Seema Mathew

Urinary and colorectal-anal distress in women
- prevalence, risk factors and effect of pelvic floor muscle exercise in women with pelvic organ prolapse

Doctoral thesis

NTNU
Norwegian University of
Science and Technology

Seema Mathew

Urinary and colorectal-anal distress in women
- prevalence, risk factors and effect of pelvic floor muscle exercise in women with pelvic organ prolapse

Thesis for the Degree of Philosophiae Doctor

Trondheim, June 2021

Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Clinical and Molecular Medicine

NTNU
Norwegian University of
Science and Technology

> *"Two roads diverged in a yellow wood,*
>
> *And sorry I could not travel both*
>
> *And be one traveller, long I stood*
>
> *And looked down one as far as I could*
>
> *To where it bent in the undergrowth;"*

Robert Frost: 'The road not taken' (1961)

This page and last page art by Grethe By Rise

SUMMARY

Background: The continence mechanism is complex. The influence of levator ani muscle (LAM) injury and other pelvic floor changes in the long-term development of urinary and colorectal-anal distress is not clear. Women with pelvic organ prolapse (POP) have concomitant symptoms of incontinence. The prevalence of anal sphincter defects and associated anal incontinence (AI) in women with POP needs further evaluation. Pelvic floor muscle training (PFMT) is the first line treatment for mild POP and urinary incontinence (UI). Whether intensive pelvic floor exercise improve urinary and colorectal-anal distress and quality of life in women with advanced POP needs further investigation.

Aims

> 1. Study possible associations between LAM trauma and urinary and colorectal-anal distress, including UI and fecal incontinence (FI). Study associations between structural changes in the bladder neck and UI among parous women.

> 2. Assess the prevalence of anal sphincter defects and association with AI in women with symptomatic POP undergoing POP surgery.

> 3. Explore the effect of preoperative PFMT on urinary and colorectal-anal distress and related quality of life in women scheduled for POP surgery.

Methods: Data were collected from two study populations; a cross-sectional study of 608 women examined 15-21 years after first delivery (Paper 1) and a randomized controlled trial of women with symptomatic POP undergoing POP surgery (Paper 2 and 3). All participants were assessed using pelvic organ prolapse quantification system, 3D/4D transperineal ultrasound, visual analogue scale and validated questionnaires. In the randomized controlled trial, the intervention group was given individual physiotherapist guided PFMT from inclusion to the day of surgery. Multivariable regression analysis, Mann-Whitney U test and mixed models analysis were used.

Main results

> 1: We found no associations between LAM injury and symptoms of UI and FI 15-24 years after first delivery, but urethral funneling was associated with stress UI.

> 2: 25% of women scheduled for POP surgery had anal sphincter defects. EAS and IAS defects were strongly associated with FI and flatal incontinence, respectively.

> 3: Symptoms and quality of life related to urinary and colorectal-anal distress improved for all women after POP surgery, regardless of PFMT.

Conclusion: The etiology urinary and colorectal-anal distress is multifactorial and not related to LAM trauma. Bladder neck funneling was indicative of stress UI. Women with severe POP have high prevalence of anal sphincter defects and sphincter defects were associated with AI. We found no evidence of additional advantages of preoperative PFMT for improving urinary and colorectal-anal distress in women with severe POP, beyond POP surgery.

SAMMENDRAG

Bakgrunn: Kontinensmekanismen er kompleks. Sammenhengen mellom skade på bekkenbunnsmusklatur (levator muskel) og utviklingen av plager relatert til urinveier eller analkanalen er uklar. Kvinner med underlivsfremfall er ofte plaget med inkontinens. Sammenhengen mellom skader på endetarmsmusklaturen og analinkontinens blant kvinner med fremfall bør kartlegges nærmere. Bekkenbunnstrening er førstevalg ved milde fremfall eller urinlekkasje. Det trengs bedre kunnskaper om bekkenbunnstrening blant kvinner med behandlingstrengende fremfall kan redusere plager fra urinveier og analkanalen og føre til bedre livskvalitet.

Mål:

1: Undersøke assosiasjonen mellom levatorskade og plager fra urinveier og analkanalen, inkludert urin- og avføringslekkasje blant kvinner i en normal befolkning. Studere assosiasjon mellom blærehals anatomi og UI i samme populasjon.

2: Undersøke forekomst av skader på endetarmsmusklatur og analinkontinens hos kvinner som opereres for underlivsfremfall og assosiasjon mellom muskelskade og inkontinens.

3: Studere effekt av preoperativ bekkenbunnstrening på plager fra urinveier eller analkanalen og livskvalitet blant kvinner som gjennomgår kirurgi for underlivsfremfall.

Metoder: Data innsamling fra to studiepopulasjoner; tverrsnittstudie av 608 kvinner undersøkt 15-21 år etter første fødsel (Artikkel 1) og en randomisert kontrollert studie av kvinner som gjennomgikk fremfallskirurgi. (Artikkel 2 og 3). Deltakerne gjennomgikk gynekologisk undersøkelse med transperineal ultralyd av bekkenbunnnen og besvarte visuell analog skala samt validerte spørreskjema. I den randomiserte kontrollerte studien (Artikkel 3) gjennomførte intervensjonsgruppen bekkenbunnstrening fra inklusjon til dagen for fremfallskirurgi. Multivariabel regresjonsanalyse, Mann-Whitney U test og «mixed models» analyse ble brukt.

Resultater:

1: Vi fant ingen assosiasjon mellom levatorskade og symptomer på urin- eller avføringsinkontinens 15-24 år etter fødsel, men fant at utvidelse av proksimale uretra var assosiert med stress urinlekkasje.

2: 25% av kvinner med behandlingstrengende underlivsfremfall hadde skade på endetarmsmusklaturen. Skadene hadde klar sammenheng med luft- og avføringsinkontinens.

3: Vi fant ingen økt gevinst av preoperativ bekkenbunnstrening på livskvalitet eller underlivsplager relatert til urinveier eller analkanalen.

Konklusjon: Årsakene til urinveis- og anale plager er sammensatte og ikke relatert til levatorskade. Utvidelse av blærehalsen indikerer stress urinlekkasje. Kvinner med behandlingstrengende underlivsfremfall har høy forekomst av skader på endetarmsmusklaturen og slike skader er assosiert med analinkontinens. De fleste kvinnene opplevde bedring av livskvalitet og underlivsplager relatert til urinveier eller analkanalen etter fremfallskirurgi, uavhengig av preoperativ bekkenbunnstrening.

Kandidat   Seema Mathew

Hovedveileder   Ingrid Volløyhaug

Biveileder   Kjell Åsmund Salvesen

Institutt   Klinisk og molekylær medisin

Finansiering   Helse Midt-Norge, Samarbeidsorganet.

TABLE OF CONTENTS

ACKNOWLEDGEMENTS

I came upon this by chance as my supervisor and colleague asked if I would be interested in joining a study on pelvic organ prolapse. The more I got involved in the subject, the more interested and curious I became and my work in this field felt meaningful.

LIST OF PAPERS

Paper 1

Levator ani muscle injury and risk for urinary and fecal incontinence in parous women from a normal population, a cross-sectional study.

Mathew S, Guzmán Rojas RA, Salvesen KA, Volløyhaug I.

Neurourol Urodyn. 2019;38(8):2296-2302.

doi: 10.1002/nau.24138. Epub 2019 Aug 20. PMID: 31432558.

Paper 2

Prevalence of anal sphincter defects and association with anal incontinence in women scheduled for pelvic organ prolapse surgery.

Mathew S, Guzman Rojas RA, Nyhus M, Salvesen K, Volløyhaug, I.

Neurourol Urodyn. 2020;39(8):2409-2416.

doi: 10.1002/nau.24504. Epub 2020 Sep 7. PMID: 32894645.

Paper 3

The effect of preoperative pelvic floor muscle training on urinary and colorectal-anal distress in women undergoing pelvic organ prolapse surgery-a randomized controlled trial.

Mathew S, Nyhus MØ, Salvesen Ø, Salvesen KÅ, Stafne SN, Volløyhaug I.

Int Urogynecol J. 2021 Feb 13.

doi: 10.1007/s00192-021-04684-3. Epub ahead of print. PMID: 33580809.

ABBREVIATIONS

2D	2-dimensional	TUI	tomographic ultrasound imaging
3D/4D	3-dimensional/4-dimensional	UDI-6	urinary distress inventory
aOR	adjusted odds ratio	UI	urinary incontinence
AI	anal incontinence	UUI	urge urinary incontinence
BMI	body mass index	UIQ	urinary impact questionnaire
BND	bladder neck descent		
CI	confidence interval		
CRADI-8	colorectal-anal distress inventory		
CRAIQ	colorectal-anal impact questionnaire		
EAS	external anal sphincter		
FI	fecal incontinence		
IAS	internal anal sphincter		
ICS	international continence society		
LAM	levator ani muscle		
MRI	magnetic resonance imaging		
NVD	normal vaginal delivery		
OASI	obstetric anal sphincter injury		
OR	odds ratio		
PFD	pelvic floor dysfunction		
PFDI-20	pelvic floor distress inventory		
PFMT	pelvic floor muscle training		
PFIQ-7	pelvic floor impact questionnaire		
POPDI-6	pelvic organ prolapse distress inventory		
POPIQ	pelvic organ prolapse impact questionnaire		
POP	pelvic organ prolapse		
POP-Q	pelvic organ prolapse quantification		
QoL	quality of life		
RCT	randomised controlled trial		
REK	regional ethical committee		
SD	standard deviation		
SPSS	statistical package for the social sciences		
SUI	stress urinary incontinence		

1.0 INTRODUCTION

I have always been fascinated by women's health and minimal invasive surgery, so naturally I believed that if I were to immerse myself in some research it would be in this subject. This may sound like a cliché, but I started working on this project by chance as I learned of a clinical trial designed by inspiring and skilled colleagues I look up to. A complete novice at research, I have really understood the saying by Rumi: 'as you start to walk on the way, the way appears'.

As I went deeper into the field of urogynecology the more interesting and meaningful my work felt. These are women who hesitate to seek medical advice for years. The happiness on their faces after a successful treatment will always stay with me. We know so much about the function and anatomy, but there is still more to understand about the intricate interaction between the pelvic floor and incontinence. The damages done during childbirth is considered the main culprit of emerging pelvic floor dysfunction, but if so, why do symptoms appear after many years? Although damage to the pelvic floor is associated with pelvic organ prolapse, the relationship with incontinence is rather unclear.

For gynecologists, an ultrasound machine, is at our fingertips. Ultrasound technology and image quality has made considerable advances in recent years. The urogynecological patient often has complex and interlacing symptoms of more than one pelvic floor dysfunction. Transperineal ultrasound is easy to learn and reproducible, useful in diagnosing other injuries or what lies behind the prolapse, providing valuable information to the surgeon. Also, women have been overwhelmingly positive to the interactive ultrasound-guided summary of the pelvic floor anatomy and correct muscle contraction technique.

Muscle injuries are treated with progressive resistance training for increasing strength and to avoid atrophy. We know that it is possible to exercise the pelvic floor muscles even if these are injured. A defect anal sphincter may be more difficult, and we need more information on the effect of nerve injury on the development of pelvic dysfunction. Pelvic floor muscle exercise is the mainstay in many conditions improving urine leakage, sexual function and mild prolapse. Increased muscle strength should, in theory, improve symptoms related to urinary and anal canal including leakage, and it is effective for stress urinary incontinence. In women with advanced prolapses, incontinence can

persist or emerge postoperatively. Can targeted exercise delay or halt PFD symptoms? Many studies have looked at exercise after surgery, but few have studied the effects of early intervention.

This project was developed around the following research questions that I hope to answer in the course of this thesis:

1. Pelvic floor muscles and incontinence in parous women
   o What is the importance of levator ani muscle injuries and late onset urinary and colorectal-anal symptoms including incontinence in a normal population?
   o How does ultrasound diagnosed parameters of bladder neck anatomy relate to urinary incontinence?

2. Anal sphincter defects and anal incontinence in a urogynecological population
   o What is the prevalence of anal sphincter defects and anal incontinence in women with advanced pelvic organ prolapse?
   o What is the relationship between ultrasound diagnosed anal sphincter defects and anal incontinence in women awaiting pelvic organ prolapse surgery?

3. Pelvic floor muscle training
   o Can preoperative pelvic floor muscle exercise lead to better satisfaction and improvement of pelvic floor dysfunction in women undergoing prolapse surgery?

2.0 BACKGROUND
2.1 The female pelvic floor: anatomy and function

The female pelvic floor consists of bony structures, muscles, connective tissue, nerves and vasculature that cooperate to perform complex functions.

Bones

The pelvic bone consists of three fused bones: the ilium, ischium and the pubic bones, connected posteriorly by the sacrum and anteriorly to the pubic symphysis forming an oval protective case for the pelvic organs.[1] The abdominal organs are contained in the greater pelvis. The lesser pelvis is an inferior continuation where the bladder, genitalia and rectum are located. The female pelvis has a wider diameter and a more circular shape than the male pelvis, enabling childbirth but predisposes to subsequent weakness.[1,2] The anterior tilt helps against a direct gravitational force caudally.[2]

Figure 1 *The muscles of the pelvic floor. Illustrated by Deepa Mathew.*

1	M. Piriformis
2	M. Coccygeus
3	M. Illiococcygeaus
4	M. Pubococcygeus
5	M. Puborectalis
6	M. Obturatorius Internus

LAM (4, 5)
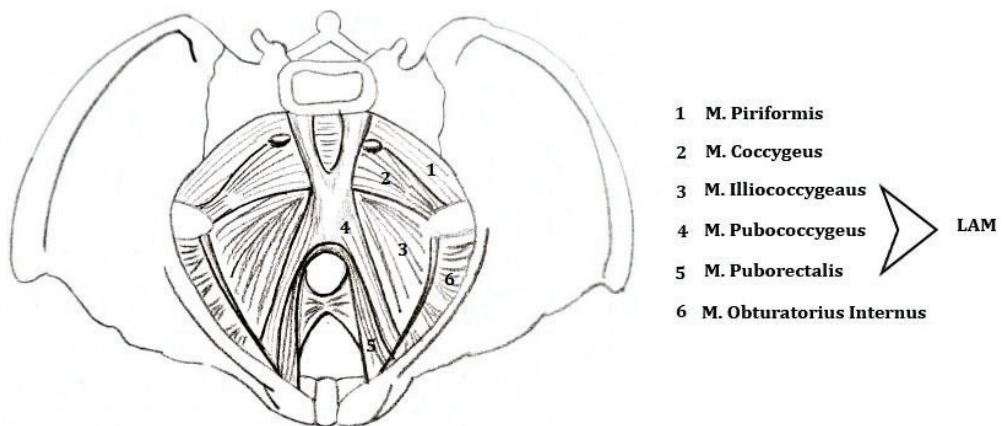
Muscles

A muscular base covers the inside of the pelvis (Figure 1). The levator ani muscle (LAM) is a broad muscle attached to the inner brim of the pelvis through the arcus tendinae laterally, consisting of three main components: iliococcygeus, pubococcygeus and puborectalis muscle.[1] Some disagreement regarding the terminology of the components of the LAM exists.[1] In this thesis, the term puborectalis is used. The LAM together with the coccygeus muscle form the pelvic floor, a musculotendinous diaphragm that lies over the pelvic outlet. The puborectalis sling is the innermost portion of the LAM that defines the levator hiatus allowing passage for the urethra, vagina and anus. LAM maintains a closed urogenital hiatus due to gravity and slight abdominal pressure.[1,2]

The external urethral sphincter is a circular striated muscle located in the middle portion of the urethra and acts by increasing the intraurethral pressure. The urethral smooth muscle has two parts: an inner longitudinal and outer circular. Urethral contraction is maintained by the circular fibers.[2,3] The combined effect of the urethral sphincters and the submucosal vascular plexus (within the bladder neck) keep the lumen closed and the urethral closure pressure higher than the bladder pressure.[2,4]

The anal canal is surrounded by the anal sphincter complex (Figure 2).[5,6] The internal anal sphincter (IAS) muscle is a continuation of the inner circular smooth muscle of the rectum. The external anal sphincter (EAS) is a striated voluntary muscle that extend to join the puborectalis superiorly. It can contract voluntarily in response to intraabdominal pressure and aids in retaining solids and fluids.[5,6] The IAS is maintained in a steady state of contraction by excitatory sympathetic fibers and inhibitory parasympathetic fibers.[7] The involuntary smooth muscles of the IAS along with the puborectalis sling and vascular plexus preserve basal continence for solids, liquids and flatus.[5,7,8] The IAS is responsible for at least 55% of the resting tone in the anal canal while EAS and the anal mucosa along with the vascular cushions contribute about 30% and 15% respectively.[5,8]

Figure 2 *The anal canal. Illustration by Deepa Mathew.*
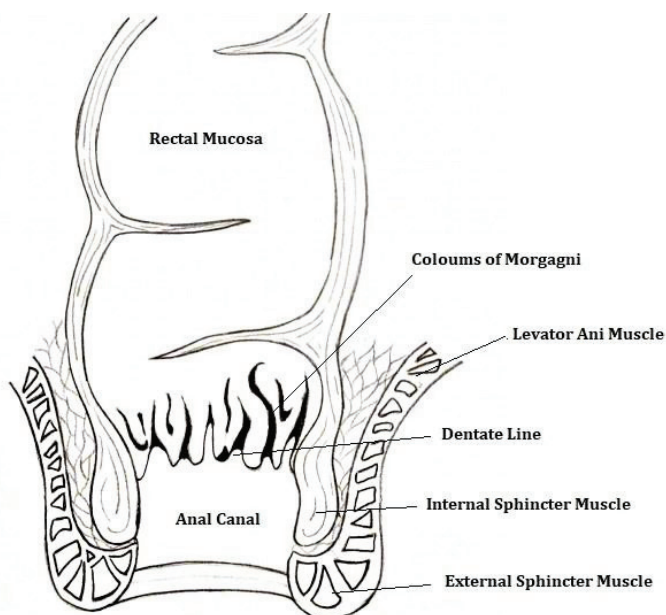
Connective tissue

The connective tissue surrounding the musculoskeletal structures consists of ligaments, fascia and fatty tissue. There are three levels of connective tissue support to the uterus and vagina as classified by DeLancey (Figure 3)[4].

Level 1(suspension): comprises of the cardinal and uterosacral ligaments supporting the uterus and the proximal vagina.

Level 2 (attachment): The broad endopelvine fascia anchors the cervix and vagina to the pubic bone and the ischial spine via the arcus tendinous fascia pelvis and contains the neurovascular supply to the pelvic organs and the supporting sacrouterine-cardinal ligament complex and the pubourethral ligaments.[2,3] The aponeurosis of the levator ani and the rectovaginal fascia support the mid vagina.

Level 3 (fusion): The urogenital diaphragm forms a dense triangular connective tissue membrane at the level of the hymen keeping the distal urethra and vagina in place, providing support anteriorly. The muscle layer is made up of the bulbocavernosus,

ischiocavernosus and the superficial tranverse perinei muscle inserting at the perineal body in the perineum.[3] The perineal body along with the external anal sphincter provides the posterior support at this level.

Figure 3 *A sagittal view of the levels of support according to DeLancey with a cross-section of each level. Illustration by Deepa Mathew.*
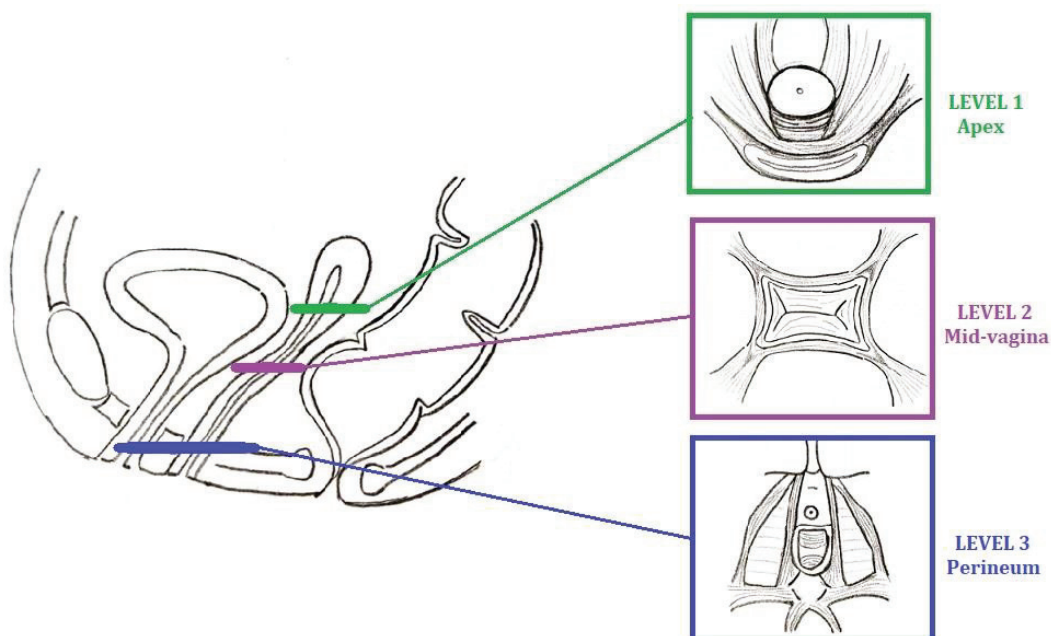
Innervation

The pudendal nerve arises from the sacral plexus (spinal nerves S2-4). It supplies sensation, motor function and carries sympathetic fibers to the external genitalia, urethra, anal canal and the voluntary EAS and external urethral sphincter.[7] The pudendal nerve is an accessory supplier to the LAM, as the levator ani nerve provides the main innervation (S3-4).[7] Pelvic splanchnic nerves arising from the inferior hypogastric plexus make up the parasympathetic innervation.[3]

2.2 The role of levator ani muscle in maintaining continence

The pelvic floor muscles are kept in a steady state of contraction by a combined activation of both brainstem and reflex pathways.[7] Voluntary micturition starts with a relaxation of the LAM and sphincters.[2] The supportive 'hammock' function of the LAM tenses the suburethral fascia, reducing bladder neck descent and compresses the urethra during sudden increases in intraabdominal pressure.[9] This maneuver called the 'Knack', is used to train coordination in preparation for possible increase in abdominal pressure during cough and physical activity.[10] Intact LAM contraction keeps the anorectal angle at 90 degrees, thus helping in maintaining anal continence.[6,8] Rectal distention prompts an IAS relaxation and further expulsion is allowed after puborectalis and EAS relaxation occurs.[8]

A normal continence mechanism depends on the synergistic action of an intact musculofascial support systems, sphincters, storage function and lifestyle habits.[1-3] Since the sling function of the LAM prevents leakage of urine and fecal matter, one would expect injury to be associated with incontinence.[11] However, the etiology of urinary and colorectal-anal symptoms including incontinence is complex and the impact of LAM injury is not fully understood.

2.3 Pelvic floor dysfunction

2.3.1 Prevalence and impact on quality of life

Pelvic floor dysfunction (PFD) is a wide term that includes prolapse, sensory and emptying irregularities of the urinary or distal gastrointestinal tract, pelvic pain and sexual dysfunction (Figure 4).[12] A third of women report at least one PFD symptom and 20% undergo surgery for pelvic organ prolapse (POP) or urinary incontinence (UI) by the age of 80.[13-16] Symptoms often overlap, as illustrated in Figure 4.[15,17] Muscle and nerve trauma sustained to the pelvic floor during childbirth lead to co-existence of different PFDs and the prevalence increases with age.[15,17-19]

Figure 4 *Illustration of the interrelated conditions for the umbrella term 'Pelvic floor dysfunction'. Image by S. Mathew.*
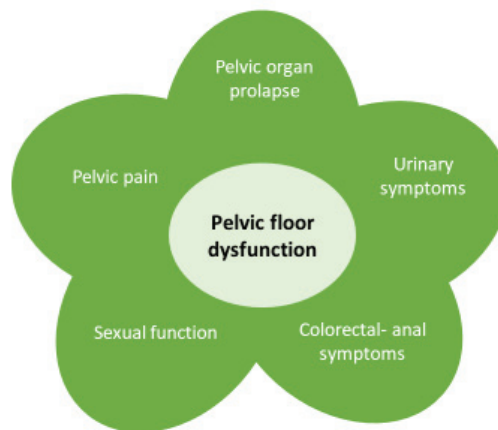
Urinary distress

Urinary distress involves incontinence, voiding difficulties, pain during micturition and urgency. The most common urinary complaint is UI and the prevalence varies from 17-69% depending on definitions and population studied.[14,15,20] UI is the involuntary loss of urine and is further divided into [12]:

- o Stress urinary incontinence (SUI) associated with physical exertion or sneezing/coughing.
- o Urge urinary incontinence (UUI), leakage associated with sudden compelling desire to void.
- o Mixed urinary incontinence, combination of the above two.
- o Chronic disorders including neurological diseases and injuries contribute to other types of urinary incontinence.

