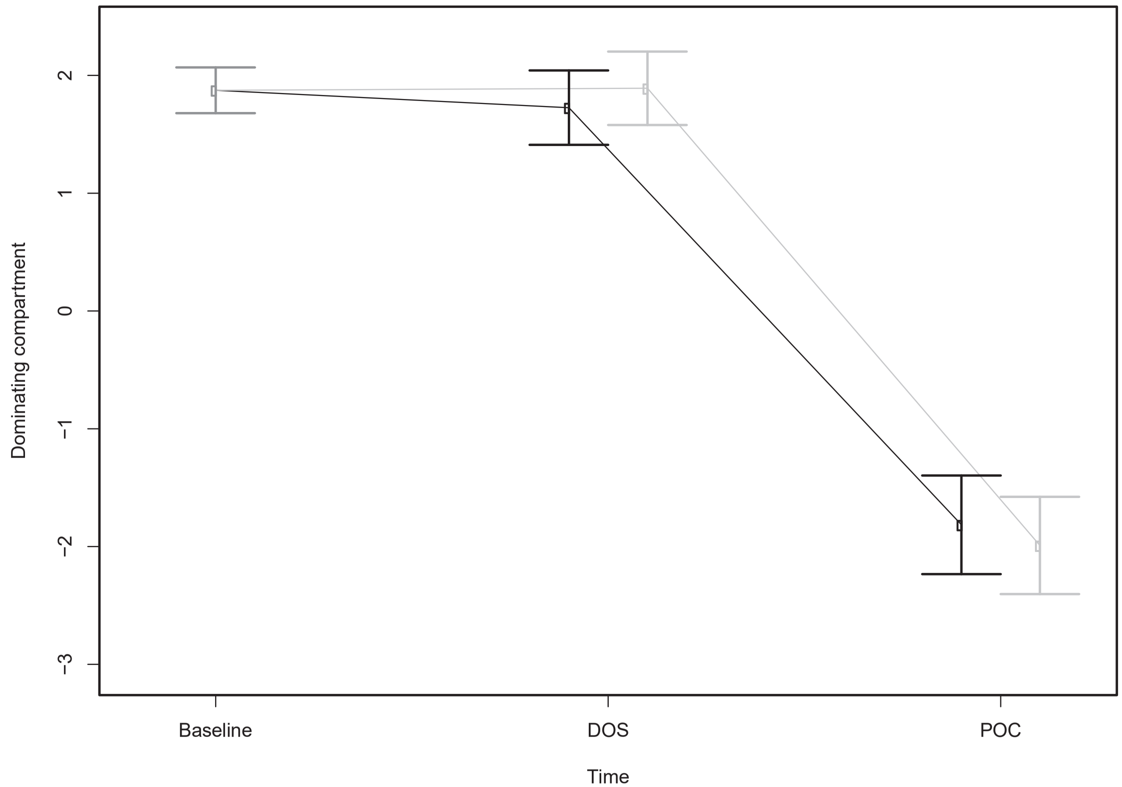
−3.0
Baseline
DOS
POC
Time



Dominating compartment
2
1
0
−1
−2
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Baseline
DOS
POC
Time

PAPER IV

This paper is awaiting publication and is not included in NTNU Open

12 Appendix II Information form

CONTRAPOP

Anatomi og muskelstyrke i bekkenbunnen hos kvinner

FORESPØRSEL OM DELTAKELSE I FORSKNINGSPROSJEKTET

Dette er et spørsmål til deg om å delta i et forskningsprosjekt for å undersøke funksjonen i bekkenbunnsmuskulaturen hos kvinner som opereres for underlivsframfall (descens). Vi ønsker å kartlegge symptomer og undersøke funksjonen i bekkenbunnen før og etter kirurgi. Vi vil finne ut om det er forhold ved forundersøkelsen som kan si oss noe om resultatet av operasjonen, og hvor fornøyd pasientene våre blir etter operasjonen. Vi ønsker også å benytte informasjonen fra undersøkelsene til å utvikle en ultralydskala for å vurdere styrke i bekkebunnen som siden kan benyttes i daglig klinisk praksis. Du kan delta i denne studien fordi du er henvist til operasjon ved Gynekologisk avdeling St Olavs hospital.