SUI is the most frequent bother affecting 14-43%.[16,20] UUI is reported in 14% and the prevalence of urge and mixed UI increases with age, with the latter becoming the most prevalent type of UI among women over 60 years of age.[20]

Colorectal-anal distress

This is an umbrella term for all symptoms related to the gastrointestinal tract including leakage of stool or flatus, emptying difficulties, pain during defecation and rectal prolapse. Anal incontinence (AI) is defined as a complaint of involuntary loss of flatus or feces.[21] Fecal incontinence (FI) is defined as a complaint of involuntary loss of feces, when feces is solid and/or when feces is liquid. Involuntary loss of flatus(gas) is termed flatal incontinence.[12] AI occurs in 6-19% depending on definitions in different studies.[15,21] As for other PFDs the real prevalence may be higher.[22,23]

Pelvic organ prolapse

POP is defined as the downward descent of the pelvic organs (bladder, uterus, lower gastrointestinal tract) causing an outwards bulging of the vaginal walls or uterus in the caudal direction.[24] The prevalence of POP is around 3-6%. However, incidental findings in as many as 50% women suggest that most are asymptomatic.[17] Symptoms include bulging, pressure, pain, bladder or bowel emptying/storage disturbances and incontinence. Type of prolapse is divided into anterior, posterior and middle compartment or a combination of compartments based on anatomical findings (Figure 5).[24,25]

Figure 5 *Different types of prolapse. Illustration by Deepa Mathew*

Normal

Posterior Compartment

Mid Compartment

Anterior Compartment
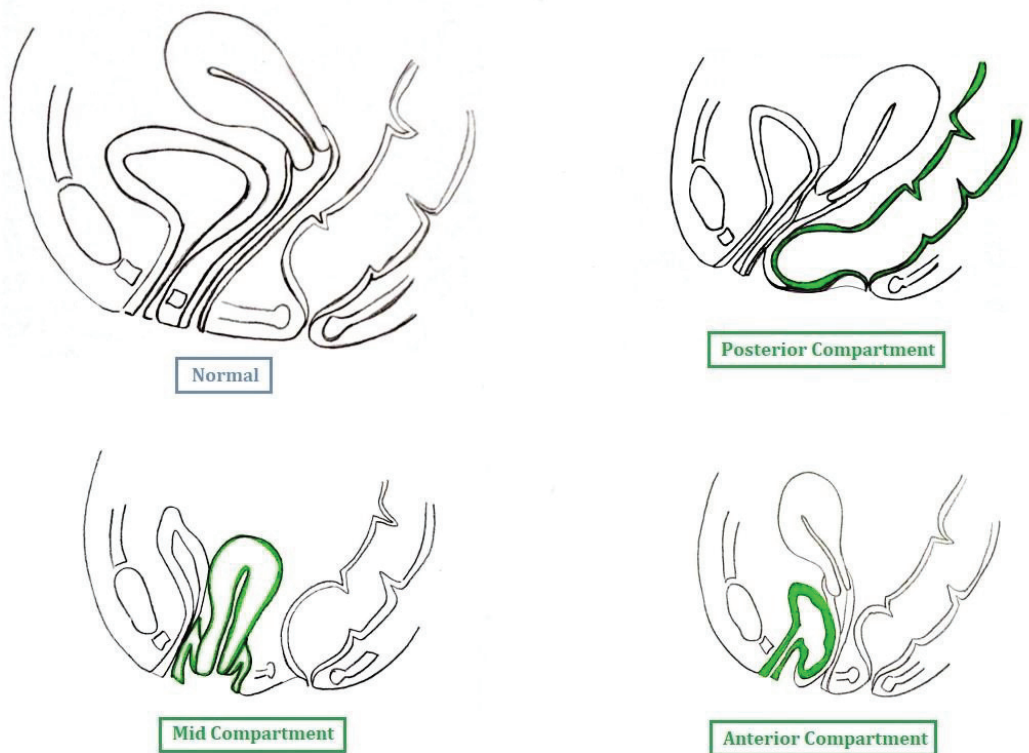
Pelvic pain

The prevalence of pelvic pain varies from 4-24% and may be underestimated.[26] Non-cyclic pain lasting more than 6 months is defined as chronic pelvic pain, and may be nociceptive, neuropathic or psychogenic.[27] Pelvic pain may also be the result of surgical treatment.[28]

Sexual dysfunction

Female sexual dysfunction is a heterogenous group of symptoms related to sexual function and arousal affecting up to 40% of women.[23] A majority of women with any PFD experience sexual dysfunction.[28] The real prevalence may be higher as many women do not seek advice for this complaint.[23]

Quality of life

PFDs have major consequences on quality of life (QoL) with impact on daily chores, sexual function and physical activity.[14,29,30] Pain and sexual dysfunction hampers physical well-being.[23] Women with AI or UI may worry about accidental soiling and are constantly concerned about toilet access.[28] This curbs travel, hobbies and outdoor activities. The different PFDs influence each other; incontinence may also lead to other PFDs like sexual dysfunction.[28] Psychological problems due to anxiety, pain or feeling of unattractiveness and body image issues demand increased health resources.[28] Increased personal expenses due to laundry and new clothes limits economic freedom in affected individuals. In addition, the use of health care and surgical interventions have major economic consequences for the society. Although younger and middle-aged women seem to constitute the bulk of women accessing medical help, this number is stipulated to increase in the coming decades.[22] Figure 6 shows the number of women seeking help according to age-groups.[22]

Figure 6 *Annual number of women (per 1000) seeking medical care due to pelvic floor dysfunction according to age in United States and predicted number in 2030. Adapted from Kirby AC et al. An update on the current and future demand for care of pelvic floor disorders in the United States. Am J Obstet Gynecol.2013. By S. Mathew*
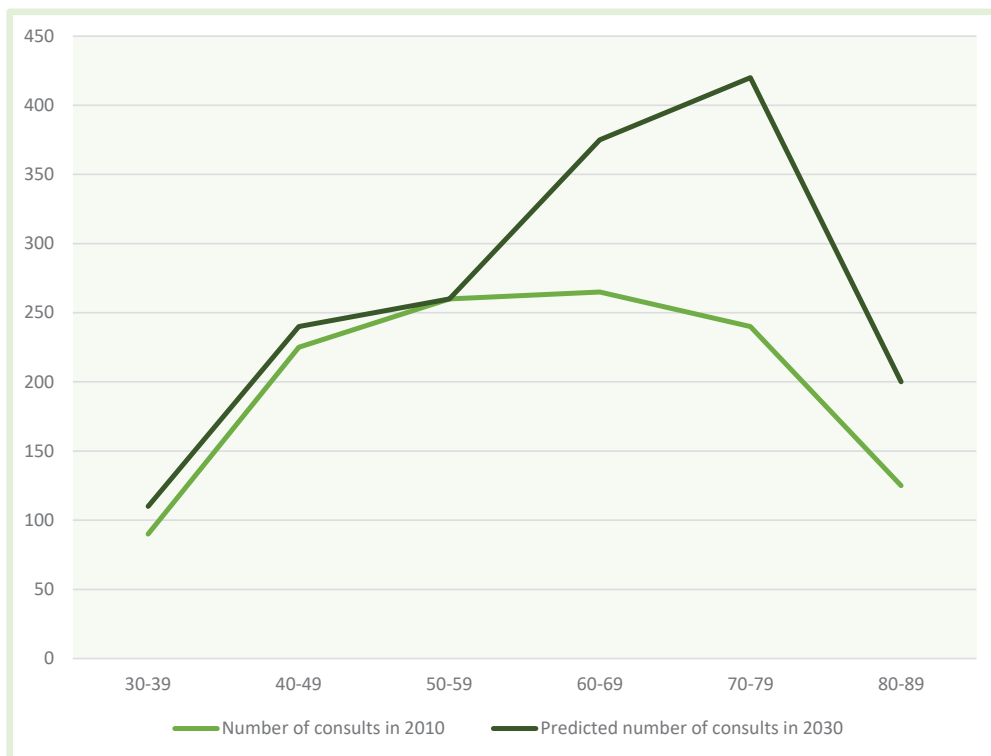
2.3.2 Risk factors for pelvic floor disorders

The etiology depends on an interaction between several factors that lead to a loss of support for pelvic organs and sphincter dysfunction. Certain risk factors are significant in different phases of life as summarized in Figure 7.[13,31,32]

A discussion of all the components of PFDs is beyond the scope of this thesis. For the purpose of this work, I will further address risk factors, diagnosis and management of POP, UI and AI.

Figure 7 *Risk factors summarized into five categories divided into three phases of life. Illustration by S. Mathew adapted from Bump and DeLancey.*
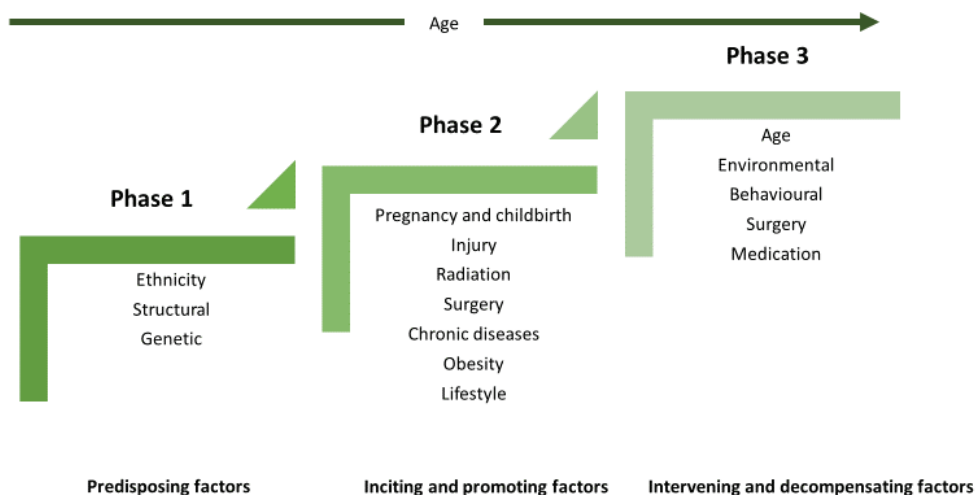
Pregnancy and parturition

Pregnancy induces hormonal and mechanical changes on the pelvic floor, but the main risk comes from the mode of delivery.[19] The LAM stretches to 1.5 - 3 times its size during delivery and striated muscles are prone to injury when forcibly stretched as in an operative vaginal delivery. [33] Birthweight, anal sphincter injury and increased duration of second stage of labor are also risk factors for LAM injury.[19,34] The mechanism of injury is either overstretching causing a permanent increase in hiatal area (microtrauma) or a uni- or bilateral rupture of the LAM from its insertion points (macrotrauma).[34] In vaginally parous women the prevalence of LAM trauma varies from 13-36% and almost one third have overdistension of the levator hiatus, detectable after delivery[35-38] Any injury to the musculofascial pelvic floor will lead to reduced support to the pelvic organs with subsequent risk for prolapse.[11,19,31] LAM injury is a risk factor for anterior and mid-compartment POP, but there is less conclusive evidence on the association between LAM injuries and posterior compartment POP, AI and UI.[11,39-41]

Obstetric anal sphincter injury (OASI) shares some common risk factors with LAM injury due to the similar causative mechanisms.[19,42] The risk for sphincter injury is highest for nullipara and prevalence of OASI varies from 4-25% depending upon the diagnostic method used.[43-45] Ultrasound diagnosed residual defects were present in 40 -85% after primary repair of OASI.[46] A study by Caudwell-Hall showed that only a third of nulliparous women really have a normal vaginal delivery without sustaining either LAM or sphincter injuries.[45] In women with OASI, concomitant LAM injury was found in almost a third. [42] Interestingly, subsequent pregnancies and deliveries do not seem to contribute much towards LAM or sphincter injury.[43,47,48] After primary repair of OASI, 43% develop AI in the immediate postpartum period. Although most symptoms resolve over time, 11% develop chronic symptoms and major defects may be predictive of persistent bother.[49]

Irreversible pudendal nerve damage due to almost 35% overstretching leads to loss of contractility and strength, adding to the decompensating factor for PFDs.[50] An EMG study showed partial denervation and terminal motor neuron latency in four of five vaginally parous women and a suboptimal recovery postpartum.[51]

Other risk factors

Age-related deterioration of striated muscle and neurological injury affect sphincter closure pressure and the LAM.[52] Recurrent urinary infections, incorrect bladder emptying habits, diet and water intake influence development of UI.[7] Obesity is associated with both increased prevalence and severity of all PFDs, especially incontinence and related QoL, with marked improvement after weight loss.[53,54] . Socioeconomic factors and smoking play a role in incontinence.[55,56] POP is common in women with chronic conditions where the intraabdominal pressure is constantly high.[14,56] Autoimmune bowel disease, chronic obstipation and diarrhea may prompt AI. [57] Ulcerative diseases of the colon affect continence both due to the mucous diarrhea associated with the autoimmune disease and surgical procedures for fistula that may influence sphincter function. POP surgery itself can lead to recurrence or failed postoperative results, and those with a higher preoperative stage of prolapse have the highest risk.[58]

2.4 Examination and diagnosis of pelvic floor anatomy, function and symptoms

2.4.1 Assessment of symptoms

A detailed history is paramount as it determines further investigation and treatment options. Patient reported symptoms using validated questionnaires are widely used in research settings and demonstrate good correlation with objective clinical findings.[59-61] Visual analogue scales (VAS) are frequently implemented in busy clinical settings for quick evaluation of many conditions. Patient reported VAS for quantification of PFDs is shown to be valid and repeatable in urogynecological populations.[62] Commonly used validated questionnaires for grading symptoms of PFDs include:

- The Pelvic Floor Distress Inventory (PFDI-20) and its subscales examine any bother related to POP, urinary and colorectal-anal tract, including leakage and pain. PFDI-20 score is a composite score (range 0-300) of its three subscales. Each subscale scores range from 0-100.
  - Pelvic Organ Prolapse Distress Inventory (POPDI -6)
  - Urinary Distress Inventory (UDI-6)
  - Colorectal-Anal Distress Inventory (CRADI-8)
- Pelvic Floor Impact Questionnaire (PFIQ-7) and its subscales assess the QoL related to POP, bowel or urinary symptoms. Each subscale poses 7 questions from daily life, psychological effects, social and physical activity to score QoL related to distress due to POP, urinary or gastrointestinal tract.
  - Pelvic Organ Prolapse Impact Questionnaire (POPIQ)
  - Urinary Impact Questionnaire (UIQ)
  - Colorectal-anal Impact Questionnaire (CRAIQ))

Higher scores equate to more bother or worse QoL. Both the PFDI-20 and PFIQ-7 with their subscales show ability to assess changes in PFD symptoms after treatment and are useful in evaluating clinically significant changes.[59]

The International Consultation of Incontinence Questionnaire on Vaginal Symptoms (ICIQ-VS) evaluates POP and sexual dysfunction while the ICIQ-UI and ICIQ-Bowel examines symptoms and QoL related to UI and bowel symptoms.[63-65]

Sandvik severity index is used to quantify UI.[61] In Norway, the validated Norwegian Female Incontinence Registry (NKIR) is widely used in clinics to report pre- and postoperative UI symptoms and QoL.[66] It also comprises of a section to record objective findings of the stress test, patient history and details of surgical procedures.

St. Marks, Wexner, American Medical Systems and Pescatori scores are short and reliable tools to grade AI bother.[60]

2.4.2 Prolapse quantification

The International Continence Society (ICS) recommends a standardization of the grade of pelvic organ prolapse using the Pelvic Organ Prolapse Quantification score (POP-Q).[24] The genital hiatus, perineal body and the distance (in cms) from the hymen to fixed points in the vaginal wall, cervix are measured under Valsalva. The total vaginal length is quantified at rest. Measuring points that are placed proximal to the hymen have negative values and those distal to the hymen have positive values (Figure 8).[24]

Based on the measurements POP is divided into the following stages:

Stage 0: No prolapse is seen. Points are above – 3 cm, with either points C and D between TVL and TVL-2cm

Stage 1: Any point is >1 cm proximal to the hymen

Stage 2: Any point is at or +/- 1 cm proximal or distal to the hymen

Stage 3: Any point protruding > 1 cm distal to the hymen

Stage 4: Complete eversion of the total length of the lower genital tract.

Figure 8 *Pelvic Organ Prolapse Quantification (POP-Q) System is recommended to grade POP in women. Six vaginal sites (Aa, Ba, Ap, Bp, C and D), genital hiatus (gh), perineal body (pb) and total vagina length (tvl) utilized for quantification with the 3x3 grid. From Bump RC et al. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. Am J Obstet Gynecol. 1996;175, with permission from Elsevier.*

anterior wall	anterior wall	cervix or cuff
Aa	Ba	C
genital hiatus	perineal body	total vaginal length
gh	pb	tvl
posterior wall	posterior wall	posterior fornix
Ap	Bp	D
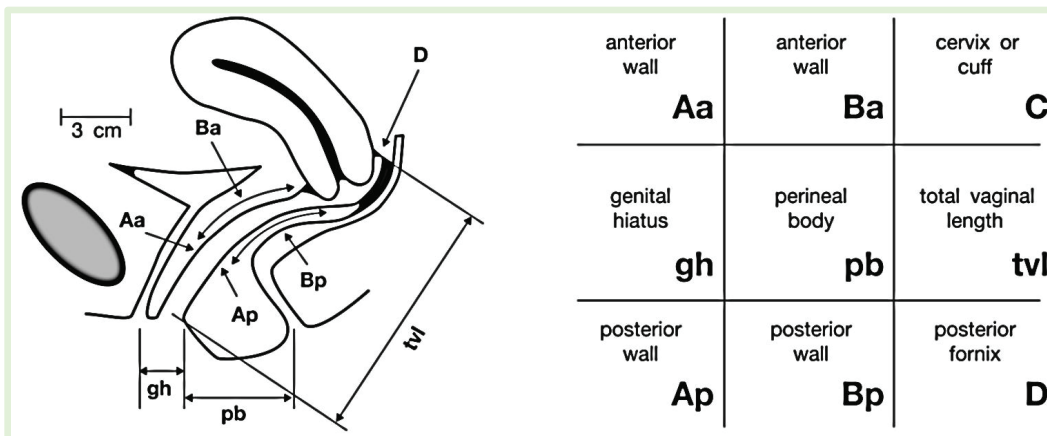
2.4.3 Muscle integrity and strength

Muscle integrity and strength is determined by several direct and indirect methods although there is no gold standard.

Palpation

Palpation is widely used during the gynecologic exam to assess resting tone, contractility, pain and muscle integrity. A digital exam is performed with 2 fingers inserted 3-4 cm into the vagina, at the level of the LAM. The resting tone and muscular pain is graded using a 6-point scale.[67] Any complete or partial muscle tears are then identified. Modified Oxford Scale (MOS), Brink scale and the PERFECT scheme are various assessment tools used for evaluation pelvic floor muscle function and strength.[68]

Perineometry

A vaginal manometer is a pressure sensitive intravaginal balloon inserted into the vagina at the level of the LAM. The highest squeeze pressure is measured in mmH_2O, as a direct measurement of LAM contraction and muscle stamina.[69]

Electromyography (EMG)

Electrical activity in the pelvic floor muscles is used as an indirect measure of contractility. A vaginal sensor is placed at the plane of the LAM and detects the electric potential generated by the muscle contraction.[70]

2.4.4 Urodynamic testing

Function of the lower urinary tract is evaluated by different invasive and non-invasive tests in line with recommendations from the ICS.[71] These may include a bother score, clinical examination, voiding diary, uroflowmetry, cystometry and measurement of residual urine.[72] Urodynamic testing delivers a systematic approach that reproduce the bother, providing better understanding of the specific problem and appropriate measures to be considered.[72]

2.4.5 Ultrasound diagnosis

Ultrasound analysis of pelvic floor anatomy is a non-invasive, well-tolerated technique that provides both objective measurements and dynamic interaction between the structures of the pelvic floor.[73,74]

Levator ani muscle

Ultrasound is a reliable and reproducible method for assessment of pelvic floor muscle anatomy and strength exhibiting moderate correlation to other techinques.[75-77] Additional advantages is that the dynamic visualization provides biofeedback when instructing women in correct pelvic floor muscle contraction and a quick overview of the pelvic organs.[78]

A curved array transducer covered with ultrasound gel is inserted into a glove. The probe is placed in the sagittal plane on the perineum or between the labia majores with the patient in the dorsal lithotomy position. Empty bowel and bladder is preferred for optimal imaging. A wide acquisition angle (over 70 degrees, preferably 85-90 degrees) enables full visualization required for analysis.[73,74]

Two dimensional (2D) images depict the pelvic floor anatomy in the mid-sagittal plane during rest, pelvic floor muscle contraction or Valsalva, showing any displacement of structures. Figure 9 shows a schematic figure of the ultrasound image rendered in the mid-sagittal plane. The 3D/4D imaging is used for the visualization of the pelvic floor in different anatomical planes, evaluating change in real-time. The recording of dynamic contraction or Valsalva maneuvers aid in evaluating functional anatomy using tomographic ultrasound imaging (TUI).[78,79] Good intra- and interrater correlation of the ultrasound measurements has been demonstrated.[75,77]

Figure 9 A: *schematic illustration of 2D transperinal ultrasound in mid-sagittal plane.* *B*: *2D transperineal ultrasound image. S=symphysis pubis, B=bladder, U=uterus, V=Vagina, R=rectum and PR=puborectalis muscle. Illustration by S Mathew.*
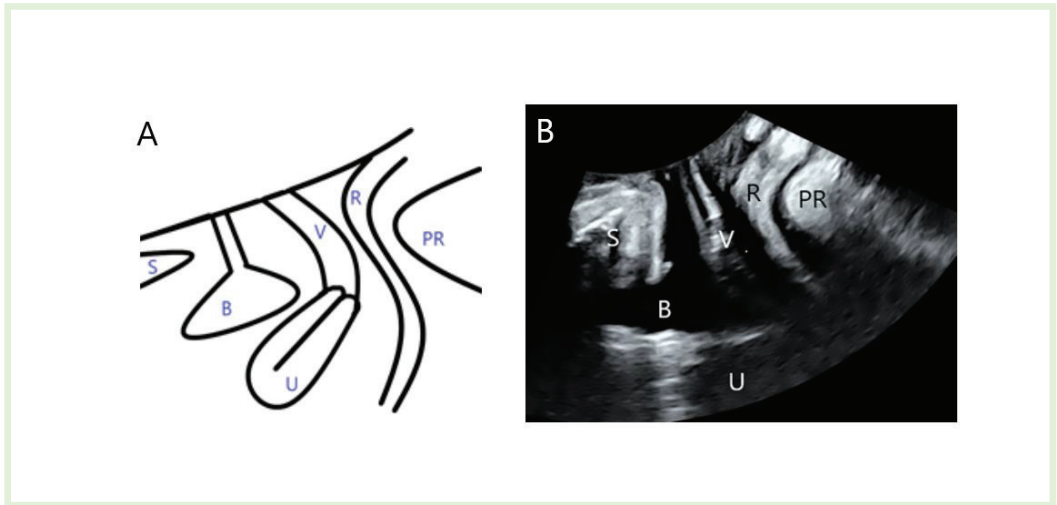
Levator muscle morphology is studied in the plane of minimal hiatal dimensions, the shortest distance between the posterior aspect of the symphysis pubis and the anterior portion of the puborectalis muscle.[79-81] Functional biometry is evaluated in different ways (Figure 10):

- o Muscle thickness and muscle area
- o 2D antero-posterior dimension at rest, contraction and Valsalva
- o 2D transverse diameter
- o 3D hiatal area at rest, contraction and Valsalva
- o Proportional change in 2D and 3D diameters and area

Contractility is usually measured as a proportional change as LAM measurements can differ in various ethnicities.[35,76]

Figure 10 *Biometry of levator ani muscle contraction at the plane of minimal hiatal dimensions. Anterio-posterior diameter at rest in 2D (**A**) and 3D(**B**) and 3D hiatal area at rest (**C**). Corresponding images at pelvic floor muscle contraction showing 2D (**D**)and 3D (**E**) anteroposterior diameter and 3D hiatal area (**F**). Images by S. Mathew.*
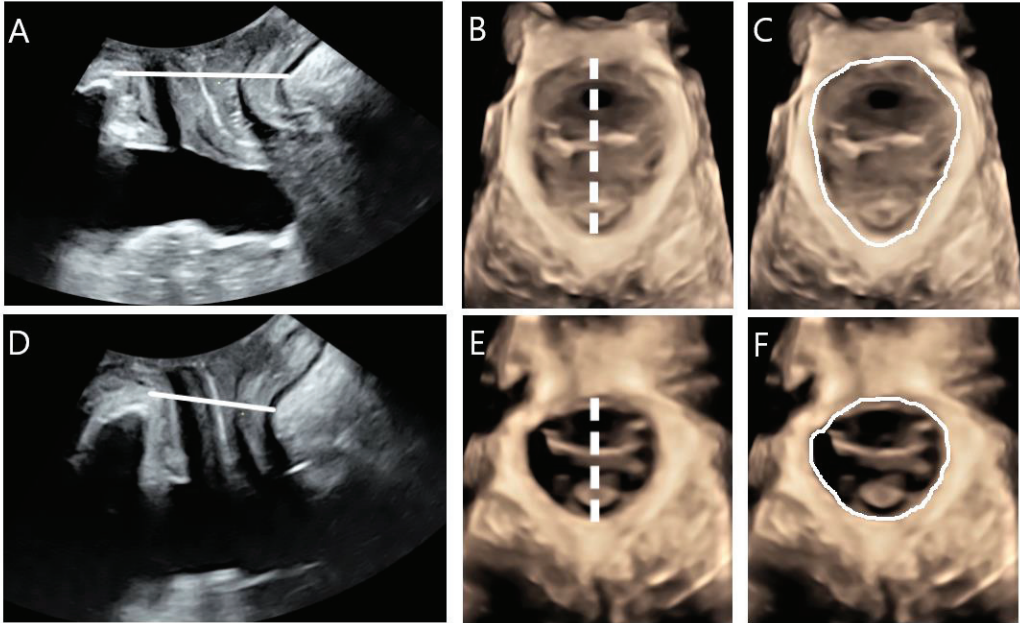
Volumes from pelvic floor muscle contraction are used for assessment of LAM integrity.[80,81] Two types of LAM injuries are defined:

o Microtrauma

Microtrauma is an expression for overstretching of the LAM causing a permanent increase in hiatal area. It is defined as more than 20% increase in the hiatal area during Valsalva compared to rest.[35]

o Macrotrauma

Macrotrauma is defined as a uni or bilateral injury to the LAM from its insertion points (Figure 11) and is normally seen as a disruption in the normal echogenicity of the muscle where it inserts into the pubic ramus arcus tendinae. Significant LAM injury is diagnosed if all three central slices; the slice in the plane of minimal hiatal dimensions and the slices 2.5 and 5.0 mm cranial to this, demonstrate abnormal muscle insertion.[81] When the distance between the LAM and the middle of the urethra (Levator Urethral Gap, LUG), exceeds 25mm, this is used as supporting evidence for LAM injury, although it needs further validation in different populations.[81]

Figure 11 Unilateral injury to the left levator ani muscle at the point of insertion on the pubic ramus (white triangle) on all central slices, plane of minimal hiatal dimension shown in **B** and the levels 2.5mm cranial (**A**) and caudal (**C**). Note the even echogenicity of the intact muscle on the right side. Adapted from Mathew et al; Levator ani muscle injury and risk for urinary and fecal incontinence in parous women from a normal population, a cross-sectional study. Neurourol Urodyn. 2019 with permission from Wiley.
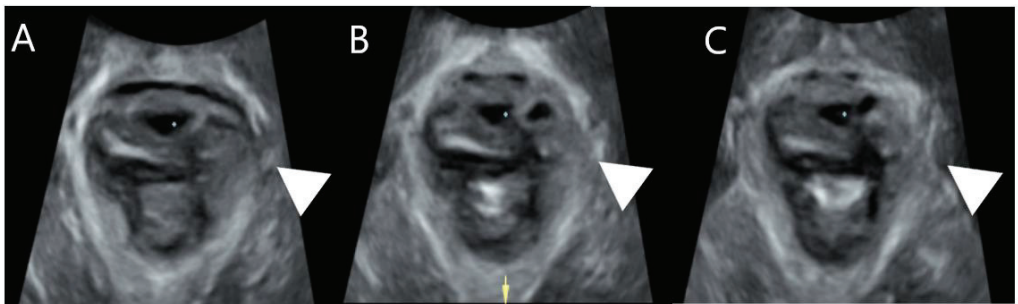
Anal sphincter

Different approaches have been described to assess the anal sphincter complex using ultrasound.

Endoanal

Endoanal ultrasound utilizes a cone-shaped radial probe providing visualization of the mucosa, submucosa, IAS, EAS and the intersphincteric space as concentric circles. With the patient in the lithotomy position, the probe is aligned and inserted into the rectum, the puborectalis muscles is used as an upper landmark for the anorectal junction.[82,83] The probe is withdrawn while capturing images at the upper, middle and lower levels.[84,85]

Defects involving half of the sphincter to less than whole sphincter thickness are defined as partial, and total defects are defined as involving the full thickness of the muscle. For quantification of anal sphincter defects different scoring systems have been developed. The Starck score evaluates the length, depth and size of the defect with no or minor defects scoring 0-8 and maximal defects scoring 16.[83] Only complete defects of IAS are recorded as defects on the Norderval score, which has a continuous grading scale from 0-7.[86] While Starck and Norderval applies a grading system to defects, Sultan et al classifies defects as significant or not based on sonographic defects of ≥30 degrees at one or more levels (deep, superficial and subcutaneous) of the anal sphincter complex.[87] Endoanal ultrasound correlates with clinical and histological findings and is considered the gold standard.[84,85,88]

Transperineal and Introital

The advantage of using an exoanal probe is that there is no distortion of the anal canal and least invasive.[89]. The patient is positioned in a lithotomy position. A curved array probe is inserted into a sufficiently gel coated glove, placed on the perineum and angled slightly caudally towards the anus. The anal sphincter is clearly visualized as shown in Figure 12 and volumes are recorded at slight pelvic floor muscle contraction to allow for best evaluation of potential defects in the sphincter complex.[90] For introital ultrasound the lubricated gloved transvaginal probe is placed in the introitus. [91] The correlation between examiners is good when using optimal ultrasound equipment and after the

initial learning curve has been completed.[92,93] Additionally the correlation to symptoms is also demonstrated to be good. [94]

Figure 12 A: Tomographic ultrasound image through the anal sphincter. **B**: schematic illustration of the components of the anal canal; hyperechogenic EAS=external anal sphincter, hypoechogenic IAS=internal anal sphincter, star like shape of the anal mucosa (AM). Illustration by S Mathew.
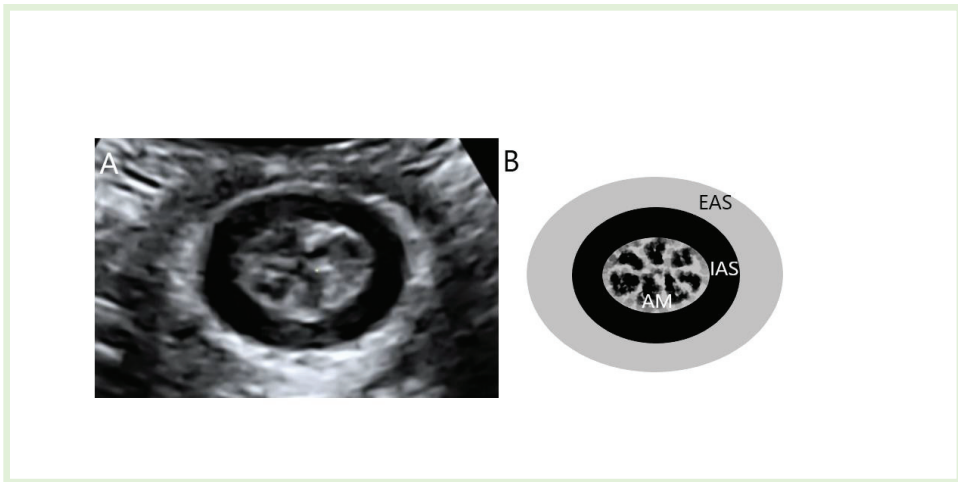
The method described by Dietz and Guzman Rojas is used to quantify anal sphincter defects with transperineal ultrasound.[90,95] TUI is used to review the EAS and IAS separately by adjusting the interslice interval to accommodate the entire length of the muscle in study. A defect of ≥30 degrees in at least four of six slices translates to a defect of more than two-thirds of the length of the muscle and is considered to be a significant defect (Figure 13).[90,94,96]

Figure 13 *Tomographic ultrasound image of the external and internal anal sphincter showing intact (**A**) and defect (**B**) external anal sphincter. Intact (**C**) and defect (**D**) internal anal sphincter. Imaging by S. Mathew.*
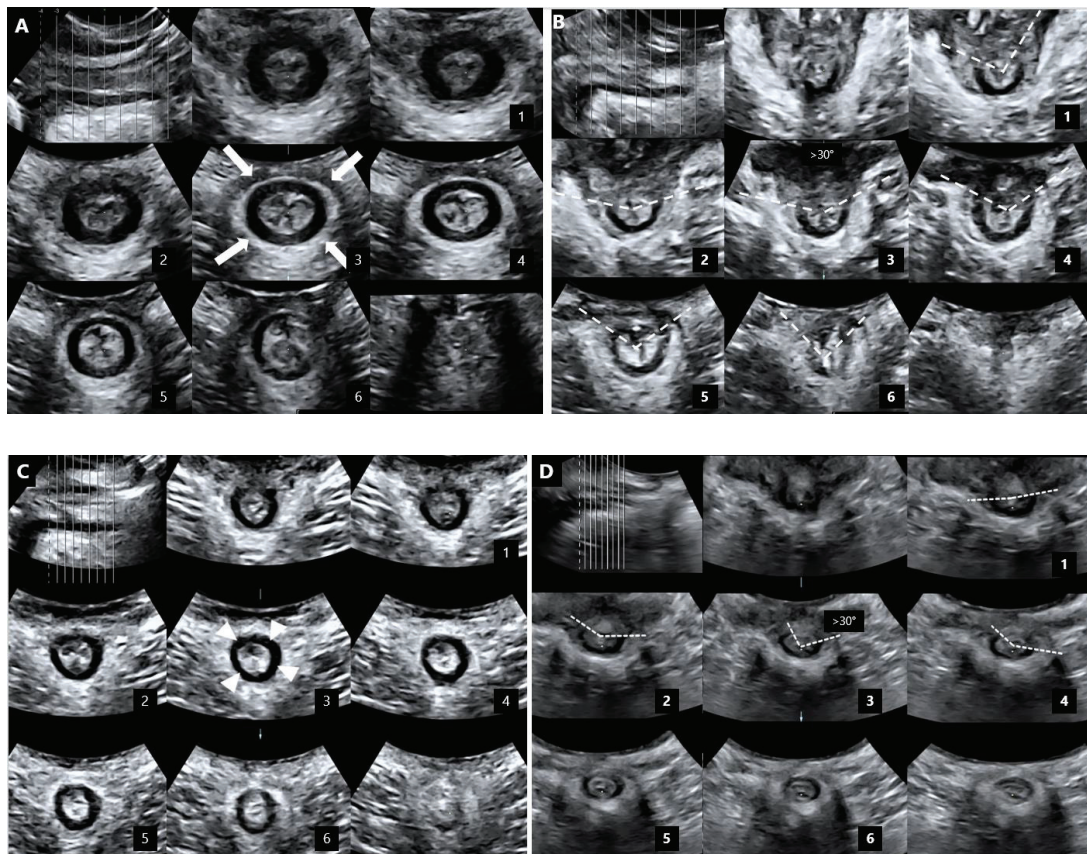
Bladder neck anatomy

Ultrasound has replaced cystourethrography to identify changes in the bladder anatomy as this avoids radiation and is readily available in urogynecological clinics[97] Although association between bladder neck descent, funneling and urethral rotation to UI is weak, the findings serve as a supplement in differentiating between types of UI.[98,99] Ultrasound evaluation of the bladder neck and proximal urethra have shown good correlation to symptoms of UI.[100] Ultrasound can also be used in evaluation of correct placement of transvaginal tapes, which are readily visualized (Figure 14). Bladder neck anatomy and urethral rotation is assessed in the midsagittal plane.

Figure 14 *2D sagittal image showing a transvaginal tape (white arrow) placed suburethrally and a rendered transverse section clearly showing the sling like placement (white arrows). Imaging by S. Mathew*
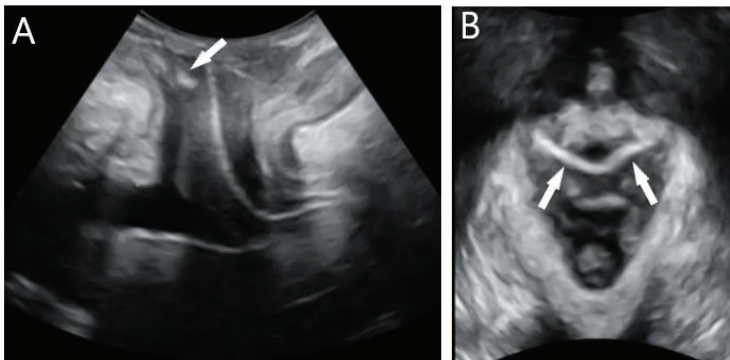
Bladder neck descent (BND)

The distance from the bladder neck to a horizontal line drawn from the posterior margin of the symphysis pubis is measured at rest and maximum Valsalva. BND is the difference between these two measures (Figure 15 A and B). BND ≥25mm has been suggested to be an indicator for abnormal bladder mobility predisposing to SUI.[9,101]

Funneling

A dilatation of the proximal urethra at bladder neck during maximum Valsalva is indicative of funneling (Figure 15 C).[102] Funneling suggests poor intrinsic sphincter activity and an objective sign of SUI.[99,103]

Figure 15 *A horizontal solid line is drawn through the inferior-posterior level of the symphysis pubis and the dashed vertical lines show the distance to the bladder neck. Bladder neck descent is measured as the difference between (**A**) rest and (**B**) Valsalva. (**C**) Urethral funneling (asterisk) is defined as a dilatation of the proximal urethra seen at Valsalva. Image by S. Mathew*

Urethral rotation and the retrovesical angle

The retrovesical angle is the angle between the axis of the urethra and a horizontal line drawn through the posterior aspect of the bladder neck. The difference in the angle at rest and Valsalva gives the urethral rotation[101,102] The urethral angle may indicate loss of bladder support and is low during increased intraabdominal pressure in women with SUI.[104] Retrovesical angle is measured at both rest and Valsalva as the angle between the proximal urethra and the posterior bladder wall/trigone.[101]

Pelvic organ prolapse

The 2D image acquired during pelvic floor muscle contraction or Valsalva gives additional information regarding the displacement of the pelvic organs, helping to identify the pelvic organs behind the bulge seen during the vaginal examination (Figure 16). Ultrasound aids in differentiating between recto- and enterocele and POP from urethral diverticula, as well as the diagnosis of other conditions such as rectal intussusception and urethrocele.

Figure 16 A 2D sagittal image showing a downward displacement of the bladder (cystocele). The white arrow points to the posterior aspect of the bladder that protrudes into the anterior vaginal wall at Valsalva.

2.4.6 Magnetic Resonance Imaging (MRI)

MRI is also a non-invasive, albeit more costly way to obtain detailed imaging of the soft tissue of the pelvic floor. Studies have shown good inter and intra-observer reproducibility of LAM parameters and moderate to good correlation between MRI and other methods used for pelvic floor anatomy evaluation as discussed above.[105]

2.5 Management of Pelvic Floor Dysfunction

Exercise during pregnancy is effective against postpartum incontinence.[106] Exercise, diet and water intake are favorable to proper bladder and bowel function in the long run. Adjusting body position at defecation may help in reducing straining. [7,8] Correct tools for handling heavy lifting, smoking cessation and optimal treatment for those with chronic diseases are preventive measures that need special mention.[56]

2.5.1 Conservative management

Treatment of PFD and POP is dictated by grade of bother. Symptoms may also not be site-specific but reflect the complex displacement of multiple compartments.[107] Mild PFDs may be kept in check by increased awareness and lifestyle changes (weight control, regular physical activity, dietary changes or change in fluid intake and toilet habits).[54,108] Bladder training, biofeedback strategies using EMG, nerve stimulation have also been proposed in the treatment of UI and AI.[7,108,109] A combination of behavioral therapy and medical treatment may prove beneficial.[110]

Pessaries

Vaginal pessaries provide improvement in POP and leakage in more than 70% and are suitable for women with contraindications to surgical treatment.[25,111] Most pessaries are ring like and equally effective in reducing bulge or voiding bother.[25] Several types of pessaries are available. Use and preference depend on symptoms, anatomical findings and availability. Intravaginal continence guards and anal plugs may be used in incontinence treatment.[112]

Pelvic floor muscle training

In 1948 Kegel described progressive resistance muscle exercises to improve perineal muscle strength and continence postpartum.[113] A 30% increase in strength was observed in healthy striated muscle in women older than 75 years after 8-12 weeks of progressive resistance training.[114,115] There are different exercise regimens used for POP and incontinence based on a model by Dumoulin et al where 8-12 contractions in 2-3 sets 4-5 times a week is proposed.[116] Increased pelvic floor muscle strength through increased contraction and changes to the bladder neck is demonstrated after intensive muscle exercise.[117] Pelvic floor muscle contraction in preparation for increased

intraabdominal pressure, termed the 'Knack' helps improve bother in women with SUI.[10] Physiotherapist supervised pelvic floor muscle training (PFMT) is considered first-line therapy for mild POP and urinary incontinence improving symptoms and QoL.[111,118-123] Improved LAM strength reinforces the hammock function, improving SUI, but exercise does not seem to improve the maximum urethral closure pressure.[9,124] PFMT coupled with biofeedback strategies including EMG has not shown additional benefits compared to PFMT alone.[125] The role of exercise in AI is not clear, but most studies have been conducted in pregnant or postpartum women.[126] Exercise seems effective in prevention of AI postpartum.[106,127]

Adherence is key to maintaining changes in strength and anatomy.[118] Injured muscle is also able to increase in strength through exercise but a complete denervation may pose challenges to effective muscle rehabilitation.[128]A weaker muscle may be more difficult to train. Age, lack of knowledge regarding the pelvic floor and contraction of incorrect muscle groups may limit attaining the full potential of muscle exercise.[129]

Pelvic floor muscle training as adjunct to surgery

PFMT induced strengthening of the pelvic floor reduces incontinence and is always attempted prior to invasive treatments.[117] Women with recurrent POP or postoperative incontinence are often counselled to perform PFMT. Although a review showed an overall improvement in POP related symptoms, we cannot conclude on effectiveness of PFMT as an adjunct to surgery in women with POP or to prevent recurrence.[121,130,131] For symptoms related to urinary or anal distress in this group, peri- or postoperative PFMT does not show clear benefits.[132-135] In women with advanced stages of POP there seems to be a slight increase in pelvic floor muscle strength assessed by palpation, but this effect dissipates after POP surgery. [130] We do not have enough evidence for preoperative PFMT or the long-term benefit of exercise.

3 Keys to pelvic floor muscle strength

<u>Strength</u> through intensive pelvic floor muscle exercise three times daily with 8-12 maximal contractions holding at least 6-8 seconds each from time of inclusion until the day of surgery

Fast repeated pelvic floor contractions to improve **<u>stamina</u>**

Better **<u>coordination</u>** through contraction of pelvic floor while sneezing, coughing, lifting and any movement that increase intra-abdominal pressure

Medical treatment

Locally administered estrogen supplements help in alleviating mild UI and are used as an adjunct postoperatively, although estrogen administration probably does not increase muscle contractility.[136,137] Anticholinergics prevents detrusor contraction by blocking muscarinic receptors in the smooth muscle in women suffering from overactive bladder or UUI. However, use is associated with side effects like dry mouth and constipation.[138] Beta 3 adrenoreceptor agonist report equal efficiency and stimulates relaxation of smooth muscle in the bladder.[139] They demonstrate better tolerance but are contraindicated in patients with hypertension. Constipating agents, motility reducing agents and fiber are often used to improve stool consistency and bulk.[7]

2.5.2 Surgical management

A wide variety of surgical procedures are available for the treatment of POP and incontinence. Selecting the preferred procedure depends on the patients age, general health and future fertility as well as surgeon's preference and experience.[140] The foremost aim of surgery is symptomatic improvement and restoration of normal anatomy.

Pelvic Organ Prolapse

Native tissue POP repairs are performed for repair of anterior or posterior compartment prolapse.[111] Vaginal hysterectomy, cervical amputation and duplication of the cardinal ligaments, sacrocolpopexy or vaginal apical suspension are some of the procedures used for a mid-compartment POP repair.[141,142] The main complications after POP surgery is bleeding, infection, constipation, pain and recurrence of POP.[141,142]

Recurrence of POP

Vaginal POP repair surgery carries 30-40% risk of failure[58,143] LAM injury, hiatal area and a higher peroperative POP stage predispose for recurrence of POP.[58] Conservative methods are primarily used but the need for recurrent surgery varies from 6-58% depending upon symptoms and patient co-morbidities.[58] Synthetic mesh surgery has been performed after failed conventional surgery. However, complications such as

chronic infections, fistula, pain, in addition to the 2011 FDA warning have reduced the use of vaginal mesh surgery to a highly selected group.[144]

Urinary Incontinence

Treatment of SUI uses both conservative and surgical options to reinforce bladder neck support like bulking agents, Burch retropubic urethropexy and mid-urethral slings.[111,140,145] Mid-urethral slings have been the gold standard if conservative treatment has been inadequate.[111]

For hyperactive bladder and UUI, posterior tibial nerve stimulation and sacral nerve modulation displays promising results.[146] Cystoscopy guided intramuscular injection of botulinum toxin is another option to treat symptoms related to urge and detrusor hyperactivity.

Anal Incontinence

Minimally invasive approach include injection of bulking agents, electrical stimulation and sacral nerve modulation.[109,147] Primarily end-to-end or overlapping sphincter repair is performed postnatally when an OASI is confirmed.[148] Secondary operative techniques may include levatorplasty, sphincter plication, postanal repair, or a combination of procedures.[148]

3.0 KNOWLEDGE GAP AND RATIONALE FOR THESIS

3.1. The association between levator ani muscle trauma and incontinence

LAM injury during vaginal delivery leading to loss of structural support for pelvic organs predisposes to POP and UI.[9,11,101,149]Although OASI remains the most important risk factor for FI, LAM injury interferes with the continence mechanism conveyed through the sling function of the puborectalis.[7,8] There is a lack of studies regarding the long-term effect of LAM injury on UI and FI.

Urethral hypermobility, manifesting on ultrasound as BND and urethral funneling, seems to be an expression for reduced bladder neck support possibly brought by LAM injury.[97,101] An association between these ultrasound findings and UI needs further investigation.

3.2 Sphincter defects and anal incontinence in a urogynecological population

The rate of OASI and AI in women with POP could be higher than the general population due to common risk factors.[18,19,42,94] Ultrasound can diagnose injuries undetected at the time of delivery, thus rendering higher estimates of the prevalence.[90,96] However, the prevalence of anal sphincter defects and the association with AI among women with advanced POP have not been properly studied.[94]

3.3 The scope of pelvic floor muscle training as an adjunct to surgery in women with advanced pelvic organ prolapse

Intensive PFMT increases strength and coordination of the pelvic floor muscle and improves symptoms of mild POP and UI.[106,118,119,123] Previous studies on the effect of PFMT on incontinence symptoms in women with POP contain predominantly postoperative exercise. [132-135,150] There is a need for further studies on the effect of preoperative PFMT on urinary and colorectal-anal symptoms on women undergoing POP surgery.

4.0 AIMS AND RESEARCH QUESTIONS

Overall aim

Better understanding of the role of pelvic floor muscles in the etiology of urinary and colorectal-anal distress both in the normal population and women undergoing POP surgery.

4.1 Paper 1

Investigate the impact of levator ani muscle injuries on urinary and fecal incontinence among women from the normal population many years after childbirth.

4.2 Paper 2

To examine the prevalence of anal sphincter defects in women with severe pelvic organ prolapse and to study a possible association between sphincter defects and anal incontinence in this population.

4.3 Paper 3

To explore the effect of PFMT as an adjunct to POP surgery to see if preoperative PFMT render improvement of symptoms related to urinary and colorectal-anal tract in women scheduled for POP surgery.

5.0 MATERIALS AND METHODS

5.1 Study design

PAPER 1	PAPER 2	PAPER 3
Cross-sectional study in a general population of parous women	Cross-sectional study in women with advanced POP, scheduled for POP surgery	A randomized controlled trial in women scheduled for POP surgery consisting of an intervention and control group

5.2. Participants and recruitment

Paper 1: UROPRO

The data source for Paper 1 was from the UROPRO study designed to assess the association between mode of delivery and pelvic floor trauma 15-24 years after delivery in parous women from a general population.[11,19,151] The study was approved by the Regional Ethics Committee (2012/666 REK-Midt) and registered in clinicaltrials.gov with ID NCT01766193. Women who delivered their first child at Trondheim University Hospital between 1st January 1990 and 31st December 1997 were identified from the Hospital Patient Administrative System. They were invited to participate and signed an informed consent form (Appendix 1). The study participants were examined at Trondheim University Hospital between 2013-2014. A questionnaire on pelvic floor dysfunction (Appendix 1) was mailed to all women and questionnaire-responders were invited for a clinical exam. The participants may have had cesarean delivery after normal or operative vaginal delivery, but no vaginal delivery after cesarean, and no operative vaginal delivery after normal delivery.[151] Women with stillbirths, breech delivery, infant birthweight below 2000g or not delivering at Trondheim University Hospital at index birth were excluded.

Paper 2 and 3: CONTRAPOP

These papers are based on data from the CONTRAPOP study conducted at Trondheim University Hospital, Norway. Participant recruitment was conducted in the period between 1st January 2017 to 29th June 2018 and all data collection ended in June 2019. The Regional Committee for Medical and Health Research Ethics (REK 2015/1751/midt) approved the study, which was registered in clinicaltrials.gov as NCT 03064750. All women ≥ 18 years, fluent in Norwegian or English language with POP stage ≥ 2 scheduled for POP surgery were recruited from the urogynecology clinic when they were referred to surgery. Women who declined participation, needed immediate surgery or had cognitive impairments were excluded. Written informed consent was obtained from all participants (Appendix 2). They completed questionnaires and were examined at baseline (inclusion), on the day of surgery (approximately 3 months later) and at a follow-up 6 months postoperatively (Appendix 3).

5.3 Randomization (Paper 3)

Using a web-based randomization tool (WebRAND) all women eligible for the study were randomized to intervention or control with an allocation ratio of 1:1. The participants were stratified using POP stage over or under 3 and age over or under 60 years. Participants were examined and patient-reported outcomes collected at 3 occasions:

1. Inclusion (baseline)
2. Day of surgery (approximately three months later)
3. Six months postoperatively.

Waiting time to surgery (approximately three months) was not influenced by group allocation.

Intervention

The intervention group performed daily PFMT from inclusion to the day of surgery, preferably 12 weeks. They were instructed in proper pelvic floor muscle contraction during the baseline ultrasound examination and provided written information (Appendix 4). Lifestyle advice regarding diet and proper emptying of bladder and bowel, as well as instructions in contraction of the pelvic floor muscles when sneezing, coughing or laughing was also given (Appendix 4). [118,152] Women had individual consultations with a dedicated pelvic floor physiotherapist (two and six weeks after inclusion) and a vaginal examination was performed to ensure proper contraction and adherence. Voluntary weekly group training sessions were offered. The women received a training dairy (Appendix 5) to register daily exercises. The training consisted of intensive pelvic floor muscle exercise with 8-12 maximal contractions holding at least 6-8 seconds three times daily from time of inclusion until the day of surgery.[115,153] The training dairy was collected at the day of surgery and those who failed to present a training diary, were interviewed on the day of surgery or later by telephone or follow-up consultation (Appendix 5) . A ≥70% completion of daily exercises was defined as adherence to protocol.[130,154] This cut-off was judged practically implementable in daily life.

Figure 17 Simple illustration of the study pathway for the intervention group. By S. Mathew.

The control group received no intervention in the waiting time for surgery. All women, regardless of group allocation, received information regarding pelvic floor anatomy and visualisation of correct pelvic floor muscle contraction during the ultrasound examination.

All postmenopausal women regardless of randomization status received local estrogen therapy unless contraindicated.

5.4 Data sources
Data sources for all papers are summarized in Table 1.

5.4.1 Background variables

For Paper 1(UROPRO) the information about infant birth weight, parity and perineal tears was obtained from the Norwegian Medical Birth Registry. Study participants answered a postal questionnaire (Appendix 1) regarding height, weight and any previous incontinence surgery. Age, parity, delivery mode, height and weight were registered at the inclusion interview for the CONTRAPOP study (Papers 2-3), see Appendix 3.

Table 1 A summary of data sources for all papers

DATA SOURCES	PAPER 1	PAPER 2	PAPER 3
Study population	UROPRO	CONTRAPOP	CONTRAPOP
Background data	Electronic patient journal Norwegian Medical Birth Registry Postal questionnaire	Electronic patient journal Questionnaire registered at inclusion	Electronic patient journal Questionnaire registered at inclusion
Patient reported outcome/Symptoms	Pelvic floor distress inventory (PFDI-20) and subscales: • Urinary distress inventory (UDI-6) • Colorectal-anal inventory (CRADI-8)	Visual analog scale (VAS)	Training diary PFDI-20 and subscales: • UDI-6 • CRADI-8 Pelvic floor impact questionnaire (PFIQ-7) and subscales: • Urinary impact questionnaire (UIQ) • Colorectal-anal impact questionnaire (CRAIQ)
Clinical examination	Pelvic floor anatomy • POP-Q • Transperineal ultrasound of levator ani muscle, bladder neck anatomy and anal sphincter	Pelvic floor anatomy • POP-Q • Transperineal ultrasound of anal sphincter muscle and levator ani muscle	Pelvic floor anatomy • POP-Q

5.4.2 Symptom assessment

For quantification of symptoms and QoL in Paper 1 and 3, validated patient-reported questionnaires were used. Participants completed the Norwegian version of the PFDI-20 and PFIQ-7 (Appendix 3).[59,155] Participants were asked to consider their symptoms over the past three months when answering at each examination point.