HVA INNEBÆRER PROSJEKTET?

Deltakelse i denne studien innebærer at du enten mottar standard behandling og informasjon, eller livsstilsråd og opplæring i bekkenbunnstrening.

Ventetiden før operasjon er like lang i begge grupper. Utvelgelsen til hvilken gruppe du havner i skjer ved randomisering, en slags loddtrekning.

Havner du i gruppen som kun mottar standard behandling og informasjon, får du råd om bruk av lokale østrogener, nytte av knipeøvelser og du får informasjon om operasjonen (varighet av sykehusopphold, mulige komplikasjoner, sykemeldingstid). Dersom du havner i treningsgruppen, vil du i tillegg til standard informasjon motta livsstilsråd og opplæring i bekkenbunnstrening hos fysioterapeut.

Du vil møte til ukentlige treningsøkter hos fysioterapeut, samtidig som du blir oppfordret til å trene daglig hjemme, og blir bedt om å føre en treningsdagbok.

Samtykke til deltakelse i studien innebærer for alle grundige undersøkelser ved tre tidspunkt:

1) Når du søkes inn til kirurgi

2) få dager før operasjonen

3) Ca 6 måneder etter operasjonen

Det skal gjøres en vanlig gynekologisk undersøkelse med gradering av ditt framfall, og en klinisk vurdering av knipeevnen. I tillegg gjøres en undersøkelse med trykkmåler i vagina. Du vil også gjennomgå en 3D ultralyd undersøkelse av bekkenbunnsmuskulaturen.

Dette gjøres ved en utvendig undersøkelse mot underlivet. Undersøkelsen tar ca 45 minutter. I tillegg skal du fylle ut et spørreskjema om hvilke symptomer og plager du har før og etter operasjonen. Du skal svare på spørsmål for gradering av hvor mye du eventuelt er plaget av fremfall og lekkasje. Vi spør i tillegg om hvor mange barn du har født, hvor gammel du var ved første og siste fødsel, og på hvilken måte du har født (normalfødsler, tang, vakum, keisersnitt).

MULIGE FORDELER OG ULEMPER

Fordeler for deg som studiedeltager er at du vil få en ekstra grundig undersøkelse av bekkenbunnsmuskulaturen din, som du ellers ikke ville fått ved vanlig pasientbehandling. Du vil få økt kunnskap om anatomi, og de som havner i treningsgruppen vil få grundig opplæring i trening av bekkenbunnsmuskulatur. I tillegg vil du få en ekstra undersøkelse 6 måneder etter operasjon, som du ikke ville fått uten deltagelse i studien. Ulemper er at det vil ta av din tid at du må møte til 2 ekstra undersøkelser, og for de som havner i treningsgruppen vil det ta tid å gjennomføre bekkenbunnstrening i forkant av operasjonen. Det er ingen risiko forbundet med undersøkelsene.

FRIVILLIG DELTAKELSE OG MULIGHET FOR Å TREKKE SITT SAMTYKKE

Det er frivillig å delta i prosjektet. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke. Dette vil ikke få konsekvenser for din videre behandling. Dersom du trekker deg fra prosjektet, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner. Dersom du senere ønsker å trekke deg eller har spørsmål til prosjektet, kan du kontakte Maria Øyasæter Nyhus eller prosjektleder Ingrid Volløyhaug (se kontaktinformasjon under)

HVA SKJER MED INFORMASJONEN OM DEG?

Informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger.

En kode knytter deg til dine opplysninger og resultat av undersøkelser gjennom en navneliste. Det er kun autorisert personell knyttet til prosjektet som har adgang til navnelisten og som kan finne tilbake til deg. Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres.

I tillegg til studieinformasjonen vil det føres journal i sykehusets elektroniske pasientjournal, slik vi gjør for alle pasienter som undersøkes ved sykehuset. Andre journalopplysninger enn de vi spør om i studien inngår ikke i prosjektet.

Informasjon om alle kvinner som opereres for framfall ved St Olavs hospital blir avidentifisert og registrert i sykehusets lokale descensregister. Samtykker du til deltakelse i prosjektet, vil informasjon fra descensregisteret brukes i studien.

Prosjektleder har ansvar for den daglige driften av forskningsprosjektet og at opplysninger om deg blir behandlet på en sikker måte. Informasjon om deg vil bli anonymisert eller slettet senest fem år etter prosjektslutt.

FORSIKRING

Ved deltagelse i studien er du forsikret i henhold til pasientskadeloven.

OPPFØLGINGSPROSJEKT

Om det skulle bli aktuelt med en oppfølgingsstudie, kan du bli kontaktet igjen.

ØKONOMI

Du får ingen økonomisk godtgjørelse for tapt arbeidstid eller utgifter til reise/parkering i forbindelse med prosjektet.

GODKJENNING

Prosjektet er godkjent av Regional Etisk komite for medisinsk og helsefaglig forskningsetikk.

Saksnummer: 2015/1751/REK midt

VED YTTERLIGERE SPØRSMÅL, KONTAKT:

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Ingrid Volløyhaug, prosjektleder og overlege PhD ved Kvinneklinikken St Olavs hospital
Ingrid.volloyhaug@ntnu.no Tlf: 06800

SAMTYKKE TIL DELTAKELSE I PROSJEKTET

JEG ER VILLIG TIL Å DELTA I PROSJEKTET

Sted og dato

Deltakers signatur

Deltakers navn med trykte bokstaver

FORESPØRSEL OM DELTAKELSE I FORSKNINGSPROSJEKTET

CONTRAPOP

Anatomi og muskelstyrke i bekkenbunnen hos kvinner

Dette er et spørsmål til deg om å delta i et forskningsprosjekt for å undersøke funksjonen i bekkenbunnsmuskulaturen hos kvinner. Vi ønsker å benytte informasjonen fra undersøkelsene til å utvikle en ultralydskala for å vurdere styrke i bekkebunnen, som siden kan benyttes i daglig klinisk praksis. Du kan delta i denne studien enten fordi du er henvist til operasjon ved Gynekologisk avdeling St Olavs hospital eller fordi du er henvist til rutineultralyd i forbindelse med din første graviditet.

HVA INNEBÆRER PROSJEKTET?

Deltagelse i studien innebærer at du kommer til 2 undersøkelser på gynekologisk avdeling

For *gravide* er den første rundt uke 20 i svangerskapet, den andre 6 måneder etter fødsel.

For *kvinner som opereres for urinlekkasje* vil den første undersøkelsen skje på operasjonsdagen og den andre ca 6 måneder etter operasjon.

Hos alle skal det gjøres en klinisk undersøkelse av muskulaturen, en undersøkelse med trykkmåler i vagina og en ultralyd undersøkelse av bekkenbunnsmuskulaturen. Dette gjøres ved en utvendig undersøkelse mot underlivet. Undersøkelsene tar ca 45 minutter.

I forbindelse med undersøkelsen ber vi om at du svarer på spørsmål for gradering av hvor mye du eventuelt er plaget av fremfall og lekkasje. Vi spør i tillegg om hvor mange barn du har født, hvor gammel du var ved første og siste fødsel, og på hvilken måte du har født (normalfødsler, tang, vakuum, keisersnitt).

MULIGE FORDELER OG ULEMPER

Fordeler for deg som studiedeltaker er at du vil få en grundig undersøkelse av bekkenbunnsmuskulaturen din, som du ellers ikke ville fått ved vanlig rutinebehandling. Du vil få økt kunnskap om anatomi og opplæring i trening av bekkenbunnsmuskulatur. I tillegg vil du få en ekstra undersøkelse 6 måneder etter fødsel/operasjon, som du ikke ville fått uten deltagelse i studien. Ulemper er at det vil ta av din tid at du må møte til 2 undersøkelser. Det er ingen risiko forbundet med undersøkelsene, hverken for gravide eller operasjonspasienter.