In Paper 1 the proportion of women with urge UI, stress UI, leakage of loose or formed stool were registered when answering 'yes' to the following questions of the UDI-6 and CRADI-8: 'Do you usually experience urine leakage associated with a feeling of urgency, i.e., a strong sensation of needing to go to the bathroom?', 'Do you usually experience urine leakage related to coughing, sneezing, or laughing?', 'Do you usually loose stool beyond your control if your stool is well-formed?', 'Do you usually loose stool beyond your control if your stool is loose?'.

For symptom assessment related to anal incontinence in paper 2 women were presented with a yes/no question regarding frequent involuntary leakage of stool or flatus. If yes, the women marked bother on a VAS from 0-100, where 100 was the most bothersome (Appendix 3).

The subscale scores (UDI-6, CRADI-8, UIQ and CRAIQ) were used for Paper 3.

5.4.3 Clinical examination

All study participants met with an empty bladder and bowel. Gynecological examination was performed with the woman in the supine position with hips and knees semi-flexed and abducted. Assessment of POP, pelvic floor muscle strength and integrity, and transperineal ultrasound of the anal sphincter and levator ani muscle were performed similarly in both UROPRO and CONTRAPOP populations. One examiner (IV) performed all assessments for Paper 1, whereas three examiners (SM, MØN, IV) contributed to Papers 2-3.

Anatomical prolapse in all compartments was assessed at maximum Valsalva and the distance (in cm) from fixed points in the vagina to the hymen was measured in increments of 0.5cm. Prolapse stage (0-4) and type were quantified according POP-Q (Figure 8).[24]

Assessment of pelvic floor muscle function was performed using digital palpation, vaginal manometry (Camtech, Norway and Peritron with PFX sensor, Cardio Design, Australia), surface electromyography (Periform, Neen Healthcare, UK) and transperineal ultrasound. Results on anatomical prolapse, pelvic floor muscle strength, anatomy and contraction (digital assessment, manometry and electromyography) have been published previously and are not included in the work presented here.[130]

5.4.4 Transperineal ultrasound

The 3D/4D ultrasound volumes of the pelvic floor and anal sphincter muscles were acquired with a GE Voluson S6, S8 or E10 device (GE Medical Systems, Zipf, Austria) using the RAB 4-8rs abdominal 3D probe and acquisition angle of 85°. We confirmed that the bladder and bowel were empty before the exam. LAM was evaluated using 3D probe placed transperineally in the sagittal plane and three volumes were acquired at maximum pelvic floor contraction and Valsalva.[81] For assessment of the anal sphincter complex, the probe was held horizontally and angled slightly caudally towards the anus. Three volumes were acquired, one at rest and two at slight pelvic floor muscle contraction, where the anal sphincter was clearly visualized.[94]

Offline analysis of the ultrasound volumes was performed 6-24 months after the ultrasound scan on a computer using the 4Dview Version 14 Ext.0 (GE Healthcare, Austria) software. The examiners (SM, MØN, IV and RGR) were blinded to all clinical data.

Levator ani muscle

The image exhibiting the best muscle contraction was chosen. TUI was used to identify significant LAM injury at pelvic floor muscle contraction. The plane of minimal hiatal dimensions was identified as a midsagittal line running from the symphysis pubis to the anterior margin of the most central part of the puborectalis muscle. A significant LAM injury (macrotrauma) was diagnosed if all three central slices; the slice in the plane of minimal hiatal dimensions and the slices 2.5 and 5.0 mm cranial to this, showed abnormal muscle insertion on one or both sides (Figure 11).[81] Injury was diagnosed as unilateral or bilateral. Offline analysis for assessment of LAM injury was carried out by single examiners: Paper 1 (IV) and Paper 3 (MØN).

Bladder anatomy

Bladder neck descent (BND) was assessed in the midsagittal view, see Figure 15. A horizontal line was drawn from the posterior-inferior margin of the pubic symphysis, and the distance from the bladder neck to this line was calculated at rest and Valsalva. BND was calculated as the difference in distance between rest and at maximum Valsalva. A cut-off of BND ≥ 25 mm was used as previous studies indicate an association between this value and stress UI.[101] A dilatation of the proximal urethra at the urethrovesical junction at Valsalva was identified as urethral funneling (see Figure 15 C).[102] Offline analysis of bladder neck anatomy was performed by a single examiner (RGR).

Anal sphincters

All anal sphincter volumes were evaluated offline by two examiners (SM, RGR). Discordant volumes were re-analyzed by a third examiner (MØN) to increase the validity. TUI was used for assessment of IAS and EAS defects. Interslice space was regulated depending on EAS and IAS length to obtain eight slices. Six slices were used for the evaluation of the entire length of the EAS: from one slice cranial to EAS and the last slice caudal to the IAS. The IAS was also depicted on six slices by placing the first slice cranial to the IAS and the last slice at the level of the subcutaneous portion of the EAS.[90,94] A defect of the EAS or IAS of ≥ 30° in at least four of the six slices on TUI was considered a significant defect, see Figure 13.[90,94,96] The proportion of women with any significant defect (either EAS or IAS or both) was noted.

5.5 Sample size calculation

The UROPRO study was powered to study the association between mode of delivery and LAM injury.[19] At a power of 80% and 5% significance level, a sample of 152 women in each delivery group (caesarean, normal vaginal, vacuum and forceps delivery) was based on the assumed prevalence of symptomatic POP in 12% and 5.5% of the operative delivery group and normal delivery group, respectively. A total of 608 women was included.[19]

One of the primary outcomes for the CONTRAPOP study was to investigate association between muscle contraction and PFMT, hence sample size was based on change in muscle strength on palpation. Using the modified Oxford scale a mean of 2.6 was anticipated and a clinically relevant change in modified Oxford scale at 6-month follow-up of 3.2 ± 1.3. With power 80%, $p = 0.05$ and sampling ratio 1:1, a study sample of 74 women in each group was considered adequate. The results are published elsewhere.[130]

5.6 Data analysis and statistics

We used IBM SPSS Statistics version 25 (SPSS Inc, Chicago, IL) and R version 3.6.3 (R Project for Statistical Computing) to perform statistical analyses. The level of statistical significance was set at 5%. For continuous variables normality was tested using histograms, QQ plots and Kolmogorov-Smirnovs test. See Table 2 for a detailed overview of all outcome variables and statistical tests.

Paper 1

To compare urinary or colorectal-anal distress with a unilateral or bilateral LAM injury and intact LAM 15-24 years, Mann-Whitney U test was performed. Associations between LAM injury and UI and FI were tested using multivariable logistic regression analysis, adjusting for potential confounders (age, body mass index (BMI), parity, infant birthweight, cystocele ≥ stage 2 (for UI) and significant anal sphincter defect on ultrasound (for FI)). Any association between bladder anatomy (bladder neck descent and urethral funneling) and UI was evaluated using multivariable logistic regression adjusting for age, BMI, parity and infant birthweight. Any differences in background variables between the women with or without LAM injury were assessed with independent samples t-test.

Paper 2

Cohen's kappa was used to review agreement between the two main examiners (SM and RGR). The values were interpreted as: 0.00 = no agreement, 0.01-0.20 = slight agreement, 0.21-0.40: fair agreement, 0.41-0.60: moderate agreement, 0.61-0.80: good agreement and 0.81-1.00: strong agreement. Multivariable logistic regression was used to determine the association between the different types of sphincter defects and incontinence, adjusting for age, parity and BMI. Additionally, EAS was entered as a confounder when testing associations between IAS and the outcome and vice versa. VAS scores were not normally distributed; hence Mann-Whitney U test was applied to evaluate the association between incontinence scores and types of sphincter defect.

Paper 3

Differences between the women who accepted or declined randomization were analyzed with independent samples t-tests. Outcomes were analyzed after an intention-to-treat principle. Due to the randomized setting the intervention and control group were assumed similar. Mixed model analysis with a five-level combined variable for time and group status as fixed effects (baseline for total population, day of surgery, follow-up) was applied to test any difference in symptom scores (UDI-6, CRADI-8) and related QoL scores (UIQ, CRAIQ) between the intervention group and control group. The model was fitted by restricted maximum likelihood estimation and unstructured covariance for the repeated measurements. There was no effect of the stratification variables (POP stage over or under 3 and age over or under 60 years). Mixed models analysis fitted with restricted maximum likelihood estimation and unstructured covariance for repeated measurements was used to examine the overall change in the total study population with time as fixed effect.

Table 2 Summary of outcome, aim and statistical analysis.

Outcomes	Primary outcome variables		Secondary outcome variables		Aim	Statistical analysis	Confounders
	Categorical	Continuous	Categorical	Continuous			
PAPER 1	Yes/no to specific questions • Urinary incontinence (UI) • Fecal incontinence (FI)	Mean pelvic floor dysfunction scores (0-100) Urinary distress inventory (UDI-6) Colorectal-anal inventory (CRADI-8)	Bladder anatomy assessment • Bladder neck descent • Urethral funneling	Continuous	Compare symptoms between women with intact and injured levator ani muscle (LAM) Association between LAM injury and UI/FI Association between BND and funneling and UI	Mann-Whitney U Logistic regression analysis	Age Parity Body mass index (BMI) Infant birthweight Cystocele≥2/anal sphincter injury
PAPER 2	Presence of anal sphincter defect • Internal anal sphincter defect • External anal spincter defect Yes/no to questions • Fecal incontinence • Flatal incontinence			Visual analogue scale (0-100) • Fecal incontinence • Flatal incontinence Results from ultrasound assessment for two main examiners	Prevalence of anal sphincter defect Association between diffent types of anal sphincter defects and anal incontinence Associaten between VAS scores and sphincter defects Agreement between examiners	Logistic regression analysis Mann-Whitney U Chi-square Cohens kappa	Age Parity BMI
PAPER 3		Mean pelvic floor dysfunction scores (0-100) • UDI-6 • CRADI-8		Mean quality of life scored related to pelvic floor dysfunction (0-100) • Urinary impact questionnaire (UIQ) • Colorectal-anal impact questionnaire (CRAIQ)	Investigate the effect of preoperative pelvic floor muscle training (PFMT) on urinary and colorectal-anal distress and related quality of life in women scheduled for pelvic organ prolapse surgery	Mixed models analysis	None

5.7 Data handling and registration

For both studies (UROPRO and CONTRAPOP), signed consent forms and data at each clinical evaluation (baseline, day of surgery, postoperative follow-up) were registered on a paper form, marked with patient ID and study-ID. Data from the clinical examinations were registered in a web-based case report file (WebCRF) on htpp://webcrf.medisin.ntnu.no, marked only with study-ID. WebCRF was provided by the Unit of Applied Clinical Research, Norwegian University of Science and Technology. The paper forms were scanned into a SPSS file. Ultrasound volumes obtained at each clinical exam, were stored on the ultrasound machine and copied to external hard-discs, marked with study-ID and date of examination. Volumes stored on the ultrasound machine were deleted. Results of the ultrasound analysis were registered on a paper sheet or directly into a SPSS file, marked with study-ID. Any source data and paper forms with patient details were contained in a locked storage in the hospital. The key between patient details and study-ID was stored in the hospital computer system according to local rules for safe storage of sensitive information, accessible only to the main examiners (SM, MØN, IV). The investigator site file contains details of data handling.

Registration in clinical trials:

UROPPRO: NCT 01766193 11.01.2013

CONTRAPOP: NCT 03064750 22.02.2017. The registration in clinical trials was unfortunately delayed as inclusion of participants commenced on 17.01.17. Twenty-two participants in total (12 of whom were in the randomized trial) were included before the registration date. The outcomes were modified and clearly specified in December 2018: Ultrasound assessment of anal sphincter, pelvic organ mobility, symptoms of pelvic floor disorders assessed by visual analog scale and implant assessment have been added to the secondary outcomes. Data collection was completed on 26.06.2019.

Tools for reporting:

STROBE and CONSORT statements were used.

5.8 Ethics

All participants signed informed consent forms (Appendix 1 and 2). The UROPRO and CONTRAPOP studies were evaluated and approved by the Regional Committee for Medical and Health Research: REK 2012/666/midt and REK 2015/1751/midt.

No complications due to the intervention were registered and the examinations did not subject the women to any risks. Full evaluation of pelvic floor dysfunction and a detailed gynecological examination including ultrasound should be considered an advantage in all participants. In one patient, incidental findings triggered the need for immediate cancer treatment. Most participants appreciated the postoperative follow-up as an extra safety as this is not provided routinely in our hospital. The examinations at inclusion and day of surgery were timed to coincide with the preoperative examination before surgery to avoid extra visits for participants. Only two women declined randomization due to a busy life schedule. Although the extra time for consultation with the pelvic floor physiotherapist may seem disadvantageous to the busy schedule of working women, this is a dedicated service with a long waiting list in our hospital and feedback was predominantly positive.

5.9 Financial support

6.0 SUMMARY OF RESULTS

6.1 Study population and demographics

6.1.1 UROPRO (Paper 1)

The work presented in Paper 1 is a secondary analysis from the UROPRO population. Figure 18 displays a synopsis over the recruitment process and Table 3 shows the background characteristics.

A total of 1216 women responding to the postal questionnaire accepted clinical exams. According to protocol, 369 women were excluded as they had an operative vaginal delivery after a cesarean section or normal vaginal delivery (n=221) or were unable to attend the scheduled clinical exam due to travel or other inconveniences (n=148).

Figure 18 *Flowchart of UROPRO population.*
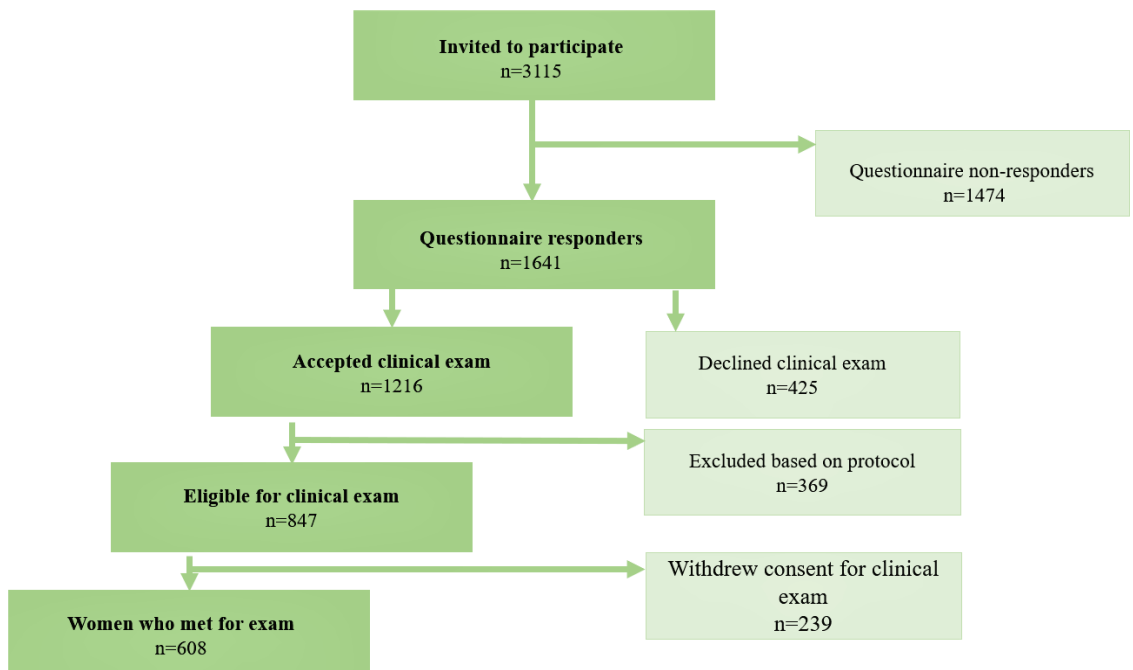
Women who declined participation lived farther away from the study centre and were significantly younger than questionnaire responders (47 vs. 48 years, p<0.01). They also had more UI (52% vs. 47%, p=0.04) but not more FI (9% vs. 11%, p=0.20). Parity, BMI, mode of delivery and infant birthweight were equally distributed.

Table 3 *Background demographics for UROPRO participants in paper 1.*

Background variables	Total population n=608	Women with LAM injury n=113	Women without LAM injury n=493
	Mean (SD)		
Age (years)	47.9 (4.9)	48.8 (4.4)	47.8 (5.0)
Parity (n)	2.2 (0.8)	2.2 (0.7)	2.3 (0.8)
BMI (kg/m²)	25.8 (4.5)	25.4 (4.2)	25.9 (4.6)
Infant birthweight (grams)	3861.1 (505.9)	3903.8 (481.2)	3852.1 (512.3)
Maternal age at index birth (years)	28.3 (4.6)	29.2 (4.0)	28.1(4.7)
	Number/total (%)		
Normal delivery	217/608 (35.7)	29/113 (25.7)	187/493 (37.9)
Operative vaginal delivery	290/608 (47.7)	84/113 (74.3)	205/493 (41.6)
Caesarean section only	101/608 (16.6)	0/113 (0.0)	101/493 (20.5)
POP-Q≥2	275/606 (45.4)	96/113 (85.0)	179/493 (36.3)
Anal sphincter defect	86/562 (15.3%)	55/108 (51.0)	31/454 (6.8)

6.1.2 CONTRAPOP (Paper 2 and 3)

Data from the CONTRAPOP study contributed to Papers 2 and 3. Paper 2 is a cross-sectional analysis of all women scheduled for POP surgery at inclusion and Paper 3 comprises of the randomized participants in this study. The flowchart in Figure 19 shows the source population for each paper.

During the recruitment period of the study, 272 women were referred for POP surgery; 72 were excluded. After inclusion, 41 declined further randomization but accepted participation and clinical exam, see flowchart in Figure 19. In all, 200 women participated in the cross-sectional study (Paper 2) and 159 women in the RCT (Paper 3). Women declining randomization were significantly older 67 vs. 61 years, p<0.01, but similar in parity, BMI and POP stage ≥3.

After randomization, three women withdrew consent and three dropped out due to cancellation of surgery (other medical conditions and/or symptomatic improvement). Two women in the control group dropped out owing to improvement of symptoms. Hundred and fifty-one (95%) women in the RCT completed the study. Table 4 shows the background characteristics of the CONTRAPOP population.

Figure 19 *Flowchart of CONTRAPOP*

Scheduled for surgery
n=272

Declining participation n=36
Missed for recruitment n=4
Not meeting eligibility criteria n=32

Eligible for assessment
n=200

Declining randomization n=41

Paper 2

Randomization
n=159

Paper 3

Baseline

Control group n=78
Drop-out n=2

Intervention group n=81
Drop-out n=6

Day of surgery

Control group n=76

Intervention group n=75

Postoperative follow-up

Control group
Examined n=76

Intervention group
Examined n=72
Missing n=3

Control group
Examined n=75
Missing n=1

Intervention group
Examined n=73
Missing n=3

Enrollment

Allocation

Analysis

Table 4 *Background variables for the 200 women scheduled for prolapse surgery in the CONTRAPOP study at inclusion.*

Background characteristics	Mean (SD)
Age (years)	61.7 (11.4)
Body mass index (kg/m²)	26.1 (4.0)
Parity (number)	2.5 (0.9)
	Number (%)
Nullipara	2 (1.0)
Primipara	18 (9.0)
Multipara	180 (90.0)
Normal vaginal delivery	145 (72.5)
Operative vaginal delivery	40 (20.0)
Vaginal breech or twin delivery	11 (5.5)
Only cesarean section	2 (1.0)

Table 5 *Background variables at baseline among the 159 women in the randomized controlled trial.*

Demographics	Intervention group N=75	Control group N=76
	Mean (SD)	
Age (years)	60.1 (11.2)	60.6 (10.9)
Body mass index (kg/m²)	26.3 (4.4)	25.7 (4.1)
Parity (number)	2.3 (0.8)	2.6 (0.9)
Waiting time before surgery (weeks)	21.6 (8.5)	23.2 (10.8)
Time to postoperative follow-up (weeks)	28.7 (8.0)	27.6 (7.6)
	N (%)	
Normal vaginal delivery	51 (68.0)	55 (72.4)
Operative vaginal delivery (including breech or twin-delivery)	22 (29.3)	20 (26.3)
Smoking	10 (13.9)	6 (7.9)
Postmenopausal	59 (79.7)	59 (77.6)
Local estrogen therapy	47 (63.5)	48 (63.2)
Previous pessary use	50 (67.6)	60 (78.9)
Previous pelvic floor muscle training	13 (17.6)	14 (18.4)
Previous pelvic organ prolapse surgery	7 (9.5)	11 (14.5)
Pelvic organ prolapse quantification (POPQ) ≥3 at baseline	44 (58.7)	48 (63.2)

6.1.3 Overview of surgical procedures and complications (Paper 3)

A combined procedure involving more than one compartment was performed in 58 (38%) women. Three of the isolated anterior repairs included use of a synthetic mesh. The proportion of women undergoing repairs in different compartments and procedures are summarized in Figure 20.

Figure 20 Venn diagram showing distribution of surgical procedures in 151 women in the randomized controlled trial.

Anterior repair:
Anterior colporrhaphy

Posterior repair:
Posterior colporrhaphy
Perineoplasty

19%   38%   18%

25%

Mid-compartment repair:
Vaginal hysterectomy
Cervical amputation and plication of cardinal ligaments
Laparoscopic sacroutero/colpopexy
Apical fixation
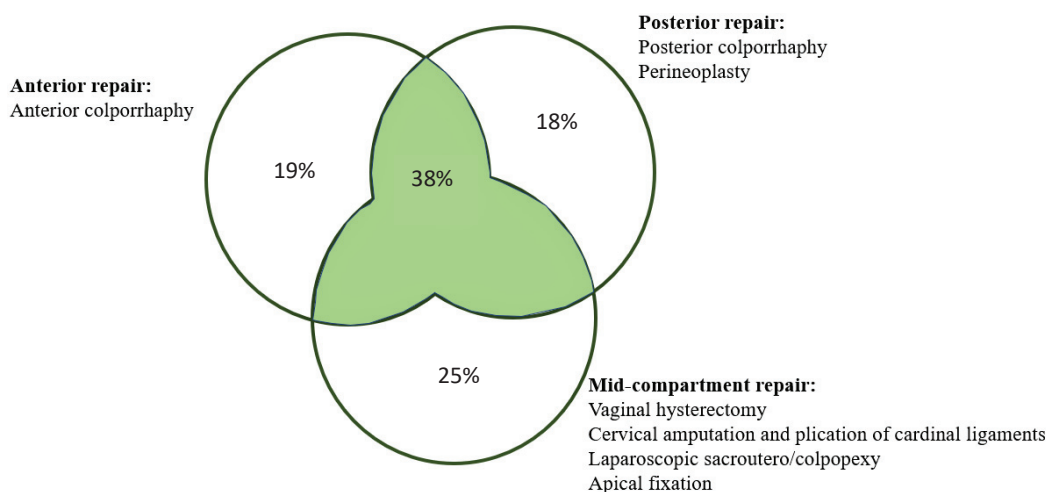
Two major complications requiring further surgical treatment occurred. One woman had intestinovaginal fistula after laparoscopic sacrocolpopexy and one experienced postoperative haemorrhage. Three women experienced postoperative urinary tract infections, and one woman had persistent residual urine after six months. No harms were registered due to the intervention (PFMT).

6.2 Main results

6.2.1 Paper 1

Levator ani muscle injury and risk for urinary and fecal incontinence in women from a normal population

One hundred and thirteen women (19%) had any LAM injury, of which 57 (9%) were bilateral. Fifty-two percent had UI or previous UI surgery and 11% had FI or previous surgery for this condition.

Women with and without LAM injury had similar median UDI-6 or CRADI-8 scores. The proportion of UI or FI was also similar in both groups. The same results were found for those with bilateral LAM injury, see Table 6. BMI was significantly associated with UI, adjusted odds ratio (aOR) 1.1 (1.0-1.1), p<0.01 and anal sphincter injury was significantly associated with FI, aOR 3.4 (1.6-7.5), p<0.01.

Only 582 ultrasound volumes were available for assessment of bladder neck anatomy (Table 7). Urethral funneling was significantly associated with SUI aOR 1.6 (1.03-2.4), p=0.04. Again, BMI was closely associated with both SUI and UUI, both aOR 1.1 (1.0-1.1), p<0.01.

We found no association between LAM injury and incontinence in parous women 15-24 years after first delivery

Urethral funneling was associated with stress urinary incontinence

Table 6 *Symptoms scores and prevalence of urinary and fecal incontinence and its association to levator ani muscle injury.*

	Intact LAM N=492	Any LAM injury (uni- or bilateral) N=113	Bilateral LAM injury N=57	Any LAM injury vs intact LAM	Bilateral LAM injury vs intact LAM
	Mean (SD) Median (range)			Mann-Whitney U test, *p*	
Urinary Distress Inventory (UDI-6) Range 0-100	12.9 (16.0) 8.3 (0-75)	11.3 (14.8) 4.2 (0-62.5)	12.0 (15.5) 4.2 (0-58.3)	0.35	0.53
Colorectal Anal Distress inventory (CRADI-8) Range 0-100	13.3 (15.8) 6.3 (0-78.1)	12.6 (14.9) 6.3(0-62.5)	10.8 (10.9) 6.3 (0-40.6)	0.90	0.75
	Number/ Total (%)			aOR (95% CI) *p*	
UUI	155/486 (31.9)	30/111 (27.0)	17/56 (30.4)	0.86 (0.5-1.4) 0.54	1.1 (0.6-1.9) 0.88
SUI	214/491 (43.6)	42/111 (37.8)	20/56 (35.7)	0.8 (0.5-1.2) 0.32	0.8 (0.4-1.4) 0.42
Any UI or surgery[1]	256/488 (52.5)	54/110 (49.1)	25/56 (44.6)	0.9 (0.6-1.4) 0.67	0.8 (0.5-1.4) 0.44
FI	51/492 (10.4)	13/113 (11.5)	3/57 (5.3)	0.7 (0.3-1.5) 0.32	0.3 (0.1-1.0) 0.06
FI or surgery[2]	52/482 (10.8)	13/111 (11.7)	3/57 (5.3)	0.7 (0.3-1.5) 0.32	0.3 (0.1-1.0) 0.05

Footnote:

[1] *BMI was associated with UUI, SUI and any UI or surgery, aOR 1.1 (1.0- 1.1), p <0.001.*
[2] *Any anal sphincter defect was associated with FI, aOR 3.5 (1.6-7.5), p <0.01 and FI or surgery, aOR 3.4 (1.5-7.3), p<0.01*

Table 7 *Prevalence of urinary incontinence and association to bladder neck descent and urethral funneling.*

	Bladder neck descent Number/total (%)			Urethral funneling Number/total (%)		
	yes	no	aOR (95% CI) *p*	yes	no	aOR (95% CI) *p*
SUI[3] N=249	154/363 (42%)	95/224 (42%)	1.0 (0.7-1.4) 0.93	58/117 (50%)	191/470 (41%)	1.6 (1.03-2.4) 0.04
UUI[4] N=183	106/360 (29%)	77/222 (35%)	0.8 (0.6-1.2) 0.34	34/116 (29%)	149/466 (32%)	0.9 (0.6-1.5) 0.78

Footnote:

[3] *BMI was associated with SUI, aOR 1.1 (1.0-1.1), p<0.01.*

[4] *BMI was associated with UUI, aOR 1.1 (1.0-1.1), p<0,001*

6.2.2 Paper 2

The prevalence of anal sphincter defects in women with severe prolapse and the association to anal incontinence

All participants had POP stage ≥2 and 61% (122/200) had stage ≥3. We found good to strong agreement between the two examiners (SM and RGR); Cohen's kappa 0.77 for EAS and 0.87 for IAS. A total of 31 discordant volumes were assessed by a third examiner (MØN).

Any anal sphincter defect was found in 25%, and 50% had LAM injury. EAS and IAS defects were independently associated with FI and flatal incontinence, respectively (Table 9). Age, parity or BMI were not associated with outcomes. Women with sphincter defects reported significantly worse bother from fecal and flatal incontinence regardless of whether they had an IAS or EAS defect as shown in Table 9. The proportion of women with an anal sphincter defect was equally distributed among those with or without a LAM injury, 26% vs. 24% (p=0.74). There was a higher proportion of AI among women with LAM injury than those without injury (59% vs. 48%) but the difference was non-significant, p=0.12. A combination of LAM injury, anal sphincter defect and any form of AI was present in 9%. The proportion of anal sphincter defect and AI were similar in a subgroup analysis of the 65 women with posterior wall POP stage ≥2 (25% and 54%) compared to 135 women with anterior and/or mid-compartment POP (25% and 53%), all p>0.05.

Women with POP had a high prevalence of anal sphincter defects and AI

Anal sphincter defects were associated with AI in women with severe POP

Table 8 *Anatomical findings in the group of 200 women scheduled for POP surgery.*

Anatomical findings	N (%)
Pelvic organ prolapse stage ≥2 in	
Anterior wall	163 (81.5)
Posterior wall	65 (32.5)
Mid compartment	72 (36.0)
Any levator ani muscle injury	100 (50.0)
Bilateral levator ani muscle injury	48 (24.0)
Any sphincter defect	50 (25.0)
Isolated EAS defect	23 (11.5)
Isolated IAS defect	8 (4.0)
Combined defect	19 (9.5)

Table 9 *The distribution of IAS and EAS defect and the association to incontinence.*

		Fecal incontinence (n=29/199)		Flatal incontinence (n=97/199)		Fecal incontinence VAS scores (n=198)		Flatal incontinence VAS scores (n=198)	
		Number (%)	aOR* (95% CI) *p*	Number (%)	aOR* (95% CI) *p*	Mean score (SD) Median (range)	Mann-Whitney U *p*	Mean score (SD) Median (range)	Mann-Whitney U *p*
IAS	Intact (n=173/200)	19 (10.9)	2.3 (0.7-7.0) 0.147	74 (43.0)	5.2 (1.6-17.2) 0.007	5.6 (14.3) 0.0 (0-95)	<0.001	18.8 (29.2) 0.0 (0-100)	<0.001
	Defect§ (n=27/200)	10 (37.0)		23 (85.2)		12.5 (24.6) 0.0 (0-82.3)		39.1 (34.9) 32.6 (0-100)	
EAS	Intact (n=158/200)	14 (8.9)	4.0 (1.5-10.8) 0.005	67 (42.7)	1.9 (0.8-4.5) 0.131	2.8 (13.5) 0.0 (0-95)	<0.001	19.6 (29.8) 0.0 (0-100)	0.006
	Defect§ (n=42/200)	15 (35.7)		30 (71.4)		12.2 (22.7) 0.0 (0-82.3)		28.8 (33.6) 10.9 (0-100)	

Footnote:

*Potential confounders adjusted for include the presence of either EAS or IAS defects, age, parity and body mass index (BMI).

§ Isolated IAS defect in 8/200 (4%) and isolated EAS defects in 23/200 (13%) was found.

6.2.3 Paper 3

The effect of preoperative pelvic floor muscle training on pelvic floor dysfunction in women with severe pelvic organ prolapse

The adherence level of ≥70% completion of daily exercises was met by 80% of participants in the intervention group. Mean (SD) and median (range) waiting time to surgery was 22 (10) and 21(7-84) weeks, and women were examined postoperatively after mean 28 (8) and median 26 (11-79) weeks, which was similar for the intervention and control groups (see Table 5). Thirty-eight (51%) women failed to submit a training diary and were interviewed by telephone. Mean postoperative scores (95 % CI) on symptoms or QoL related to urinary or colorectal-anal distress were similar between the intervention and control group: UDI-6 16 (12-21) vs. 17 (13-22), CRADI-8 15 (11-18) vs. 13 (10-16), UIQ 11 (7-15) vs. 10 (6-13) and CRAIQ 5 (2-7) vs. 6 (4-9), all $p>0.05$. Score distribution at all examination stages are summarized in Table 10. Regardless of intervention, the total study population showed overall improvement in mean scores from baseline to postoperative follow-up; UDI-6 37 (33-41) vs. 17 (14-20), CRADI-8 22 (19-25) vs. 14 (11-16); UIQ 28 (24-32) vs. 10 (7-13) and CRAIQ 16 (12-19) vs. 5 (3-7), all $p<0.01$. The main results of the mixed models analysis are presented in Figure 21.

Symptoms and QoL related to urinary and colorectal-anal distress improved in all women after POP surgery, regardless of preoperative PFMT

Table 10 *Mixed models analysis by allocation group and for the total population with mean scores and mean difference.*

	Baseline	Day of surgery				Postoperative follow-up				Postoperative follow-up	Difference between baseline and postoperative follow-up *
	n=151	Intervention n=72	Control n=76	Difference between groups¶		Intervention n=73	Control n=75	Difference between groups¶		n=148	n=148
	Mean	Mean	Mean	Mean	p	Mean	Mean	Mean	p	Mean	Mean difference	p
Symptoms subscales *(Range 0-100)*												
Urinary distress inventory (UDI-6)	37.2	37.4	40.6	-3.2	0.284	16.3	17.4	-1.1	0.718	16.9	20.3	<0.001
Colorectal anal distress inventory (CRADI-8)	21.9	23.8	23.2	0.6	0.784	14.6	13.1	1.5	0.474	13.8	8.1	<0.001
Quality of life subscales *Range (0-100)*												
Urinary impact questionnaire (UIQ)	27.7	24.7	27.0	-2.4	0.453	10.5	9.5	1.0	0.707	10.0	17.7	<0.001
Colorectal anal impact questionnaire (CRAIQ)	15.7	14.9	13.8	1.1	0.645	4.6	6.0	-1.4	0.428	5.3	10.4	<0.001

RESULTS BY ALLOCATION GROUP

RESULTS BY TOTAL POPULATION

Footnote:

¶ *A positive mean difference in symptoms scores (UDI-6 and CRADI-8) and quality of life parameters (UIQ and CRAIQ) indicates improvement in the control group whereas a negative mean difference indicated improvement in the intervention group.*

* *Positive values indicates reduction of symptoms and related impact on quality of life scores postoperatively.*

Figure 21 Illustration of the mean scores and 95% confidence interval for each subscale. Symptoms and related quality of life in the intervention group (red line) and the control group (blue line) from baseline to the day of surgery and the postoperative follow-up, using linear mixed models analysis. Examination time (baseline, day of surgery and postoperative follow-up) on the x-axis and mean score with 95% confidence interval on the y-axis of the A) urinary distress inventory (UDI-6), B) colorectal-anal distress inventory (CRADI-8), C) urinary impact questionnaire (UIQ) and D) colorectal-anal impact questionnaire (CRAIQ).
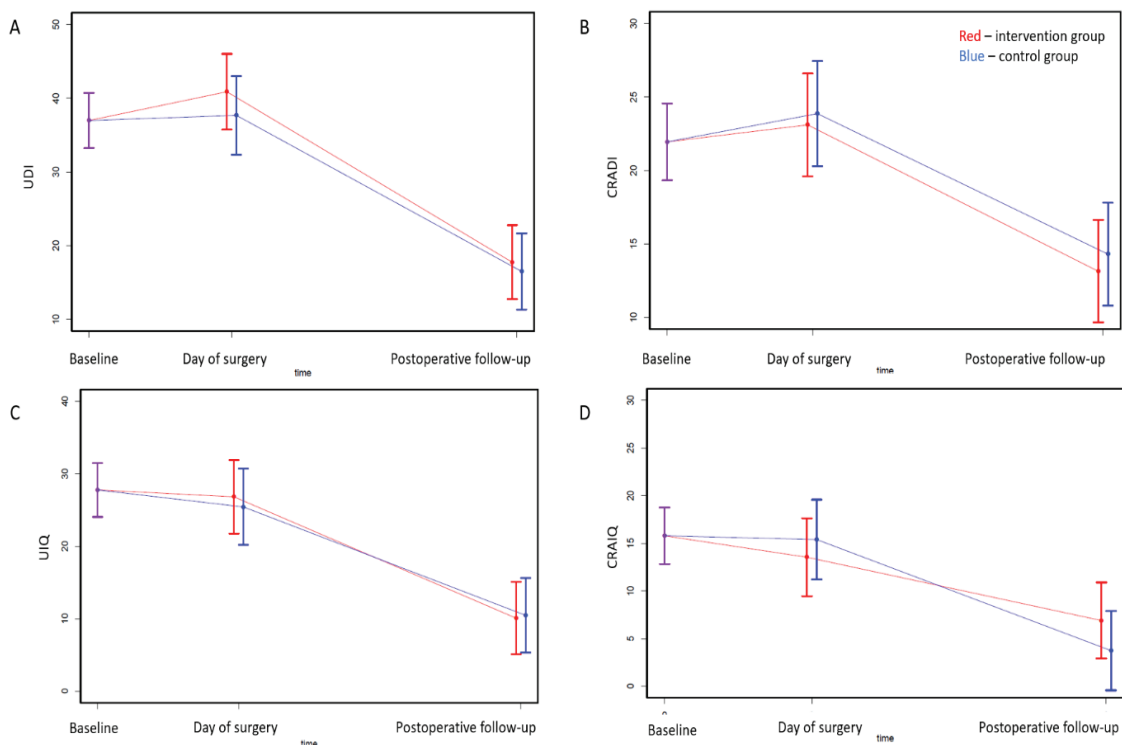
In women undergoing POP surgery, UDI-6 and CRADI-8 scores were evenly distributed among women with and without a LAM injury (Table 11). The yes/no responses to specific questions regarding UI and AI in the UDI-6 and CRADI-8 questionnaires were selected. Of the 75% (107/142) women reporting UI at inclusion, 50% (70/140) reported persistent UI postoperatively. For AI, the proportion was 68% (100/147) and 52% (72/139), respectively. Nine percent (6/33) and 11% (8/45) of women developed de novo UI and AI, respectively. A reduction in the proportion of women with AI was observed among those without any anal sphincter injury postoperatively (61% vs. 44%, p<0.001), but not in women with sphincter injury (82% vs. 79%, p=0.086) Both women with and without an anal sphincter injury had significant improvement in CRADI-8 scores postoperatively (Table 12).

Table 11 *Symptom scores related to urinary distress and colorectal-anal distress in women with and without levator ani muscle (LAM) injury at baseline.*

	Intact LAM n=76	**Any LAM injury** (macrotrauma) n=75	**Any LAM injury vs. intact LAM**
Symptom scores (range 0-100)	Mean (SD)		Mann-Whitney U *p*
Urinary Distress Inventory (UDI-6)	36.0 (23.0)	37.5 (26.0)	0.89
Colorectal-Anal Distress Inventory (CRADI-8)	20.3 (15.6)	24.1 (17.8)	0.25

Table 12 *Pre- and postoperative prevalence of anal incontinence and colorectal-anal bother (CRADI-8) scores among women with and without any significant anal sphincter injury.*

	'Yes' to any Anal incontinence			Colorectal Anal Distress Inventory (CRADI-8) Range 0-100		
	Preoperative	Postoperative	Chi-square/ Fishers exact test	Preoperative score	Postoperative score	Wilcoxon signed rank test
	Number (%)		p	Mean (SD)		p
Intact sphincter n=101	62 (61.4)	44 (43.6)	<0.001	20.6 (15.6)	12.6 (13.2)	<0.001
Any sphincter Defect n=34	28 (82.4)	27 (79.4)	0.086	29.2 (18.7)	18.9 (18.2)	0.001

7.0 DISCUSSION
7.1 Comparison with existing knowledge

7.1.1 Association between levator ani muscle injury and urinary and fecal incontinence

In Paper 1, the prevalence of UI and FI were 52% and 11% respectively, which is comparable to prior studies of parous women from a general population (UI: 16-69% and FI: 6-9%).[14,17,21,151] The reported prevalence of UI in the UROPRO study is at the high end of the spectrum and only one study reports prevalence as high as 69% in women older than 40 years.[15] This may be explained by the higher mean age of participants in both these studies. Our population also had a higher proportion of operative vaginal delivery (47%), a possible risk factor for developing UI in later years.[156]

The proportion of women who experienced any incontinence and the symptom scores were similar in those with or without a LAM injury. This corresponds well with an MRI study that failed to show an association between LAM status and lower urinary tract symptoms.[41] Previous MRI and ultrasound studies have reported a lower prevalence of UI in parous women diagnosed with major LAM defects. [41,157] These findings concurs with a case-control study of 103 women where no difference in LAM defects was observed between women with SUI compared to continent women.[158] In contrast, Chan et al found a two-fold risk of SUI in women with LAM injury 3-5 years postpartum. [47] SUI may be more common in the immediate years postpartum before any protective effects of anterior wall prolapse occur. Ultrasound evaluation of 400 women over 50 years of age did not find evidence to support any association between LAM and FI.[40] A recently published study on LAM trauma and the long-term development of both UI and AI, arrived at the same conclusion as our findings, after examining 450 women 6-17 years after their first delivery. [159]

A supplementary analysis of the CONTRAPOP population of women undergoing POP surgery showed that the prevalence and severity of incontinence was not associated with LAM injury, further substantiating our findings that LAM injury alone is not associated with bother of incontinence in women from a normal population and women with POP. [9,39,40,42]

7.1.2 Association between bladder neck anatomy and urinary incontinence

The downward displacement of the bladder neck at Valsalva, measured as BND, is associated with SUI in urogynecological populations.[100,101] In a cohort study of 179 women with urinary distress, Dietz et al reported that BND and urethral hypermobility was strongly associated with SUI.[100] This is contrary to our findings, but a case-control study by DeLancey demonstrated that urethral support was not associated with SUI when comparing to a normal population.[158] In our study population of parous women, funnelling was found to be associated with SUI. An MRI examination of 21 women showed a positive correlation between funneling, urethral sphincter length and SUI.[160] Weak bladder neck support was seen as urethral funneling in an ultrasound study in 125 women with UI, but the association with UI was not clear due to the study design (women who had either UI or undergone UI surgery).[102] However, the finding of funnelling along with other bladder neck abnormalities was shown to increase the risk of SUI by two-fold in an observational study by Dietz et al.[97] Other studies demonstrate decreasing postoperative funneling as indicative of successful sling surgery, indirectly agreeing with our results.[102,103,161]

7.1.3 The prevalence of anal sphincter defects and anal incontinence in urogynecological population

A high prevalence of sphincter defects and AI in women with POP is documented in literature studying the coexistence of PFDs. [18,30,32] Our findings of 25% anal sphincter defects correlates well with an analysis of women with PFDs, aged around 55 years, where one-fifth were diagnosed with a sphincter injury.[94] Guzman Rojas et al reported a prevalence of 12% IAS and 18% EAS defects in women attending a urogynecological clinic, corresponding with the findings in our population (14 % and 21%).[94] Any AI was reported by 54% of the CONTRAPOP population. This is high, as similar studies cite the prevalence of any AI as 14-20%. However, these studies included heterogenous populations with predominantly UI, contrary to our study consisting of women with severe POP awaiting surgery. [18,94] In another study, AI was observed in 42% of women with POP stage ≥ 3.[30] This corroborates well with our results where two-thirds of the participants had advanced POP. One-third of women who had undergone POP surgery

reported flatal incontinence in a study by Rømmen et al, which is lower than our results (48%).[21] In Rømmen et al, the participants marked for any incontinence if this occurred in the month before the questionnaire was presented contrary to our study where symptoms during the last three months were considered.[21] Our findings of 15% FI is higher than Meschia et al that found 8% FI in women with POP, but a fifth of the study population included women without POP or UI. [18] The prevalence of AI in women with posterior wall prolapse (rectocele) was similar to the total population (54%) in our study. Similarly, no association between anal symptoms and degree of posterior POP was shown in 70 women with posterior POP stage ≥2 by da Silva et al.[162]

7.1.4 Association between anal sphincter defects and type of anal incontinence in women undergoing prolapse surgery

The association between sphincter defects, particularly EAS defects, and FI or AI have been well-documented in studies among parous women. [46,49,96] One of these is a previous publication from the UROPRO population finding a 50% increased risk of FI in the presence of EAS defects.[96] In women with PFD, Guzman-Rojas et al found that significant EAS defects gave an 18-fold increase in risk for AI, indicating a high risk in similar populations.[94] IAS and EAS defects were strongly associated with flatal incontinence and FI. EAS being a voluntary muscle, is shown to affect FI, while IAS contributes more to the basal tone and affects gas leakage. [57,88]

7.1.5 Effect of pelvic floor muscle exercise on urinary and anal distress and related quality of life in women undergoing POP surgery

In this RCT we found no additional benefits of PFMT on urinary and colorectal-anal symptoms or QoL in women undergoing POP surgery. Duarte et al included 2 weeks preoperative PFMT and showed marginally improved QoL in the intervention group without any change in urinary or anal bother quantified by PFDI, PFIQ and its subscales.[132] This study covered a shorter postoperative follow-up of 90 days and excluded women with previous POP surgery, whereas 12% of the CONTRAPOP population had undergone previous POP surgery.[132] Other previous publications include mostly postoperative exercise sessions, whereas our participants exercised for an average of 22 weeks preoperatively .[132,135,150] McClurg et al found no reduction in the bother of incontinence using adjunctive treatments in addition to one preoperative PFMT session. [135] Frawley et al examined a similar group and found less de novo stress

incontinence after PFMT, but the intervention consisted of a single supervised preoperative PFMT session with the rest being postoperative.[150] In the above-mentioned studies, participants had milder POP and included heterogenous groups, not limited to POP patients and utilized other treatment modalities along with PFMT, a possible explanation to why these findings vary from our results.[119,134,135,150] Braekken et al and Hagen et al show significant symptom relief after PFMT and lifestyle advice after 12 – 16 weeks for POP symptoms, but these studies involved women with POP stage 1-3.[119,122] More than 60% of the CONTRAPOP population comprised of women with advanced POP. Systematic reviews on FI indicate diverging results when comparing PFMT to other conservative treatment (dietary changes, biofeedback, medical treatment) for both genders.[163]

Overall, the participants reported improvement in urinary and colorectal-anal symptoms and QoL, regardless of intervention. Reduced bother and improved QoL after POP surgery are also demonstrated in most of the above-mentioned studies.[132,135,150]

7.2 Strengths and limitations

7.2.1 Study design

A cross-sectional study design provides a status of the factor studied at a specific time and is suitable to compare associations between various parameters and to study prevalence of a disease or condition.[164] This type of study is prone to be influenced by confounders and biases, necessitating cautious interpretation of causality.[164,165]

One of the strengths of Paper 1 (UROPRO study) is the long time-interval between LAM injury and assessment of symptoms, for estimation of long-term risk.

To study the effect of exercise a randomized controlled design was used (Paper 3). The main strength of this design is that systematic errors are minimized owing to randomization and any persisting differences between the intervention and control group at baseline are due to chance. RCTs are perceived as the gold standard to study the effect of an intervention in medical research.

7.2.2 Study size and population

Results from Paper 1 are based on 608 women from the normal population. An enlisting of this magnitude from a normal population is considered a strength. In comparison, other similar studies involved less than 455 women.[40,41,157,159]

CONTRAPOP includes a large population of women awaiting POP surgery (n=200), with POP in all compartments as seen in a clinical setting. The RCT is a large trial, comprised of 151 women, whereas most other studies included less than 100 women. [132,135,150]

7.2.3 Quality of tools

Examination

POP-Q measurements are standardized and easy to learn. However, measurements are subjected to the knowledge and expertise of the examiner. One strength of UROPRO is that one skilled gynecologist (IV) assessed all participants. In CONTRAPOP, three experienced gynecologists (SM, MØN and IV) examined all women. However, multiple examiners may introduce the possibility of variation in measurements.

Questionnaires and VAS

Paper 1 and 3 employ validated questionnaires approved for assessing PFDs and related QoL, adding to strength.[155] Paper 1 utilizes the individual questions as well as the complete questionnaire showing similar outcomes.

Only VAS along with yes/no responses were used to estimate FI and flatal incontinence in Paper 2. Standardized questionnaires may have improved the estimates and nuances between types of incontinence in Paper 2.

Ultrasound

Ultrasound provides superior visualisation of pelvic floor anatomy. Data volumes were studied offline, using 4D view software. Non-invasive and well-established validated methods to evaluate pelvic floor anatomy were used in both studies. [81,90,101]

Transperineal ultrasound is less invasive compared to endoanal approach in anal sphincter diagnosis. One expert examiner (IV) performed ultrasound and analysed all levator volumes in the UROPRO study, while another (RGR) assessed the bladder anatomy, minimizing variation. Three gynecologists (SM, MØN, IV) performed ultrasound of all participants for CONTRAPOP and all anal sphincter volumes were analysed by two examiners (SM and RGR). The reproducibility and reliability exhibited were similar to previous publications in experienced examiners.[75,92,93,166] Endoanal ultrasound is considered the gold standard, therefore transperineal ultrasound may have more missed diagnosis. However, transperineal ultrasound has high negative predictive value, making it suitable for preliminary diagnosis.[89,167] Another advantage of using ultrasound was ensuring real-time guidance of proper pelvic floor muscle contraction in the RCT.

7.2.4 Intervention

The intervention was designed to be practically implementable in the busy lives of working women. We achieved a high adherence rate (80%) of at least 70% of daily PFMT. Healthy striated muscle needs about 12 weeks of progressive resistance training to attain hypertrophy and strength. [114,119] Although there is no consensus on the correct models of PFMT, the preferred model proposed by Dumoulin et al was used in the CONTRAPOP study. [116] The average intervention time of 22 weeks in the PFMT group

was therefore considered adequate to bring forth increased strength sufficient to alter symptoms.[114-116] During the preoperative intervention, two individual consultations with a dedicated physiotherapist ensured correct exercise techniques in the PFMT group.

We offered weekly training sessions to the intervention group, but none of the participants attended this. Whether this was due to busy schedules, lack of incentives, motivational or economic reasons is not known, but should be addressed when designing related studies. Electrostimulation was utilized in one woman due to problems in learning correct contraction technique.

7.2.5 Statistical considerations

For Paper 1, suitable non-parametric tests were utilized to compare associations (Mann-Whitney U). The specific questions in the respective questionnaires were individually checked for associations to LAM injury using multivariable regression analysis adjusting for confounders. Paper 1 was a secondary analysis of data collected based on other primary outcomes (associations between delivery mode and LAM injury). In a population with more than 600 women, we presumed that any significant differences between the groups would be uncovered. In the UROPRO study, prevalence of UI and/or previous UI surgery was high (50%) and AI and/or previous AI surgery was around 10%. One-fifth of the women had LAM injury. Thus, we expected high probability for finding a true difference in incontinence bother between women with and without a LAM injury in this population.

In Paper 2 we assessed correlation between two examiners using Cohen's kappa, evaluating the reproducibility of transperineal ultrasound in anal sphincter diagnosis. Available confounders were addressed by using multivariable regression analysis for the association between sphincter injury and AI. Mann-Whitney U test was also used to assess differences in VAS scores for FI and flatal incontinence between women with and without EAS or IAS defect.

In Paper 3, a mixed models analysis enabled the use of all data for assessment of outcomes over time and between groups, even in the presence of missing data. Sample size calculation for the CONTRAPOP population was based on differences in pelvic floor muscle contraction, under the assumption that a clinically relevant change would

manifest in a comparable change in symptom and QoL scores. Sample size of 74 women in each group was calculated based on differences in pelvic floor muscle contraction which is earlier published.[130] No a priori power calculation was performed for outcome measures in Paper 3 (symptom and QoL scores), but the participants had high symptom scores between 20-40 out of 100. Hence, we expected to find a clinical and statistically significant difference if there were any effect of PFMT.

7.2.6 Internal validity and bias

Internal validity is affected by random error and systematic error (bias). A large sample size (UROPRO) helps reduce random error. Appropriate statistical analysis in Paper 1 and 2, adjusted for possible other explanations that influence both exposure and outcome. Good to strong correlation between examiners in Paper 2 increase precision of outcome. Another way to ensure internal validity is by using RCTs in studying the effect of a treatment or intervention, as in the case of Paper 3.

Selection bias

Symptomatic women volunteer to participate in studies to a greater extent than women without symptoms, introducing possible sampling bias during recruitment for both UROPRO and CONTRAPOP.[165] The women who failed to respond to the UROPRO questionnaire were younger, possibly less symptomatic. Of the 53% of women who responded to the questionnaire, 72% met for a clinical examination in the UROPRO study. Any previous PFMT or neuromuscular disorders that can influence UI, FI and distress scores were not recorded.