FRIVILLIG DELTAKELSE OG MULIGHET FOR Å TREKKE SITT SAMTYKKE

Det er frivillig å delta i prosjektet. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke. Dette vil ikke få konsekvenser for din videre behandling. Dersom du trekker deg fra prosjektet, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner. Dersom du senere ønsker å trekke deg eller har spørsmål til prosjektet, kan du kontakte Maria Øyasæter Nyhus eller prosjektleder Ingrid Volløyhaug (se kontaktinformasjon under)

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Prosjektleder har ansvar for den daglige driften av forskningsprosjektet og at opplysninger om deg blir behandlet på en sikker måte. Informasjon om deg vil bli anonymisert eller slettet senest fem år etter prosjektslutt.

FORSIKRING

Ved deltagelse i studien er du forsikret i henhold til pasientskadeloven.

OPPFØLGINGSPROSJEKT

Om det skulle bli aktuelt med en oppfølgingsstudie, kan du bli kontaktet igjen.

ØKONOMI

Du får ingen økonomisk godtgjørelse for tapt arbeidstid eller utgifter til reise/parkering i forbindelse med prosjektet.

GODKJENNING

Prosjektet er godkjent av Regional Etisk komite for medisinsk og helsefaglig forskningsetikk.

Saksnummer:

VED YTTERLIGERE SPØRSMÅL, KONTAK:

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06800/97549124

SAMTYKKE TIL DELTAKELSE I PROSJEKTET

JEG ER VILLIG TIL Å DELTA I PROSJEKTET

Sted og dato

Deltakers signatur

Deltakers navn med trykte bokstaver

13 Appendix III Clinical examination and Visual analogue scale

Fødselsnummer:__ __ __ _ _ _ _ _

Deltakernummer:_ _ _ _

CONTRAPOP

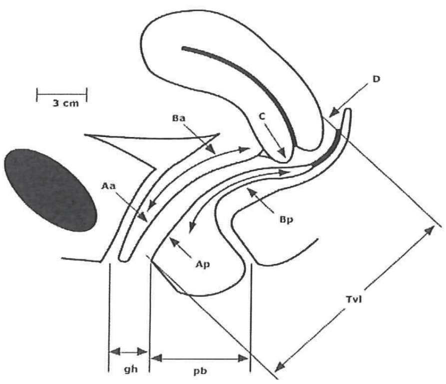
klinisk undersøkelse

Symptoms, anatomy and muscle CONTRAction in women with Pelvic Organ Prolapse, incontinence and in pregnancy

Symptomer, anatomi og styrke i bekkenbunnsmuskulatur hos kvinner med descens, inkontinens og hos gravide

1) Gradering av descens.

POP-Q



Aa	Ba	C
Gh	Pb	Tvl
Ap	Bp	D

Grad	0	1	2	3	4
Cystocele	□	□	□	□	
Uterusdescens/ellongatio	□	□	□	□	□
Rectocele	□	□	□	□	
Enterocele	□	□	□	□	
Vaultprolaps	□	□	□	□	□

2) Palpasjon og måling av styrke og integritet av levatormuskulaturen

Hviletonus 0-5 av 5 H □ V □

palpasjon

0= muskel ikke palpabel, **1**=muskel palpabel, men veldig slapp, vid hiatus, minimal motastand ved strekk, **2**= vid hiatus, men noe motstand ved strekk, **3**= Hiatus temmelig smal, middels motstand, men lett å strekke, **4**= Hiatus smal, muskelen kan strekkes, men høy motstand mot strekk, ingen smerte, **5**= Hiatus veldig smal, ingen strekk mulig, "treet" følelse, mulig med smerte: "vaginisme"

Muskelstyrke Modified Oxford Scale 0-5 av 5

H □ V □

palpasjon

0=ingen kontraksjon, **1**=flakkende, **2**=svak, **3**=moderat, **4**=god, **5**=sterk