Among women eligible for the CONTRAPOP study, 74% accepted inclusion (Paper 2), but we did not collect background information on the women that declined participation. Only 2 % failed to fill out the simpler VAS completely in Paper 2, minimizing missing data. Confounding by indication was avoided in Paper 3, as this was a randomized study where participants were randomly allocated to intervention or control by a computer program. Only eight women were lost to follow-up in the RCT (Paper 3). Thus, the study is less likely to suffer from attrition bias.

Information bias

Standardization of POP-Q and offline analysis, blinded to all participant details, ensured against informational bias in both UROPRO and CONTRAPOP studies. Further risk of bias is reduced by clearly defined questionnaires. Extracting the positive responses to the individual questions on UI and AI without considering the severity of symptoms, may give a higher prevalence of the symptoms studied in Paper 1. This also applies for Paper 2, where we used the positive responses to questions on FI and flatal incontinence and may represent a non-differential misclassification bias, that is equally distributed in all groups.

Telephone interviews in Paper 3 for those who failed to deliver the training diary introduces a possibility of recall bias. Both intervention and control group were given thorough knowledge regarding pelvic floor anatomy and how to perform correct pelvic floor contractions during the baseline examination. This may introduce a misclassification bias in the RCT (Paper 3), although it is unlikely that the control group learned perfect PFMT from one baseline examination. The examiners and participants were not blinded to the randomization. However, this is not an issue since offline analysis was performed after a time interval, and participants were registered only with their study number. Patients who had PFMT may expect more improvement and controls may believe they are worse since they did not receive any 'intervention'. This may affect the symptom scores and VAS, a possible observer bias, but patient-reported questionnaires were used in both studies.

Confounding

For the UROPRO study (Paper 1) data regarding previous incontinence surgery were recorded adding to the strength. Selection of suitable analysis accounting for known confounders that may influence both exposure and outcome for Paper 1 and 2 were discussed in statistical considerations. The main shortcoming in Paper 2 is that we did not record if the women had sustained OASI at delivery or underwent repairs. Other diseases or previous incontinence surgery were not registered for the CONTRAPOP population. These potential confounders could distort the true association between muscle injury and incontinence in these studies. The advantage of conducting an RCT

(Paper 3) is that any confounders are assumed evenly distributed between the intervention and control group.

External validity

The general obstetric practice in Norway that favoured forceps deliveries in the era involving both the UROPRO and CONTRAPOP population and subsequent underdiagnosis of pelvic floor injuries (including anal sphincter injuries) represents a possibility for selection of patients in both populations. Recently, the obstetric practice has changed to more caesarean and vacuum deliveries rather than forceps deliveries. Thus, it is possible that future study populations will be different. Both studies were performed in a predominantly Caucasian population and external validity is therefore limited compared with other ethnicities.

The UROPRO population consisted of women in their late forties, representing a slightly skewed population, therefore the results may not apply to women from other age groups. Due to the study design and aim of the parent study, there was a higher percentage of women with operative vaginal deliveries, leading to an overrepresentation of LAM injuries and subsequent PFDs. This may constitute a limitation to the external validity.

The CONTRAPOP study included all women with severe POP and recurrent POP in any compartment, representing a typical sample encountered in a urogynecological practice. Only four women were missed for recruitment. Still, the results may not apply towards a younger population with mild POP. A randomized controlled design may not provide a correct generalisability, but a high inclusion rate argues against this point for the CONTRAPOP population. For Paper 3, forty-one women declining randomization were older and had a higher percentage of previous POP surgery.

7.3 Possible explanations to the results

7.3.1 Association between pelvic floor anatomy and incontinence in women

Paper 1

Our findings validate the assumption that multiple factors contribute to UI and FI many years after delivery. [39,40,96] Chronic diseases, OASI and age exert a larger influence on UI and FI, than LAM injury.[16,29] LAM injury is implicated in the development of anterior wall descent that may camouflage SUI due to a kinking of the urethra, explaining any protective effects.[11] The etiology behind incontinence in the immediate years beyond delivery may be different than decades after delivery as BMI, hormonal and age-related changes seem more important than LAM injury.[15,157,158]

Funneling may very well be an indicator of a weak intrinsic sphincter. Evidence for funneling in SUI is not clear but preoperative funneling carries a poorer prognosis after colposuspension and tension-free vaginal tape surgery, with decreased funneling seen in patients achieving continence.[99,161] PFMT induced strengthening of the pelvic floor reduces the caudal movement of the bladder neck and improves symptoms in women with SUI.[117] Therefore, it is surprising that we did not find any association between UI and BND in a normal population. It is possible that urethral sphincter and urethral closure pressure play a bigger part in the pathophysiology of SUI than urethral support.[158] Mucosal turgor and striated muscle in the urethra decrease with age influencing closure pressure.[52,158] BND may be more related to the downward displacement of the anterior wall in a cystocele than UI. [101]

Paper 2

Due to the population with severe POP and the use of ultrasound that can identify occult injury, the reported prevalence of anal sphincter defects was expected to be higher than studies on clinically diagnosed sphincter defects .[44,45,96]

Anal sphincter injury leads to a loss of both basal tone and ability to voluntary contract the sphincter muscle affecting the continence mechanism.[57] It is therefore logical that this also applies for women with severe POP.[94,96] This is also demonstrated by the fact that a larger proportion of women without anal sphincter defects reported curation of AI postoperatively compared to women with sphincter defects in the CONTRAPOP

population. The isolated IAS defects may be due to missed diagnosis of an IAS tear at delivery or an incomplete repair at time of injury.[96] IAS contributes to mean anal basal pressure, hence a defect will compromise flatal continence.[57] We expected to find an association between IAS and leakage of fecal material, but the number of participants, age and the presence of FI for other reasons in a urogynecological population may have limited this association.[15] Several risk factors beyond obstetric trauma converge in these patients, explaining the high prevalence of AI.[13,31,32] Another explanation may be that a third of the participants in this study had severe POP (stage≥3). Severe posterior wall weakness may cause rectal distention predisposing for overflow incontinence.[168]

7.3.2 The effect of pelvic floor muscle exercise on urinary and colorectal-anal bother

One must bear in mind that this is a special population with a high rate of pelvic floor muscle injuries as well as possible nerve damage. In a previous publication from the CONTRAPOP study, there was no difference in muscle strength among the intervention and control group.[130] Expecting an effect on urinary and anal complaints may be futile, thereby explaining our results.[130] The RCT evaluates all bother from the urinary or anal tract. PFMT is shown helpful in incontinence, pain and urgency; hence a change was expected.[28] The presence of a major prolapse may prevent women from correct exercise technique. The large reduction in overall symptoms postoperatively may blur any minor effects of PFMT after POP surgery.

This RCT contains exclusively preoperative intervention with a sufficient duration.[114,115,131,132,134] However, urinary and colorectal bother are influenced by a number of factors. Women with extensive pelvic floor injuries inclusive nerve damage may require multiple strategies (lifestyle changes, electrical stimulation, biofeedback, sacral nerve modulation) alongside PFMT to effectively rehabilitate pelvic floor muscle. It is also possible that a longer duration and intensity of exercise is needed for improvement in other PFDs than it is for POP improvement. The follow-up time (24 weeks) may be too short to evaluate lasting effects or diagnose de novo symptoms in this type of patients.

7.3.3 Effect of POP surgery on incontinence

Due to the operating technique that reinforces the anterior wall, it is expected that anterior compartment repairs may provide more improvement in UI than surgery in any other compartment.[169] That explains the overall improvement in UDI bother scores Some women with anterior wall POP may also have occult SUI, and the true prevalence of SUI may only come forth after restorative surgery reinforcing the the anterior wall.[11] Our results showed that 9% and 11% reported de novo UI and AI. The etiology for AI is not as closely linked to POP as UI.[40] POP can lead to constipation and overflow incontinence.[168] However, the improvement in AI was significant only for women without anal sphincter defects, indicating sphincter defects as the main risk factor for AI, also in women with severe POP. In terms of colorectal-anal bother, both women with and without anal sphincter defects, signalized improvement after surgical POP correction, possibly due to an improvement in emptying difficulties after a strengthening of the posterior wall. In a previous publication from CONTRAPOP, women experienced improved pelvic floor contraction after surgery, which may explain our findings of improved symptoms and QoL postoperativly.[130]

7.4 Clinical implications for understanding and managing incontinence in women

Etiology of urinary and colorectal-anal distress in women is not solely dependent on pelvic floor muscles. Urethral funneling and other ultrasound parameters of the bladder neck anatomy may offer additional information about the incontinence mechanism of UI in affected women. Although we found overall improvement in urinary and colorectal-anal bother after POP surgery, further studies on other ultrasound parameters (bladder anatomy) are needed for better diagnosis of women at risk of postoperative incontinence.

The prevalence of anal sphincter injury and AI are high in women with advanced POP. Additionally, the women with intact anal sphincter had significantly less AI after POP repair compared with women with anal sphincter injury. Therefore, ultrasound diagnosis of the anal sphincters is particularly valuable in the preoperative counselling of women reporting AI symptoms. Women can benefit from better knowledge about possible alleviation of AI postoperatively. Further investigation and treatment options can be pursued in case of persistent symptoms. If AI is a concern, further investigation by a colorectal surgeon may be beneficial. Multidisciplinary approach (dietary changes, muscle exercise, sacral nerve modulation, electrical stimulation, medical or surgical treatment) may be considered in symptomatic patients who remain incontinent, despite all conservative measures.

The main clinical implication of the findings in Paper 3 is that women awaiting POP surgery have no additional benefit of PFMT on urinary and colorectal-anal symptoms. Additional physiotherapy resources before POP surgery may be spared. Other chronic diseases and lifestyle habits need to be addressed.[14] Corrective surgery could prelude PFMT to enhance exercise technique in women with both severe POP and incontinence, if in fact a large prolapse physically hinders effective muscle contraction.

8.0 CONCLUSION

Paper 1

LAM injuries were not associated with UI or FI in parous women from a normal population two decades after delivery. Thus, the development of incontinence involves a more complex etiology and is not solely due to pelvic floor muscle injury.

Funneling of the proximal urethra on Valsalva was a predictor of SUI in a general population.

Paper 2

One-fourth of women with severe POP had a sphincter defect. We found a high prevalence of AI in this urogynecological population. Sphincter defects were closely associated with fecal and flatal incontinence.

Symptomatic women may benefit from a transperineal ultrasound of the anal sphincter complex that can prompt further investigation and optimal treatment.

Paper 3

Women with advanced POP experienced improvement of urinary and colorectal anal distress and related quality of life six months after POP surgery.

No additional impact from preoperative PFMT was seen in women scheduled for POP surgery. Exploring other adjunct treatments or intensifying PFMT needs further investigation in this population.

9.0 FUTURE RESEARCH

9.1 Follow-up of the CONTRAPOP study

The etiology of incontinence after POP surgery is not clear. It would be interesting to investigate the proportion of de novo incontinence in women who undergo POP surgery in a longer follow-up study of the CONTRAPOP population. Frawley et al found that the intervention group had fewer cases of postoperative SUI.[150] Will there be any differences in the groups some years after POP surgery? How many women in the intervention group continue to exercise? The long-term effect of PFMT needs further evaluation.

9.2 Ultrasound parameters for urinary incontinence

Most studies on bladder neck anatomy were conducted in women with UI. Our study elicits the need to investigate if abnormal bladder neck anatomy, funneling or other signs can predict the outcome of UI after POP surgery. From the available ultrasound volumes, it is possible to examine changes in bladder anatomy postoperatively and the association to women who achieve continence versus those with persistent or de novo incontinence. Additionally, the correlation of bladder neck anatomy to clinical findings and patient reported distress questionnaires can be evaluated. The displacement of anterior wall can mask SUI but not all with cystocele develop UI postoperatively. It would be of value to gather information regarding predictive signs preoperatively to consider concomitant continence surgery in selected patients.

9.3 Adjunct treatments in incontinence management

Estrogen treatment and early initiation of pelvic floor muscle exercise in postmenopausal women with a weak pelvic floor need further evaluation in the treatment of incontinence. Standard PFMT may not be as effective in women with advanced prolapse, demanding a second look on other available treatment options.

In this patient category, we hypothesize that a more rigorous exercise regimen or a combination of adjunct treatments are needed to counteract the effects of complex pelvic floor injuries. Long-term studies of intensive PFMT in women after POP surgery are needed to examine any effects on urinary and colorectal-anal distress and de novo incontinence.

9.4 Can a simple VAS score be used in a clinical setting?

Detailed questionnaires are mostly applicable in research settings. Although these questionnaires are sensitive, they are cumbersome to use in a busy clinical practice. VAS is used in daily clinical work for several conditions. A quick VAS covering all PFDs and grade of bother, helps the clinician to focus on the main complaint as well as mindfulness for unreported symptoms, that may warrant other approaches. We demonstrated that 97% completed a simple VAS questionnaire and only 85% completed the longer PFDI-20. However, VAS has not been validated in POP patients. To be able to implement the easier VAS we need further studies on the correlation of VAS to validated questionnaires and POP-Q.

10.0 REFERENCES

1.   Herschorn S. Female pelvic floor anatomy: the pelvic floor, supporting structures, and pelvic organs. *Rev Urol.* 2004;6 Suppl 5(Suppl 5):S2-S10.
2.   Ashton-Miller JA, DeLancey JO. Functional anatomy of the female pelvic floor. *Ann N Y Acad Sci.* 2007;1101:266-296.
3.   Perucchini D, DeLancey J. Functional Anatomy of the Pelvic Floor and Lower Urinary Tract. In:2008:3-21.
4.   DeLancey JO. The anatomy of the pelvic floor. *Curr Opin Obstet Gynecol.* 1994;6(4):313-316.
5.   Erlichman DB, Kanmaniraja D, Kobi M, Chernyak V. MRI anatomy and pathology of the anal canal. *J Magn Reson Imaging.* 2019;50(4):1018-1032.
6.   Quigley EM. Impact of pregnancy and parturition on the anal sphincters and pelvic floor. *Best Pract Res Clin Gastroenterol.* 2007;21(5):879-891.
7.   Sultan AH, Nugent K. Pathophysiology and nonsurgical treatment of anal incontinence. *BJOG.* 2004;111:84-90.
8.   Palit S, Lunniss PJ, Scott SM. The physiology of human defecation. *Dig Dis Sci.* 2012;57(6):1445-1464.
9.   DeLancey JO. Structural support of the urethra as it relates to stress urinary incontinence: the hammock hypothesis. *Am J Obstet Gynecol.* 1994;170(6):1713-1723.
10.   Miller JM, Ashton-Miller JA, DeLancey JO. A pelvic muscle precontraction can reduce cough-related urine loss in selected women with mild SUI. *J Am Geriatr Soc.* 1998;46(7):870-874.
11.   Volloyhaug I, Morkved S, Salvesen KA. Association between pelvic floor muscle trauma and pelvic organ prolapse 20 years after delivery. *International urogynecology journal.* 2016;27(1):39-45.
12.   Haylen BT, Maher CF, Barber MD, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic organ prolapse (POP). *International urogynecology journal.* 2016;27(2):165-194.
13.   Bump RC, Norton PA. Epidemiology and natural history of pelvic floor dysfunction. *Obstet Gynecol Clin North Am.* 1998;25(4):723-746.
14.   Wu JM, Vaughan CP, Goode PS, et al. Prevalence and trends of symptomatic pelvic floor disorders in U.S. women. *Obstet Gynecol.* 2014;123(1):141-148.
15.   Rortveit G, Subak LL, Thom DH, et al. Urinary incontinence, fecal incontinence and pelvic organ prolapse in a population-based, racially diverse cohort: prevalence and risk factors. *Female Pelvic Med Reconstr Surg.* 2010;16(5):278-283.
16.   Wu JM, Matthews CA, Conover MM, Pate V, Jonsson Funk M. Lifetime risk of stress urinary incontinence or pelvic organ prolapse surgery. *Obstet Gynecol.* 2014;123(6):1201-1206.
17.   Nygaard I, Barber MD, Burgio KL, et al. Prevalence of symptomatic pelvic floor disorders in US women. *JAMA.* 2008;300(11):1311-1316.
18.   Meschia M, Buonaguidi A, Pifarotti P, Somigliana E, Spennacchio M, Amicarelli F. Prevalence of anal incontinence in women with symptoms of urinary incontinence and genital prolapse. *Obstet Gynecol.* 2002;100(4):719-723.
19.   Volloyhaug I, Morkved S, Salvesen O, Salvesen KA. Forceps delivery is associated with increased risk of pelvic organ prolapse and muscle trauma: a cross-sectional study 16-24 years after first delivery. *Ultrasound Obstet Gynecol.* 2015;46(4):487-495.
20.   Ebbesen MH, Hunskaar S, Rortveit G, Hannestad YS. Prevalence, incidence and remission of urinary incontinence in women: longitudinal data from the Norwegian HUNT study (EPINCONT). *BMC Urol.* 2013;13:27-27.
21.   Rømmen K, Schei B, Rydning A, Sultan AH, Mørkved S. Prevalence of anal incontinence among Norwegian women: a cross-sectional study. *BMJ open.* 2012;2(4):e001257.
22.   Kirby AC, Luber KM, Menefee SA. An update on the current and future demand for care of pelvic floor disorders in the United States. *Am J Obstet Gynecol.* 2013;209(6):584.e581-585.

23.   Clayton AH, Valladares Juarez EM. Female Sexual Dysfunction. *Med Clin North Am.* 2019;103(4):681-698.

24.   Bump RC, Mattiasson A, Bo K, et al. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. *Am J Obstet Gynecol.* 1996;175(1):10-17.

25.   Culligan PJ. Nonsurgical Management of Pelvic Organ Prolapse. *Obstet Gynecol.* 2012;119(4):852-860.

26.   Righarts A, Osborne L, Connor J, Gillett W. The prevalence and potential determinants of dysmenorrhoea and other pelvic pain in women: a prospective study. *BJOG.* 2018;125(12):1532-1539.

27.   Speer L, Mushkbar S, Erbele T. Chronic pelvic pain in women. *Am Fam Physician.* 2016;93(5):380-387.

28.   Verbeek M, Hayward L. Pelvic Floor Dysfunction And Its Effect On Quality Of Sexual Life. *Sexual medicine reviews.* 2019;7(4):559-564.

29.   Boreham MK, Richter HE, Kenton KS, et al. Anal incontinence in women presenting for gynecologic care: prevalence, risk factors, and impact upon quality of life. *Am J Obstet Gynecol.* 2005;192(5):1637-1642.

30.   de Mello Portella P, Feldner PC, Jr., da Conceição JC, Castro RA, Sartori MG, Girão MJ. Prevalence of and quality of life related to anal incontinence in women with urinary incontinence and pelvic organ prolapse. *Eur J Obstet Gynecol Reprod Biol.* 2012;160(2):228-231.

31.   Hallock JL, Handa VL. The Epidemiology of Pelvic Floor Disorders and Childbirth: An Update. *Obstet Gynecol Clin North Am.* 2016;43(1):1-13.

32.   Delancey JO, Low L, Miller JM, Patel DA, Tumbarello JA. Graphic integration of causal factors of pelvic floor disorders: an integrated life span model. *Am J Obstet Gynecol.* 2008;199(6):610.e611-615.

33.   Lien K-C, Mooney B, DeLancey JOL, Ashton-Miller JA. Levator ani muscle stretch induced by simulated vaginal birth. *Obstet Gynecol.* 2004;103(1):31-40.

34.   Shek K, Dietz H. Intrapartum risk factors for levator trauma. *BJOG.* 2010;117(12):1485-1492.

35.   Dietz HP, Lanzarone V. Levator trauma after vaginal delivery. *Obstet Gynecol.* 2005;106(4):707-712.

36.   Stær-Jensen J, Siafarikas F, Hilde G, Benth JŠ, Bø K, Engh ME. Postpartum Recovery of Levator Hiatus and Bladder Neck Mobility in Relation to Pregnancy. *Obstet Gynecol.* 2015;125(3):531-539.

37.   Shek KL, Kruger J, Dietz HP. The effect of pregnancy on hiatal dimensions and urethral mobility: an observational study. *International urogynecology journal.* 2012;23(11):1561-1567.

38.   Van Geelen H, Ostergard D, Sand P. A review of the impact of pregnancy and childbirth on pelvic floor function as assessed by objective measurement techniques. *International urogynecology journal.* 2018;29(3):327-338.

39.   Heilbrun ME, Nygaard IE, Lockhart ME, et al. Correlation between levator ani muscle injuries on magnetic resonance imaging and fecal incontinence, pelvic organ prolapse, and urinary incontinence in primiparous women. *Am J Obstet Gynecol.* 2010;202(5):488.e481-486.

40.   Chantarasorn V, Shek KL, Dietz HP. Sonographic detection of puborectalis muscle avulsion is not associated with anal incontinence. *Aust N Z J Obstet Gynaecol.* 2011;51(2):130-135.

41.   Morgan DM, Cardoza P, Guire K, Fenner DE, DeLancey JO. Levator ani defect status and lower urinary tract symptoms in women with pelvic organ prolapse. *International urogynecology journal.* 2010;21(1):47.

42.   Volløyhaug I, Taithongchai A, Van Gruting I, Sultan A, Thakar R. Levator ani muscle morphology and function in women with obstetric anal sphincter injury. *Ultrasound Obstet Gynecol.* 2019;53(3):410-416.

43.   Kamisan Atan I, Lin S, Dietz HP, Herbison P, Wilson PD. It is the first birth that does the damage: a cross-sectional study 20 years after delivery. *International urogynecology journal.* 2018.

44.   Andrews V, Sultan AH, Thakar R, Jones PW. Occult anal sphincter injuries--myth or reality? *BJOG.* 2006;113(2):195-200.

45.   Caudwell-Hall J, Kamisan Atan I, Guzman Rojas R, Langer S, Shek KL, Dietz HP. Atraumatic Normal Vaginal Delivery: How many women get what they want? *Am J Obstet Gynecol.* 2018.

46.   Sideris M, McCaughey T, Hanrahan JG, et al. Risk of obstetric anal sphincter injuries (OASIS) and anal incontinence: A meta-analysis. *European Journal of Obstetrics & Gynecology and Reproductive Biology.* 2020.

47.   Chan SSC, Cheung RYK, Lee LL, Choy RKW, Chung TKH. Longitudinal follow-up of levator ani muscle avulsion: does a second delivery affect it? *Ultrasound Obstet Gynecol.* 2017;50(1):110-115.

48.   Li Y, Shek KL, Subramaniam N, Friedman T, Dietz HP. Parity and anal sphincter trauma. *International urogynecology journal.* 2020;31(3):553-556.

49.   Vaccaro C, Clemons JL. Anal sphincter defects and anal incontinence symptoms after repair of obstetric anal sphincter lacerations in primiparous women. *International urogynecology journal.* 2008;19(11):1503-1508.

50.   Lien KC, Morgan DM, Delancey JO, Ashton-Miller JA. Pudendal nerve stretch during vaginal birth: a 3D computer simulation. *Am J Obstet Gynecol.* 2005;192(5):1669-1676.

51.   Snooks SJ, Swash M, Henry MM, Setchell M. Risk factors in childbirth causing damage to the pelvic floor innervation. *Int J Colorectal Dis.* 1986;1(1):20-24.

52.   Rud T. Urethral pressure profile in continent women from childhood to old age. *Acta Obstet Gynecol Scand.* 1980;59(4):331-335.

53.   Chen CCG, Gatmaitan P, Koepp S, et al. Obesity is associated with increased prevalence and severity of pelvic floor disorders in women considering bariatric surgery. *Surg Obes Relat Dis.* 2009;5(4):411-415.

54.   Cuicchi D, Lombardi R, Cariani S, Leuratti L, Lecce F, Cola B. Clinical and instrumental evaluation of pelvic floor disorders before and after bariatric surgery in obese women. *Surg Obes Relat Dis.* 2013;9(1):69-75.

55.   Lee JA, Johns TS, Melamed ML, et al. Associations between Socioeconomic Status and Urge Urinary Incontinence: An Analysis of NHANES 2005 to 2016. *J Urol.* 2020;203(2):379-384.

56.   Bump RC, McClish DK. Cigarette smoking and urinary incontinence in women. *Am J Obstet Gynecol.* 1992;167(5):1213-1218.

57.   Rao SSC. Pathophysiology of adult fecal incontinence. *Gastroenterology.* 2004;126:S14-S22.

58.   Friedman T, Eslick GD, Dietz HP. Risk factors for prolapse recurrence: systematic review and meta-analysis. *International urogynecology journal.* 2018;29(1):13-21.

59.   Barber MD, Walters MD, Bump RC. Short forms of two condition-specific quality-of-life questionnaires for women with pelvic floor disorders (PFDI-20 and PFIQ-7). *Am J Obstet Gynecol.* 2005;193(1):103-113.

60.   Vaizey CJ, Carapeti E, Cahill JA, Kamm MA. Prospective comparison of faecal incontinence grading systems. *Gut.* 1999;44(1):77-80.

61.   Sandvik H, Hunskaar S, Seim A, Hermstad R, Vanvik A, Bratt H. Validation of a severity index in female urinary incontinence and its implementation in an epidemiological survey. *J Epidemiol Community Health.* 1993;47(6):497-499.

62.   Ulrich D, Guzman Rojas R, Dietz HP, Mann K, Trutnovsky G. Use of a visual analog scale for evaluation of bother from pelvic organ prolapse. *Ultrasound Obstet Gynecol.* 2014;43(6):693-697.

63.   Abrams P, Avery K, Gardener N, Donovan J, Board IA. The international consultation on incontinence modular questionnaire: www. iciq. net. *The Journal of urology.* 2006;175(3):1063-1066.

64. Price N, Jackson S, Avery K, Brookes S, Abrams P. Development and psychometric evaluation of the ICIQ Vaginal Symptoms Questionnaire: the ICIQ-VS. *BJOG.* 2006;113(6):700-712.

65. Cotterill N, Norton C, Avery KNL, Abrams P, Donovan JL. Psychometric Evaluation of a New Patient-Completed Questionnaire for Evaluating Anal Incontinence Symptoms and Impact on Quality of Life: The ICIQ-B. *Dis Colon Rectum.* 2011;54(10):1235-1250.

66. Kulseng-Hanssen S, Borstad E. The development of a questionnaire to measure the severity of symptoms and the quality of life before and after surgery for stress incontinence. *BJOG.* 2003;110(11):983-988.

67. Dietz HP, Shek KL. The quantification of levator muscle resting tone by digital assessment. *Int Urogynecol J Pelvic Floor Dysfunct.* 2008;19(11):1489-1493.

68. Laycock J, Jerwood D. Pelvic Floor Muscle Assessment: The PERFECT Scheme. *Physiotherapy.* 2001;87(12):631-642.

69. McKey PL, Dougherty MC. The circumvaginal musculature: correlation between pressure and physical assessment. *Nurs Res.* 1986;35(5):307-309.

70. Enck P, Vodušek DB. Electromyography of pelvic floor muscles. *J Electromyogr Kinesiol.* 2006;16(6):568-577.

71. Rosier PFWM, Schaefer W, Lose G, et al. International Continence Society Good Urodynamic Practices and Terms 2016: Urodynamics, uroflowmetry, cystometry, and pressure-flow study. *Neurourol Urodyn.* 2017;36(5):1243-1260.

72. Drake MJ, Doumouchtsis SK, Hashim H, Gammie A. Fundamentals of urodynamic practice, based on International Continence Society good urodynamic practices recommendations. *Neurourol Urodyn.* 2018;37(S6):S50-s60.

73. Dietz H. Ultrasound imaging of the pelvic floor. Part II: three-dimensional or volume imaging. *Ultrasound Obstet Gynecol.* 2004;23(6):615-625.

74. Dietz H. Ultrasound imaging of the pelvic floor. Part I: two-dimensional aspects. *Ultrasound Obstet Gynecol.* 2004;23(1):80-92.

75. Nyhus MO, Oversand SH, Salvesen O, Salvesen KA, Mathew S, Volloyhaug I. Ultrasound assessment of pelvic floor muscle contraction: reliability and development of an ultrasound-based contraction scale. *Ultrasound Obstet Gynecol.* 2020;55(1):125-131.

76. V[o]lløyhaug I, Mørkved S, Salvesen Ø, Salvesen K. Assessment of pelvic floor muscle contraction with palpation, perineometry and transperineal ultrasound: a cross-sectional study. *Ultrasound Obstet Gynecol.* 2016;47(6):768-773.

77. Brækken IH, Majida M, Ellstrøm-Engh M, Dietz HP, Umek W, Bø K. Test–retest and intra-observer repeatability of two-, three-and four-dimensional perineal ultrasound of pelvic floor muscle anatomy and function. *International urogynecology journal.* 2008;19(2):227-235.

78. van Delft K, Thakar R, Sultan AH. Pelvic floor muscle contractility: digital assessment vs transperineal ultrasound. *Ultrasound Obstet Gynecol.* 2015;45(2):217-222.

79. Salsi G, Cataneo I, Dodaro G, et al. Three-dimensional/four-dimensional transperineal ultrasound: clinical utility and future prospects. *International Journal of Women's Health.* 2017;9:643-656.

80. Dietz H, Shek C, Clarke B. Biometry of the pubovisceral muscle and levator hiatus by three-dimensional pelvic floor ultrasound. *Ultrasound Obstet Gynecol.* 2005;25(6):580-585.

81. Dietz HP, Bernardo MJ, Kirby A, Shek KL. Minimal criteria for the diagnosis of avulsion of the puborectalis muscle by tomographic ultrasound. *International urogynecology journal.* 2011;22(6):699-704.

82. Law PJ, Bartram CI. Anal endosonography: Technique and normal anatomy. *Gastrointest Radiol.* 1989;14(1):349-353.

83. Starck M, Bohe M, Valentin L. Results of endosonographic imaging of the anal sphincter 2–7 days after primary repair of third- or fourth-degree obstetric sphincter tears. *Ultrasound Obstet Gynecol.* 2003;22(6):609-615.

84. Sultan A, Kamm M, Talbot I, Nicholls R, Bartram C. Anal endosonography for identifying external sphincter defects confirmed histologically. *Br J Surg.* 1994;81(3):463-465.

85.   Abdool Z, Sultan AH, Thakar R. Ultrasound imaging of the anal sphincter complex: a review. *The British Journal of Radiology.* 2012;85(1015):865-875.

86.   Norderval S, Markskog A, Rossaak K, Vonen B. Correlation between anal sphincter defects and anal incontinence following obstetric sphincter tears: assessment using scoring systems for sonographic classification of defects. *Ultrasound Obstet Gynecol.* 2008;31(1):78-84.

87.   Scheer I, Thakar R, Sultan AH. Mode of delivery after previous obstetric anal sphincter injuries (OASIS)—a reappraisal? *International urogynecology journal.* 2009;20(9):1095-1101.

88.   Volløyhaug I, Taithongchai A, Arendsen L, van Gruting I, Sultan AH, Thakar R. Is endoanal, introital or transperineal ultrasound diagnosis of sphincter defects more strongly associated with anal incontinence? *International urogynecology journal.* 2020:1-8.

89.   Taithongchai A, van Gruting IM, Volløyhaug I, Arendsen LP, Sultan AH, Thakar R. Comparing the diagnostic accuracy of 3 ultrasound modalities for diagnosing obstetric anal sphincter injuries. *Am J Obstet Gynecol.* 2019;221(2):134. e131-134. e139.

90.   Guzman Rojas RA, Shek KL, Langer SM, Dietz HP. Prevalence of anal sphincter injury in primiparous women. *Ultrasound Obstet Gynecol.* 2013;42(4):461-466.

91.   Timor-Tritsch IE, Monteagudo A, Smilen SW, Porges RF, Avizova E. Simple ultrasound evaluation of the anal sphincter in female patients using a transvaginal transducer. *Ultrasound Obstet Gynecol.* 2005;25(2):177-183.

92.   Turel Fatakia F, Subramaniam N, Bienkiewicz J, Friedman T, Dietz HP. How repeatable is assessment of external anal sphincter trauma by exoanal 4D ultrasound? *Ultrasound Obstet Gynecol.* 2019;53(6):836-840.

93.   Turel F, Shek KL, Dietz HP. How Valid Is Tomographic Ultrasound Imaging in Diagnosing Levator and Anal Sphincter Trauma? *J Ultrasound Med.* 2019;38(4):889-894.

94.   Guzmán Rojas RA, Kamisan Atan I, Shek KL, Dietz HP. Anal sphincter trauma and anal incontinence in urogynecological patients. *Ultrasound Obstet Gynecol.* 2015;46(3):363-366.

95.   Dietz HP. Exoanal Imaging of the Anal Sphincters. *J Ultrasound Med.* 2018;37(1):263-280.

96.   Guzman Rojas RA, Salvesen KA, Volloyhaug I. Anal sphincter defects and fecal incontinence 15-24 years after first delivery: a cross-sectional study. *Ultrasound Obstet Gynecol.* 2018;51(5):677-683.

97.   Dietz HP, Nazemian K, Shek KL, Martin A. Can urodynamic stress incontinence be diagnosed by ultrasound? *International urogynecology journal.* 2013;24(8):1399-1403.

98.   Volloyhaug I, van Gruting I, van Delft K, Sultan AH, Thakar R. Is bladder neck and urethral mobility associated with urinary incontinence and mode of delivery 4 years after childbirth? *Neurourol Urodyn.* 2017;36(5):1403-1410.

99.   Tunn R, Goldammer K, Gauruder-Burmester A, Wildt B, Beyersdorff D. Pathogenesis of urethral funneling in women with stress urinary incontinence assessed by introital ultrasound. *Ultrasound Obstet Gynecol.* 2005;26(3):287-292.

100.   Dietz HP, Clarke B, Herbison P. Bladder Neck Mobility and Urethral Closure Pressure as Predictors of Genuine Stress Incontinence. *International urogynecology journal.* 2002;13(5):289-293.

101.   Naranjo-Ortiz C, Shek KL, Martin AJ, Dietz HP. What is normal bladder neck anatomy? *International urogynecology journal.* 2016;27(6):945-950.

102.   Dietz HP, Wilson PD. Anatomical assessment of the bladder outlet and proximal urethra using ultrasound and videocystourethrography. *International urogynecology journal.* 1998;9(6):365-369.

103.   Huang W-C, Yang J-M. Bladder neck funneling on ultrasound cystourethrography in primary stress urinary incontinence: a sign associated with urethral hypermobility and intrinsic sphincter deficiency. *Urology.* 2003;61(5):936-941.

104.   Pregazzi R, Sartore A, Bortoli P, Grimaldi E, Troiano L, Guaschino S. Perineal ultrasound evaluation of urethral angle and bladder neck mobility in women with stress urinary incontinence. *BJOG.* 2002;109(7):821-827.

105. Lammers K, Kluivers KB, Vierhout ME, Prokop M, Fütterer JJ. Inter- and intraobserver reliability for diagnosing levator ani changes on magnetic resonance imaging. *Ultrasound Obstet Gynecol.* 2013;42(3):347-352.

106. Woodley SJ, Lawrenson P, Boyle R, et al. Pelvic floor muscle training for preventing and treating urinary and faecal incontinence in antenatal and postnatal women. *Cochrane Database Syst Rev.* 2020;5(5):CD007471.

107. Ellerkmann RM, Cundiff GW, Melick CF, Nihira MA, Leffler K, Bent AE. Correlation of symptoms with location and severity of pelvic organ prolapse. *Am J Obstet Gynecol.* 2001;185(6):1332-1338.

108. Lukacz ES, Santiago-Lastra Y, Albo ME, Brubaker L. Urinary Incontinence in Women: A Review. *JAMA.* 2017;318(16):1592-1604.

109. Carrington E, Evers J, Grossi U, et al. A systematic review of sacral nerve stimulation mechanisms in the treatment of fecal incontinence and constipation. *Neurogastroenterol Motil.* 2014;26(9):1222-1237.

110. Burgio KL, Kraus SR, Menefee S, et al. Behavioral therapy to enable women with urge incontinence to discontinue drug treatment: a randomized trial. *Ann Intern Med.* 2008;149(3):161-169.

111. Wu YM, Welk B. Revisiting current treatment options for stress urinary incontinence and pelvic organ prolapse: a contemporary literature review. *Res Rep Urol.* 2019;11:179-188.

112. Lipp A, Shaw C, Glavind K. Mechanical devices for urinary incontinence in women. *Cochrane Database Syst Rev.* 2014(12):CD001756.

113. Kegel AH. Progressive resistance exercise in the functional restoration of the perineal muscles. *Am J Obstet Gynecol.* 1948;56(2):238-248.

114. Skelton DA, Young A, Greig CA, Malbut KE. Effects of resistance training on strength, power, and selected functional abilities of women aged 75 and older. *J Am Geriatr Soc.* 1995;43(10):1081-1087.

115. Garcia-Sanchez E, Avila-Gandia V, Lopez-Roman J, Martinez-Rodriguez A, Rubio-Arias JA. What Pelvic Floor Muscle Training Load is Optimal in Minimizing Urine Loss in Women with Stress Urinary Incontinence? A Systematic Review and Meta-Analysis. *Int J Environ Res Public Health.* 2019;16(22).

116. Dumoulin C, Glazener C, Jenkinson D. Determining the optimal pelvic floor muscle training regimen for women with stress urinary incontinence. *Neurourol Urodyn.* 2011;30(5):746-753.

117. McLean L, Varette K, Gentilcore-Saulnier E, Harvey MA, Baker K, Sauerbrei E. Pelvic floor muscle training in women with stress urinary incontinence causes hypertrophy of the urethral sphincters and reduces bladder neck mobility during coughing. *Neurourol Urodyn.* 2013;32(8):1096-1102.

118. Dumoulin C, Cacciari LP, Hay-Smith EJC. Pelvic floor muscle training versus no treatment, or inactive control treatments, for urinary incontinence in women. *Cochrane Database Syst Rev.* 2018;10(10):CD005654.

119. Braekken IH, Majida M, Engh ME, Bo K. Can pelvic floor muscle training reverse pelvic organ prolapse and reduce prolapse symptoms? An assessor-blinded, randomized, controlled trial. *Am J Obstet Gynecol.* 2010;203(2):170.e171-177.

120. Radzimińska A, Strączyńska A, Weber-Rajek M, Styczyńska H, Strojek K, Piekorz Z. The impact of pelvic floor muscle training on the quality of life of women with urinary incontinence: a systematic literature review. *Clin Interv Aging.* 2018;13:957-965.

121. Li C, Gong Y, Wang B. The efficacy of pelvic floor muscle training for pelvic organ prolapse: a systematic review and meta-analysis. *International urogynecology journal.* 2016;27(7):981-992.

122. Hagen S, Stark D, Glazener C, et al. Individualised pelvic floor muscle training in women with pelvic organ prolapse (POPPY): a multicentre randomised controlled trial. *The Lancet.* 2014;383(9919):796-806.

123.   Bo K. Pelvic floor muscle training in treatment of female stress urinary incontinence, pelvic organ prolapse and sexual dysfunction. *World J Urol.* 2012;30(4):437-443.

124.   Zubieta M, Carr RL, Drake MJ, Bø K. Influence of voluntary pelvic floor muscle contraction and pelvic floor muscle training on urethral closure pressures: a systematic literature review. *International urogynecology journal.* 2016;27(5):687-696.

125.   Ayeleke RO, Hay-Smith EJ, Omar MI. Pelvic floor muscle training added to another active treatment versus the same active treatment alone for urinary incontinence in women. *Cochrane Database Syst Rev.* 2015;2015(11):Cd010551.

126.   Sigurdardottir T, Steingrimsdottir T, Geirsson RT, Halldorsson TI, Aspelund T, Bo K. Can postpartum pelvic floor muscle training reduce urinary and anal incontinence?: An assessor-blinded randomized controlled trial. *Am J Obstet Gynecol.* 2020;222(3):247 e241-e248.

127.   Stafne SN, Salvesen KA, Romundstad PR, Torjusen IH, Morkved S. Does regular exercise including pelvic floor muscle training prevent urinary and anal incontinence during pregnancy? A randomised controlled trial. *BJOG.* 2012;119(10):1270-1280.

128.   Hilde G, Staer-Jensen J, Siafarikas F, Gjestland K, Ellström Engh M, Bø K. How well can pelvic floor muscles with major defects contract? A cross-sectional comparative study 6 weeks after delivery using transperineal 3D/4D ultrasound and manometer. *BJOG.* 2013;120(11):1423-1429.

129.   Tibaek S, Dehlendorff C. Pelvic floor muscle function in women with pelvic floor dysfunction: a retrospective chart review, 1992-2008. *International urogynecology journal.* 2014;25(5):663-669.

130.   Nyhus MO, Mathew S, Salvesen O, Salvesen KA, Stafne S, Volloyhaug I. Effect of preoperative pelvic floor muscle training on pelvic floor muscle contraction and symptomatic and anatomical pelvic organ prolapse after surgery: randomized controlled trial. *Ultrasound Obstet Gynecol.* 2020;56(1):28-36.

131.   Zhang F-W, Wei F, Wang H-L, et al. Does pelvic floor muscle training augment the effect of surgery in women with pelvic organ prolapse? A systematic review of randomized controlled trials. *Neurourol Urodyn.* 2016;35(6):666-674.

132.   Duarte TB, Bo K, Brito LGO, et al. Perioperative pelvic floor muscle training did not improve outcomes in women undergoing pelvic organ prolapse surgery: a randomised trial. *J Physiother.* 2020;66(1):27-32.

133.   Haya N, Feiner B, Baessler K, Christmann-Schmid C, Maher C. Perioperative interventions in pelvic organ prolapse surgery. *Cochrane Database Syst Rev.* 2018;8(8):Cd013105.

134.   Jarvis SK, Hallam TK, Lujic S, Abbott JA, Vancaillie TG. Peri-operative physiotherapy improves outcomes for women undergoing incontinence and or prolapse surgery: Results of a randomised controlled trial. *Aust N Z J Obstet Gynaecol.* 2005;45(4):300-303.

135.   McClurg D, Hilton P, Dolan L, et al. Pelvic floor muscle training as an adjunct to prolapse surgery: a randomised feasibility study. *International urogynecology journal.* 2014;25(7):883-891.

136.   Weber M, Kleijn M, Langendam M, Limpens J, Heineman M, Roovers J. Local oestrogen for pelvic floor disorders: a systematic review. *PLoS One.* 2015;10(9):e0136265.

137.   Dietz HP, Socha M, Atan IK, Subramaniam N. Does estrogen deprivation affect pelvic floor muscle contractility? *International urogynecology journal.* 2020;31(1):191-196.

138.   Kalder M, Pantazis K, Dinas K, Albert U-S, Heilmaier C, Kostev K. Discontinuation of treatment using anticholinergic medications in patients with urinary incontinence. *Obstet Gynecol.* 2014;124(4):794-800.

139.   Wagg A, Staskin D, Engel E, Herschorn S, Kristy RM, Schermer CR. Efficacy, safety, and tolerability of mirabegron in patients aged≥ 65 yr with overactive bladder wet: a phase IV, double-blind, randomised, placebo-controlled study (PILLAR). *Eur Urol.* 2020;77(2):211-220.

140.   Dwyer L, Weaver E, Rajai A, Cox S, Reid F. "Voice your choice": a study of women's choice of surgery for primary stress urinary incontinence. *International urogynecology journal.* 2019:1-9.

141. Oversand SH, Staff AC, Vølløyhaug I, Svenningsen R. Impact of levator muscle avulsions on Manchester procedure outcomes in pelvic organ prolapse surgery. *Acta Obstet Gynecol Scand.* 2019;98(8):1046-1054.

142. Maher C, Feiner B, Baessler K, Schmid C. Surgical management of pelvic organ prolapse in women. *Cochrane Database Syst Rev.* 2013(4):Cd004014.

143. Germain A, Thibault F, Galifet M, et al. Long-term outcomes after totally robotic sacrocolpopexy for treatment of pelvic organ prolapse. *Surg Endosc.* 2013;27(2):525-529.

144. Mangir N, Roman S, Chapple CR, MacNeil S. Complications related to use of mesh implants in surgical treatment of stress urinary incontinence and pelvic organ prolapse: infection or inflammation? *World J Urol.* 2020;38(1):73-80.

145. Itkonen Freitas AM, Mentula M, Rahkola-Soisalo P, Tulokas S, Mikkola TS. Tension-Free Vaginal Tape Surgery versus Polyacrylamide Hydrogel Injection for Primary Stress Urinary Incontinence: A Randomized Clinical Trial. *J Urol.* 2020;203(2):372-378.

146. Olivera CK, Meriwether K, El-Nashar S, et al. Nonantimuscarinic treatment for overactive bladder: a systematic review. *Am J Obstet Gynecol.* 2016;215(1):34-57.

147. Guerra F, La Torre M, Giuliani G, et al. Long-term evaluation of bulking agents for the treatment of fecal incontinence: clinical outcomes and ultrasound evidence. *Tech Coloproctol.* 2015;19(1):23-27.

148. Brown SR, Wadhawan H, Nelson RL. Surgery for faecal incontinence in adults. *Cochrane Database Syst Rev.* 2010(9):CD001757.

149. van Delft K, Sultan AH, Thakar R, Schwertner-Tiepelmann N, Kluivers K. The relationship between postpartum levator ani muscle avulsion and signs and symptoms of pelvic floor dysfunction. *BJOG.* 2014;121(9):1164-1171.

150. Frawley HC, Phillips BA, Bø K, Galea MP. Physiotherapy as an adjunct to prolapse surgery: an assessor-blinded randomized controlled trial. *Neurourol Urodyn.* 2010;29(5):719-725.

151. Volloyhaug I, Morkved S, Salvesen O, Salvesen K. Pelvic organ prolapse and incontinence 15-23 years after first delivery: a cross-sectional study. *BJOG.* 2015;122(7):964-971.

152. Bo K, Frawley HC, Haylen BT, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for the conservative and nonpharmacological management of female pelvic floor dysfunction. *International urogynecology journal.* 2017;28(2):191-213.

153. Bø K, Talseth T, Holme I. Single blind, randomised controlled trial of pelvic floor exercises, electrical stimulation, vaginal cones, and no treatment in management of genuine stress incontinence in women. *BMJ.* 1999;318(7182):487-493.

154. Dumoulin C, Hay-Smith J, Frawley H, et al. 2014 consensus statement on improving pelvic floor muscle training adherence: International Continence Society 2011 State-of-the-Science Seminar. *Neurourol Urodyn.* 2015;34(7):600-605.

155. Teig CJ, Grotle M, Bond MJ, et al. Norwegian translation, and validation, of the Pelvic Floor Distress Inventory (PFDI-20) and the Pelvic Floor Impact Questionnaire (PFIQ-7). *International urogynecology journal.* 2017;28(7):1005-1017.

156. Blomquist JL, Muñoz A, Carroll M, Handa VL. Association of Delivery Mode With Pelvic Floor Disorders After Childbirth. *JAMA.* 2018;320(23):2438-2447.

157. Dietz HP, Kirby A, Shek KL, Bedwell PJ. Does avulsion of the puborectalis muscle affect bladder function? *Int Urogynecol J Pelvic Floor Dysfunct.* 2009;20(8):967-972.

158. DeLancey JO, Trowbridge ER, Miller JM, et al. Stress urinary incontinence: relative importance of urethral support and urethral closure pressure. *The Journal of urology.* 2008;179(6):2286-2290.

159. Handa VL, Blomquist JL, Roem J, Muñoz A, Dietz HP. Pelvic floor disorders after obstetric avulsion of the levator ani muscle. *Female Pelvic Med Reconstr Surg.* 2019;25(1):3-7.

160. Macura KJ, Thompson RE, Bluemke DA, Genadry R. Magnetic resonance imaging in assessment of stress urinary incontinence in women: Parameters differentiating urethral

hypermobility and intrinsic sphincter deficiency. *World journal of radiology.* 2015;7(11):394-404.

161. Pędraszewski P, Wlaźlak E, Wlaźlak W, Krzycka M, Pająk P, Surkont G. The role of TVT position in relation to the pubic symphysis in eliminating the symptoms of stress urinary incontinence and urethral funneling. *Journal of ultrasonography.* 2019;19(78):207-211.

162. da Silva GM, Gurland B, Sleemi A, Levy G. Posterior vaginal wall prolapse does not correlate with fecal symptoms or objective measures of anorectal function. *Am J Obstet Gynecol.* 2006;195(6):1742-1747.

163. Simillis C, Lal N, Pellino G, et al. A systematic review and network meta-analysis comparing treatments for faecal incontinence. *Int J Surg.* 2019;66:37-47.

164. Kesmodel US. Cross-sectional studies - what are they good for? *Acta Obstet Gynecol Scand.* 2018;97(4):388-393.

165. Levin KA. Study design III: Cross-sectional studies. *Evidence-based dentistry.* 2006;7(1):24-25.

166. Gillor M, Shek KL, Dietz HP. How comparable is clinical grading of obstetric anal sphincter injury with that determined by four-dimensional translabial ultrasound? *Ultrasound Obstet Gynecol.* 2020;56(4):618-623.

167. Cornelia L, Stephan B, Michel B, Antoine W, Felix K. Trans-perineal versus endo-anal ultrasound in the detection of anal sphincter tears. *European Journal of Obstetrics & Gynecology and Reproductive Biology.* 2002;103(1):79-82.

168. Felt-Bersma RJ, Sloots CE, Poen AC, Cuesta MA, Meuwissen SG. Rectal compliance as a routine measurement: extreme volumes have direct clinical impact and normal volumes exclude rectum as a problem. *Dis Colon Rectum.* 2000;43(12):1732-1738.

169. Ugianskiene A, Kjærgaard N, Larsen T, Glavind K. What happens to urinary incontinence after pelvic organ prolapse surgery? *International urogynecology journal.* 2019;30(7):1147-1152.

11.0 PAPERS

Paper 1

Paper 2

Paper 3

1

ORIGINAL CLINICAL ARTICLE

Neurourology Urodynamics ICS SUFU WILEY

Levator ani muscle injury and risk for urinary and fecal incontinence in parous women from a normal population, a cross-sectional study

Seema Mathew[1,2] | Rodrigo A. Guzmán Rojas[3,4] | Kjell A. Salvesen[1,2] | Ingrid Volløyhaug[1,2]

[1]Department of Gynecology and Obstetrics, St. Olavs University Hospital, Trondheim, Norway

[2]Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway

[3]Departamento de Ginecología y Obstetricia, Facultad de Medicina, Clínica Alemana-Universidad del Desarrollo, Santiago, Chile

[4]Departamento de Ginecología y Obstetricia, Hospital Clínico de la Universidad de Chile, Santiago, Chile

Correspondence
Seema Mathew, Department of Gynecology and Obstetrics, St. Olavs University Hospital, Postboks 3250 Torgarden, 7006 Trondheim, Norway.
Email: Seema.Mathew@stolav.no

Abstract

Aims: To study possible associations between levator ani muscle (LAM) injury and urinary incontinence (UI) and fecal incontinence (FI) and possible associations between bladder neck descent (BND), urethral funneling, and UI.

Methods: A cross-sectional study of 608 women with first delivery in 1990 to 1997 assessed in 2013 to 2014. The Urinary Distress Inventory (UDI-6) and Colorectal Anal Distress Inventory (CRADI-8) were used to quantify symptoms (range, 0-100). The proportion of women with UI and FI was calculated. LAM injury, BND ≥25 mm, and funneling were diagnosed with transperineal ultrasound. Women with LAM injury, BND, and urethral funneling were compared to those without, using the Mann-Whitney U test (symptom scores) and multiple logistic regression analysis (UI and FI).

Results: Four-hundred ninety-three (81%) women had intact LAM and 113 (19%) had LAM injury. They had similar median (range) UDI-6 score 8.3 (0-75) vs 4.2 (0-62.5), $P = .35$, and CRADI-8 score 6.3 (0-78.1) vs 6.3 (0-62.5), $P = .90$. Three hundred eleven out of six hundred (52%) women had UI and 65 of 594 (11%) had FI. This was similar for women with intact vs injured LAM; UI 53% vs 49%, $P = .67$; FI 11% vs 12%, $P = .44$ and with and without BND; stress UI 42% vs 42%, $P = .93$; urge UI 29% vs 35%, $P = .34$. Stress UI was more common in women with urethral funneling (50% vs 40%), odds ratio 1.56 (95% confidence interval: 1.03-2.37), $P = .04$.

Conclusion: We found no associations between LAM injury and symptoms of UI and FI 15 to 24 years after the first delivery, but urethral funneling was associated with stress UI.