Muskelintegritet

palpasjon:	avrivning	H □	V □
	Delvis avrivning	H □	V □
	Intakt	H □	V □

Muskelstyrke/ vaginaltrykk

v bruk av apparat (Camtech) max av tre kontraksjoner: □ cm H_2O

Muskelstyrke/ muskelaktivitet

Elektromyografi (EMG) beste av tre kontraksjoner □ mV

ALLE SPØRSMÅL STILLES ETTER AT UNDERSØKELSENEN ER GJENNOMFØRT

Spørsmål om svangerskap

Antall barn totalt: ☐☐

Alder/årstall ved første fødsel ☐☐

Alder/årstall ved siste fødsel ☐☐

Tvillinger ☐ Ja ☐ Nei

Operativ vaginal forløsning ☐ Ja ☐ Nei

Kun keisersnitt ☐ Ja ☐ Nei

Spørsmål om symptomer

Kan du vanligvis se eller kjenne en kul i skjedeåpningen? ☐ Ja ☐ Nei
Hvis ja, hvor mye plager det deg?

Ingen plager ———————— Verst tenkelige plager ☐☐☐ Ikke skriv her

Har du vanligvis lekkasje for urin ved sterk trang? ☐ Ja ☐ Nei
Hvis ja, hvor mye plager det deg?

Ingen plager ———————— Verst tenkelige plager ☐☐☐ Ikke skriv her

Har du vanligvis lekkasje for urin ved fysisk anstrengelse, eller hoste, nys, latter? ☐ Ja ☐ Nei
Hvis ja, hvor mye plager det deg?

Ingen plager ———————— Verst tenkelige plager ☐☐☐ Ikke skriv her

Har du vanligvis lekkasje for avføring? ☐ Ja ☐ Nei
Hvis ja, hvor mye plager det deg?

Ingen plager ———————— Verst tenkelige plager ☐☐☐ Ikke skriv her

Har du vanligvis lekkasje for luft? ☐ Ja ☐ Nei
Hvis ja, hvor mye plager det deg?

Ingen plager ———————— Verst tenkelige plager ☐☐☐ Ikke skriv her

14 Appendix IV Information to intervention group

Måned	Dato	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	Anmerkning
	A																																
	B																																
	C																																
	A																																
	B																																
	C																																
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	A																																
	B																																
	C																																

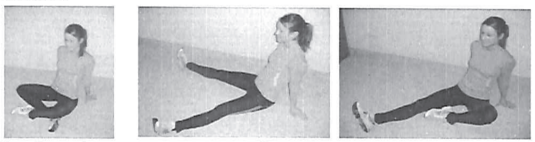
Råd om livsstil og bekkenbunnstrening til deg som er deltager i CONTRAPOP-studien

Vi ber deg følge treningsprogram og livsstilsråd under treningsperioden frem mot operasjonen og som vi anbefaler at du fortsetter etter at du er operert.

Bekkenbunnsøvelsene skal gjennomføres <u>daglig</u> i perioden fram til operasjon. Øvelsene skal føres i treningsdagboken som er vedlagt

1. **Prøv å få kontakt med bekkenbunnsmusklene.** Dette kan ta kortere eller lenger tid. Musklene er lokalisert rundt urinrør/skjede/endetarm, innvendig i bekkenet. Trekk sammen rundt åpningen, forsøk å løfte opp og inn i kroppen, og slipp ut igjen uten å trykke aktivt nedover.
2. **Sjekk om du får tak i rette muskler.** Hold en hånd under skjede/endetarm utenpå trusen, og tenk at du løfter opp og vekk fra hånden. Forsøk å stanse dryppingen på slutten av vannlatingen. NB! Ikke gjør dette som regelmessig trening.
3. **Velg en utgangsstilling.** Det er individuelt hvilke som passer best.

Sittende:



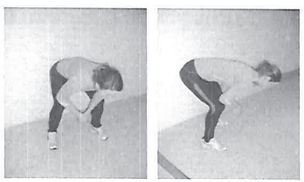
Froskestilling:

Mageliggende:

Ryggliggende:

Stående oppreist:

Stående foroverlent:



4. **De vanligste feilene når man trener:** Bruk av sete, lår eller magemuskler (tipping av bekkenet) i stedet for bekkenbunnsmusklene. Unngå kraftig innpust eller overdreven hold av pusten, samt trykking nedover i stedet for løft opp og inn (noe som kan forverre eventuelle symptomer på lekkasje).
5. **Konsentrer deg.** Ikke forsøk å trene samtidig som du gjør andre ting. Da yter du ikke maksimalt, det er lettere at du trener feil, og treningen blir ikke så effektiv.
6. **Gjør flere lette sammentrekninger etter hverandre.**
7. **Treningsdosering:** Ideelt sett skal du klare 8-12 repetisjoner x 3 runder daglig. De 3 rundene kan gjøres på ett tidspunkt på dagen med kun en liten pause mellom hver runde, eller du kan spre de 3 rundene utover dagen slik det passer deg.
8. **Intensiv bekkenbunnstrening:** Når du begynner å få kontakt med bekkenbunnsmusklene, kan du intensivere treningen. Trekk sammen så hardt du kan, og forsøk å holde hver sammentrekning lenger og lenger. NB! Hvis du kjenner et inntrekk av den tverrgående magemuskelen (helt nederst i magen), så er det ok, og skyldes et naturlig samspill med bekkenbunnsmusklene. Når du klarer å holde hver muskelsammentrekning i 6-8 sekunder, kan du legge til 3-4 raske sammentrekninger videre innover på slutten av holdeperioden.
9. **Oppsummering av intensivt treningsprogram:** For hver repetisjon: trekk sammen bekkenbunnsmusklene, hold 6-8 sek, gjør 3-4 raske løft, slipp ut igjen, 3-4 sek pause. Daglig treningsdose: 8-12 repetisjoner x 3 runder.
10. **Knip også før du hoster, nyser og gjør tunge løft for å motvirke belastningen på bekkenbunnen ved økt buktrykk.**
11. **Vedlikeholdstrening etter studien er slutt:** Det er individuelt hvor mye som skal til for å vedlikeholde muskelstyrke og forebygge lekkasje og fremfall. Det anbefales å gjøre 8-12 sammentrekninger så hardt som mulig 1-2 ganger per uke. Husk at trening er ferskvare – du mister treningseffekten du har bygd opp dersom du tar lengre pauser fra treningen.

Unngåhard/treg avføring

Det er viktig å holde avføringen myk for å unngå stort press på bekkenbunnen og bekkenorganene ved avføring. Et variert kosthold med fiber, mosjon og tilstrekkelig med væskeinntak bidrar til dette

- Fiber: Kostfiber gjør avføringen fyldigere og mykere, finnes i helkornsprodukter og plantemat
- Mosjon: Det er vist at mindre til moderat mengde trening kan forebygge forstoppelse. Dette kan for eksempel være å gå eller løpe en tur daglig.
- Væske: Inntak av væske kan gjøre avføringen tyngre og glattere.

Kilder:
St Olavs hospital:
https://stolav.no/behandlinger/bekkenbunnstrening
Helsenorge:
https://helsenorge.no/sykdom/mage-og-tarm/forstoppelse
Kompetanseportal for inkonstinens og bekkenbunnssykdom:
http://kurs.helsekompetanse.no/kib-pasient/55567

Dovaner og sittestilling

Optimal sittestilling på toalettet er viktig for en komplett tømming uten å måtte presse overdrevent. Det viser seg at mange har feil sittestilling på toalettet, og kombinert med hard avføring presse for å få tømt seg. Stort buktrykk bidrar til å trykke fram underlivsframfallet. Det er derfor viktig å lære seg riktig sittestilling og hvordan bekkenet påvirkes negativt av stort buktrykk/press. Ved anbefalt sittestilling holdes ryggen rett, og knærne er høyere enn hoften. Oppbygging (krakk) under beina bidrar til det. Hvis man i tillegg puster med magen og slapper av vil tarmen tømme seg lettere. Regelmessige dobesøk til samme tidspunkt "lærer" tarmen å tømme seg regelmessig. Det samme gjelder også ved vannlating der man skal unngå å presse, men la blæren tømme seg spontant.

Lykke til!

NTNU
Kunnskap for en bedre verden

ST. OLAVS HOSPITAL
UNIVERSITETSSYKEHUSET I TRONDHEIM

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