KEYWORDS
fecal incontinence, levator ani muscle, pelvic floor, ultrasound imaging, urinary bladder, urinary incontinence

1 | INTRODUCTION

Pelvic floor disorders (PFD) affect a large proportion of adult women with an estimated prevalence of 16% to 69% for urinary incontinence (UI) and 6% to 9% for fecal incontinence (FI) in population-based studies.[1,2] The prevalence of UI and FI increases with advancing age, but the etiology is believed to be multifactorial.[3,4] Pregnancy, vaginal delivery, parity, smoking, and body mass index (BMI) are additional risk factors for developing PFD.[5,6]

The levator ani muscle (LAM) is subjected to excessive tension and stretch during vaginal delivery.[6] Previous studies have demonstrated a strong association between LAM injury, occurring during vaginal delivery, and symptoms and signs of pelvic organ prolapse.[7,8] Loss of bladder neck and urethral support is believed to be important for developing UI.[9] Since LAM injury is closely associated with prolapse in the anterior vaginal wall, it is plausible that this may influence the bladder neck and urethral support. Obstetric anal sphincter tear is strongly associated with the development of FI, but the loss of support to the rectum caused by a LAM injury may also contribute.[10] However, only a few studies have investigated a possible association between LAM injury and FI and UI, and most of them were conducted in the early postpartum period.[8,11,12] There is contrasting evidence regarding the association between LAM injury and UI and FI in later life, and the influence of LAM injury on UI and FI several years after delivery needs to be addressed.[11,13,14]

Previous studies have demonstrated an association between stress urinary incontinence (SUI) and bladder neck descent (BND) and urethral mobility.[9,15] These studies have shown that SUI is associated with urethral hypermobility in urogynecological populations, but women from a normal population have not been examined.[9,15] Loss of bladder neck support can be seen as urethral funneling on ultrasound[16] but any association with UI has been sparsely studied.

Our primary aim was to study a possible association between LAM injury and symptoms of UI and FI in a general population of women 15 to 24 years after first delivery. Our secondary aim was to examine a possible association between BND, urethral funneling, and UI.

2 | MATERIALS AND METHODS

This is a secondary analysis of a cross-sectional study of 608 women with first delivery at Trondheim University Hospital, Norway, between 1 January 1990 and 31 December 1997. The primary aim of this study was to examine differences in PFD and LAM injury after different modes of delivery, and results have been published elsewhere.[5] Women who were still alive and had a postal address in Norway in 2013 were identified from the Hospital Patient Administrative System. All women who underwent operative vaginal and cesarean deliveries from January to December and normal vaginal deliveries from January to July of each calendar year were invited to participate in the study. Following the inclusion criteria of the parent study, participants may have had cesarean delivery after normal or operative vaginal delivery, but no vaginal delivery after cesarean, and no operative vaginal delivery after normal delivery.[5] Exclusion criteria were stillbirth, breech delivery, and infant birth weight less than 2000 g at the index birth. However, they were not excluded if these conditions occurred in subsequent pregnancies. Flowchart of the study population is presented in Figure 1. The study was approved by the Regional Committee for Medical and Health Research Ethics (REK midt 2012/666) and registered in clinical-trials.gov NCT01766193. Written informed consent was obtained from all study participants.

Information about infant birth weight, parity, and perineal tears was obtained from the Norwegian Medical Birth Registry. All study participants answered a postal questionnaire regarding height, weight, any previous incontinence surgery, and a Norwegian translation of the Pelvic Floor Distress Inventory (PFDI-20).[17] For quantification of symptoms we used the subscores from the
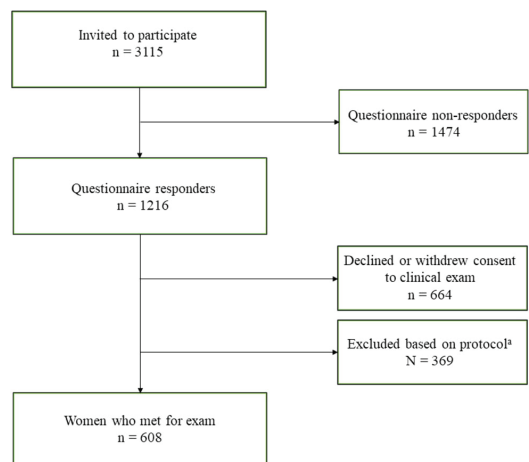

FIGURE 1 Flowchart of the study population.[a] Three-hundred sixty nine women were excluded based on the protocol of parent study[7,19] (due to operative vaginal delivery after a cesarean or normal vaginal delivery or lived too far from Trondheim in 2013 or unable to meet for the exam during inclusion period)
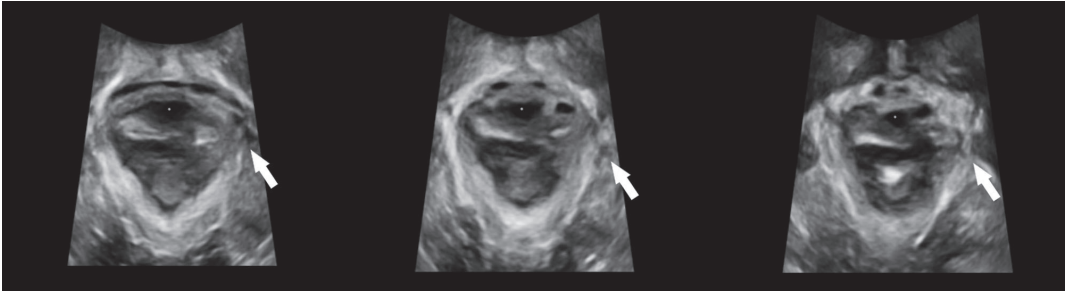
FIGURE 2 Left sided levator ani muscle (LAM) injury (white arrow) on tomographic ultrasound imaging at maximal levator contraction. Intact LAM on the right side

Urinary Distress Inventory (UDI-6) and Colorectal Anal Distress Inventory (CRADI-8), range, 0 to 100.[17] We also registered the proportion of women with urge urinary incontinence (UUI), SUI, and leakage of loose or formed stool, when answering "yes" to the questions: "Do you usually experience urine leakage associated with a feeling of urgency, ie, a strong sensation of needing to go to the bathroom?", "Do you usually experience urine leakage related to coughing, sneezing, or laughing?," "Do you usually loose stool beyond your control if your stool is well-formed?," "Do you usually loose stool beyond your control if your stool is loose?." The proportion of women with any UI or FI was calculated, including women who had undergone any previous incontinence surgery, as some of them were now asymptomatic.

Women living in both urban and rural areas who responded to the questionnaire, who still lived within the referral districts for Trondheim University Hospital and consented to clinical examination, were invited to a clinical exam including transperineal ultrasound (Figure 1). They met with empty urinary bladder and bowel, which was confirmed during the ultrasound examination. They were asked to withhold any information regarding previous deliveries, prolapse and incontinence symptoms, pelvic floor muscle exercise, and gynecological surgery until the examination had been completed. They were examined in the supine position in a gynecological examination chair,

with knees and hips semiflexed and abducted. Three-dimensional (3D)/4D ultrasound volumes of the pelvic floor and anal sphincter muscles were acquired with a GE Voluson S6 device (GE Medical Systems, Zipf, Austria) using the RAB 4-8RS abdominal 3D probe and acquisition angle of 85°. Three volumes were acquired during pelvic floor muscle contraction and at Valsalva.

Offline analysis of the ultrasound volumes was performed 6 to 24 months after the ultrasound scan on a computer using the 4D view Version 14 Ext.0 (GE Healthcare, Austria) software, blinded to all clinical data. Tomographic ultrasound imaging was used to identify significant LAM injury at pelvic floor muscle contraction. A significant LAM injury was diagnosed if all three central slices; the slice in the plane of minimal hiatal dimensions and the slices 2.5 and 5.0 mm cranial to this, showed abnormal muscle insertion (Figure 2).[18] Injury was diagnosed as unilateral or bilateral, and the number of women with significant levator injury (unilateral or bilateral) was registered. A defect of the external or internal anal sphincter of ≥30° in at least four of six slices on tomographic ultrasound imaging was considered a significant defect.[19] BND was assessed in the midsagittal view, see Figure 3. A horizontal line was drawn from the posterior-inferior margin of the pubic symphysis, and the distance from the bladder neck to this horizontal line was measured at rest and Valsalva. BND was calculated as the
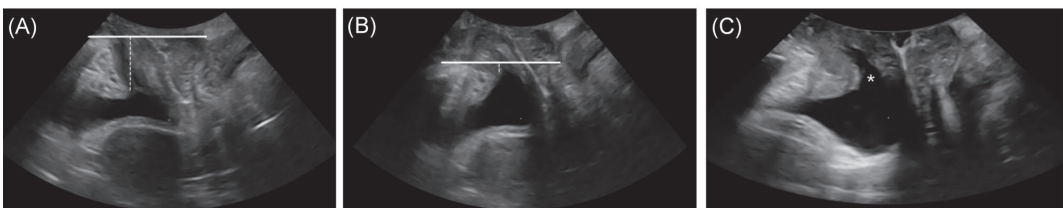

FIGURE 3 Bladder neck descent is measured as the difference between (A) rest and (B) Valsalva. The horizontal solid line is drawn through the inferior-posterior level of the symphysis pubis and the dashed vertical lines show the distance to the bladder neck. (C) Urethral funneling (asterisk) is seen as a dilatation of the proximal urethra at Valsalva

difference between rest and at maximum Valsalva. Earlier studies have suggested that SUI is associated with BND ≥25 mm, hence we used this value as a cut off for significant BND.[9] Finally, the number of women displaying urethral funneling, ie, dilatation of the proximal urethra at the urethrovesical junction during Valsalva, was noted, see Figure 3.[16]

2.1 | Statistical analyses

We used SPSS version 25 (SPSS Inc, Chicago, IL) to perform statistical analysis and $P < .05$ was considered statistically significant. The symptom scores were not normally distributed. The Mann-Whitney U test was used to compare symptoms between women with injured (unilateral or bilateral) and intact LAM. We performed a subanalysis comparing women with bilateral injury to those with intact LAM. A multiple logistic regression analysis was used to calculate the adjusted odds ratio (aOR) for SUI, UUI, and any UI (including previous surgery) comparing women with intact and injured LAM, adjusting for age, BMI, parity, infant birth weight, and cystocele (≥stage 2). Multiple logistic regression analysis was also used to calculate the aOR for FI (including previous surgery) for women with injured vs intact LAM adjusting for the variables above (except cystocele) and any significant external or internal anal sphincter defect on ultrasound. Furthermore, we calculated the aOR for UUI and SUI for women with and without significant BND and urethral funneling with multiple logistic regression, adjusting for age, BMI, parity, and infant birth weight. Possible confounders were selected based on results from previous studies and clinical experience.[7,19]

3 | RESULTS

In all, 608 women were examined. Mean (standard deviation) age was 47.9 years (4.9), BMI was 25.8 kg/m^2 (4.5), parity was 2.2 (0.8), birth weight of the largest infant was 3861g (506). Overall, 217 of 608 (36%) women had a normal delivery, 290 of 608 (47%) had an operative vaginal delivery and 101 of 608 (17%) women had delivered by cesarean section only. Compared to women who declined examination, the women examined were slightly older 47.3 vs 47.9 years ($P < .01$) and had more UI 46.9% vs 51.8% ($P = .04$) but not FI 9.1% vs 10.9% ($P = .2$) and were similar regarding parity, BMI, mode of delivery, and infant birth weight.

A significant external or internal anal sphincter defect was found in 86 (15.3%) women. In total, 493 (81%) women had intact LAM and 113 (19%) had LAM injury,

of which 57 (9%) were bilateral. For two women LAM injury was not possible to determine. We found that 311 of 600 (52%) had UI or previous surgery and 65 of 594 (11%) had FI or previous surgery. The mean (SD) and median (range) UDI-6 and CRADI-8 scores, and the proportions of women with UI, FI, or previous surgery are presented in Table 1. Both the median UDI-6 and CRADI-8 scores and the proportion of women with UI and FI were similar for women with intact and injured LAM. A subanalysis of women with bilateral LAM injury did not change the results. None of the selected confounders, except BMI, were associated with UI (Table 1). Anal sphincter defect was the only risk factor associated with FI (Table 1).

BND and urethral funneling were available for assessment in 582 women, and the associations with SUI and UUI are shown in Table 2. Fifty percent of the women with urethral funneling had SUI, and urethral funneling was significantly associated with SUI (aOR, 1.56 [95% confidence interval, 1.03-2.37]); $P = .04$). A similar trend was seen for BND, but this difference was not statistically significant. BND and urethral funneling were not associated with UUI. BMI was associated with UUI and SUI (Table 2).

4 | DISCUSSION

This cross-sectional study showed no association between LAM injury and UI or FI in parous women recruited from a normal population 15 to 24 years after the first delivery. The results remained unchanged in a sub-analysis of women with bilateral LAM injuries. However, we found that urethral funneling was associated with SUI.

LAM injuries usually occur during the first delivery,[6] whereas UI and FI are diagnosed years later. One strength of this study is a long time interval between the first delivery and assessment of symptoms.[5,7,19] Another strength is that women were recruited from the normal population, ensuring that the results are relevant for parous women in general, and not only for patient populations. Evaluation of ultrasound volumes was blinded, since the examiner was unaware of the obstetric history and any PFD symptoms. Detailed analyses of symptoms were performed using both symptom scores and a positive response to single questions and previous incontinence surgery. A sub-analysis comparing women with bilateral LAM injury and women with intact LAM made it possible to study if a more severe pelvic floor injury had a greater impact on symptoms.

TABLE 1 Symptom scores and prevalence of stress urinary incontinence, urge urinary incontinence, and fecal incontinence according to intact and injured levator ani muscle

	Mean (SD) Median (range)			Mann-Whitney U test, P	
	Intact LAMN = 492	Any LAM injury (uni- or bilateral) N = 113	Bilateral LAM injury N = 57	Any LAM injury vs intact LAM	Bilateral LAM injury vs intact LAM
Urinary Distress Inventory (UDI-6)	12.9 (16.0)	11.3 (14.8)	12.0 (15.5)	0.35	.53
Range, 0-100	8.3 (0-75)	4.2 (0-62.5)	4.2 (0-58.3)		
Colorectal Anal Distress Inventory (CRADI-8)	13.3 (15.8)	12.6 (14.9)	10.8 (10.9)	0.90	.75
Range, 0-100	6.3 (0-78.1)	6.3 (0-62.5)	6.3 (0-40.6)		
	Number/total(%)			aOR (95% CI), P	
UUI	155/486	30/111	17/56	0.86 (0.5-1.4)	1.1 (0.6-1.9)
	(31.9)	(27.0)	(30.4)	0.54	.88
SUI	214/491	42/111	20/56	0.8 (0.5-1.2)	.8 (0.4-1.4)
	(43.6)	(37.8)	(35.7)	0.32	.42
Any UI or surgery[a]	256/488	54/110	25/56	0.9 (0.6-1.4)	.8 (0.5-1.4)
	(52.5)	(49.1)	(44.6)	0.67	.44
FI	51/492	13/113	3/57	0.7 (0.3-1.5)	.3 (0.1-1.0)
	(10.4)	(11.5)	(5.3)	0.32	.06
FI or surgery[b]	52/482	13/111	3/57	0.7 (0.3-1.5)	.3 (0.1-1.0)
	(10.8)	(11.7)	(5.3)	0.32	.05

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; FI, fecal incontinence; LAM, levator ani muscle; SUI, stress urinary incontinence; UI, urinary; UUI, urge urinary incontinence.

[a]BMI was associated with UUI, SUI and any UI or surgery, aOR, 1.1 (1.0-1.1), $P < .001$.

[b]Any anal sphincter defect was associated with FI, aOR, 3.5 (1.6-7.5), $P < .01$, and FI or surgery, aOR, 3.4 (1.5-7.3), $P < .01$.

Since this is a cross-sectional study, we cannot determine causality. One limitation was that the population consisted of a large proportion of women with operative vaginal deliveries, due to the design of the parent study. Instrumental delivery has been associated with an increased risk for anal sphincter defects and LAM injury as shown in earlier studies.[5,19] Since operative vaginal deliveries are associated with PFDs this study population could be more symptomatic than the normal population they were recruited from. We also acknowledge that this study was performed in a homogenous Caucasian population and may not be representative of other ethnic groups. Pelvic floor muscle training can influence UI symptoms.[20] Some women in this study population may have received physiotherapy counseling, which may have alleviated symptoms. Furthermore, women with symptoms may be more willing to participate in studies, and this may introduce possible selection bias in the study. We had no information about

TABLE 2 Prevalence of urinary incontinence among women with and without bladder neck descent and urethral funneling

	Bladder neck descent number/total (%)			Urethral funneling number/total (%)		
	Yes	No	aOR (95% CI) P	Yes	No	aOR (95% CI) P
SUI[a]	154/363	95/224	1.0 (0.7-1.4)	58/117	191/470	1.6 (1.03-2.4)
N = 249	(42%)	(42%)	0.93	(50%)	(41%)	0.04
UUI[b]	106/360	77/222	0.8 (0.6-1.2)	34/116	149/466	0.9 (0.6-1.5)
N = 183	(29%)	(35%)	0.34	(29%)	(32%)	0.78

Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; SUI, stress urinary incontinence; UUI, urge urinary incontinence.

[a]BMI was associated with SUI, aOR, 1.1 (1.0-1.1), $P < .01$.

[b]BMI was associated with UUI, aOR, 1.1 (1.0-1.1), $P < .001$.

neuromuscular disorders that can contribute to the development of FI and UI.

Intact musculature is important for the support of the anterior vaginal wall, and some authors have suggested that muscle injury may have an impact on the support of the urethra and bladder neck.[8] If this is correct, we could expect that LAM injury was associated with SUI, however, this was not demonstrated. One possible explanation could be that an anterior wall prolapse camouflages the symptoms due to a kinking of the urethra, and a previous publication found a high prevalence (45%) of pelvic organ prolapse stage 2 among these women.[7] Therefore, some women may have occult UI, which may become evident after prolapse treatment. Thus, an underestimation of an association between LAM injury and UI is possible. In this study, however, including cystocele as a factor in the analysis, did not change the results. BND may be associated with anterior wall prolapse, and it is therefore not surprising that we found no association with UI.[9] Previous studies using magnetic resonance imaging and ultrasound have reported a decreased prevalence of UI among women with major LAM defects.[13,21] A true association between LAM defects and UI might be difficult to assess unless a follow-up study of women undergoing treatment for pelvic organ prolapse is performed. The continence mechanism is, however, complex, and it seems that other factors, such as BMI, intrinsic urethral closure pressure, hormonal changes, and pelvic floor muscle exercise, and strength may be more important than LAM injury. DeLancey et al[22] found that maximal urethral closure pressure strongly correlated with SUI. Urethral closure pressure is dependent upon the action of mucosal turgor, smooth, and striated muscles, which in turn decreases due to age-dependent striated muscle loss.[22,23] These findings agree with previous studies demonstrating no association between LAM injury and UI.[21,24]

Interestingly, urethral funneling was associated with SUI. This is consistent with other studies which relate funneling and length of the urethral sphincter with the type of incontinence.[25] Ultrasound parameters like urethral funneling may provide physicians with additional information about the incontinence mechanism for women with UI. However, further studies are needed to establish if urethral funneling is a risk factor for UI after prolapse surgery. Studies are also needed to address if LAM injury is a risk factor for UI after surgical correction of anterior wall prolapse.

Previous studies have identified obstetric anal sphincter injuries as the main risk factor for FI after delivery.[19] In this study, we found a strong association between FI and anal sphincter defects on ultrasound, consistent with those studies.

5 | CONCLUSION

In this study of parous women examined 15 to 24 years after first delivery we found that LAM injury was not associated with UI or FI. Although LAM injury results in decreased support of the anterior vaginal wall, other factors seem more relevant as contributors to the complex etiology of incontinence. Urethral funneling was associated with SUI. Further studies are needed to establish if LAM injury is a risk factor for the development of UI after prolapse surgery.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

ORCID

Seema Mathew http://orcid.org/0000-0002-5007-9322
Ingrid Volløyhaug http://orcid.org/0000-0001-9392-1674

REFERENCES

1. Rortveit G, Subak LL, Thom DH, et al. Urinary incontinence, fecal incontinence and pelvic organ prolapse in a population-based, racially diverse cohort: prevalence and risk factors. *Female Pelvic Med Reconstr Surg.* 2010;16(5):278-283.
2. Nygaard I, Barber MD, Burgio KL, et al. Prevalence of symptomatic pelvic floor disorders in US women. *JAMA.* 2008;300(11):1311-1316.
3. Boreham MK, Richter HE, Kenton KS, et al. Anal incontinence in women presenting for gynecologic care: prevalence, risk factors, and impact upon quality of life. *Am J Obstet Gynecol.* 2005;192(5):1637-1642.
4. Wu JM, Matthews CA, Conover MM, Pate V, Jonsson Funk M. Lifetime risk of stress urinary incontinence or pelvic organ prolapse surgery. *Obstet Gynecol.* 2014;123(6):1201-1206.

5. Volløyhaug I, Mørkved S, Salvesen Ø, Salvesen K. Pelvic organ prolapse and incontinence 15-23 years after first delivery: a cross-sectional study. *BJOG*. 2015;122(7):964-971.

6. Kamisan Atan I, Gerges B, Shek K, Dietz H. The association between vaginal parity and hiatal dimensions: a retrospective observational study in a tertiary urogynaecological centre. *BJOG*. 2015;122(6):867-872.

7. Volløyhaug I, Mørkved S, Salvesen KÅ. Association between pelvic floor muscle trauma and pelvic organ prolapse 20 years after delivery. *Int Urogynecol J*. 2016;27(1):39-45.

8. van Delft K, Sultan A, Thakar R, Schwertner-Tiepelmann N, Kluivers K. The relationship between postpartum levator ani muscle avulsion and signs and symptoms of pelvic floor dysfunction. *BJOG*. 2014;121(9):1164-1172.

9. Naranjo-Ortiz C, Shek KL, Martin AJ, Dietz HP. What is normal bladder neck anatomy? *Int Urogynecol J*. 2016;27(6):945-950.

10. Oberwalder M, Connor J, Wexner SD. Meta-analysis to determine the incidence of obstetric anal sphincter damage. *Br J Surg*. 2003;90(11):1333-1337.

11. Heilbrun ME, Nygaard IE, Lockhart ME, et al. Correlation between levator ani muscle injuries on magnetic resonance imaging and fecal incontinence, pelvic organ prolapse, and urinary incontinence in primiparous women. *Am J Obstet Gynecol*. 2010;202(5):488.e1-488.e6.

12. Chan SSC, Cheung RYK, Yiu KW, Lee LL, Chung TKH. Effect of levator ani muscle injury on primiparous women during the first year after childbirth. *Int Urogynecol J*. 2014;25(10):1381-1388.

13. Morgan DM, Cardoza P, Guire K, Fenner DE, DeLancey JOL. Levator ani defect status and lower urinary tract symptoms in women with pelvic organ prolapse. *Int Urogynecol J*. 2010;21(1):47-52.

14. Chantarasorn V, Shek KL, Dietz HP. Sonographic detection of puborectalis muscle avulsion is not associated with anal incontinence. *Aust N Z J Obstet Gynaecol*. 2011;51(2):130-135.

15. Dietz HP, Nazemian K, Shek KL, Martin A. Can urodynamic stress incontinence be diagnosed by ultrasound? *Int Urogynecol J*. 2013;24(8):1399-1403.

16. Dietz HP, Wilson PD. Anatomical assessment of the bladder outlet and proximal urethra using ultrasound and videocystourethrography. *Int Urogynecol J Pelvic Floor Dysfunct*. 1998;9(6):365-369.

17. Barber MD, Walters MD, Bump RC. Short forms of two condition-specific quality-of-life questionnaires for women with pelvic floor disorders (PFDI-20 and PFIQ-7). *Am J Obstet Gynecol*. 2005;193(1):103-113.

18. Dietz HP, Bernardo MJ, Kirby A, Shek KL. Minimal criteria for the diagnosis of avulsion of the puborectalis muscle by tomographic ultrasound. *Int Urogynecol J*. 2011;22(6):699-704.

19. Guzmán Rojas RA, Salvesen KÅ, Volløyhaug I. Anal sphincter defects and fecal incontinence 15-24 years after first delivery: a cross-sectional study. *Ultrasound Obstet Gynecol*. 2018;51(5):677-683.

20. Dumoulin C, Hay-Smith J, Habée-Séguin GM, Mercier J. Pelvic floor muscle training versus no treatment, or inactive control treatments, for urinary incontinence in women: a short version Cochrane systematic review with meta-analysis. *Neurourol Urodyn*. 2015;34(4):300-308.

21. Dietz HP, Kirby A, Shek KL, Bedwell PJ. Does avulsion of the puborectalis muscle affect bladder function? *Int Urogynecol J Pelvic Floor Dysfunct*. 2009;20(8):967-972.

22. DeLancey JOL, Trowbridge ER, Miller JM, et al. Stress urinary incontinence: relative importance of urethral support and urethral closure pressure. *J Urol*. 2008;179(6):2286-2290.

23. Rud T. Urethral pressure profile in continent women from childhood to old age. *Acta Obstet Gynecol Scand*. 1980;59(4):331-335.

24. Shek KL, Pirpiris A, Dietz HP. Does levator avulsion increase urethral mobility? *Eur J Obstet Gynecol Reprod Biol*. 2010;153(2):215-219.

25. Macura KJ, Thompson RE, Bluemke DA, Genadry R. Magnetic resonance imaging in assessment of stress urinary incontinence in women: parameters differentiating urethral hypermobility and intrinsic sphincter deficiency. *World J Radiol*. 2015;7(11):394-404.

2

ORIGINAL CLINICAL ARTICLE

Neurourology Urodynamics ICS SUFU Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction WILEY

Prevalence of anal sphincter defects and association with anal incontinence in women scheduled for pelvic organ prolapse surgery

Seema Mathew[1,2] | Rodrigo A. Guzman Rojas[3] | Maria Ø. Nyhus[1,2] |
Kjell Å. Salvesen[1,2] | Ingrid I. Volløyhaug[1,2]

[1]Department of Obstetrics and Gynecology, St. Olavs Hospital, Trondheim, Norway

[2]Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway

[3]Departamento de Ginecología y Obstetricia, Facultad de Medicina, Clínica Alemana-Universidad del Desarrollo, Santiago, Chile

Correspondence
Seema Mathew, Department of Obstetrics and Gynecology, St. Olavs Hospital, Postboks 3250 Torgarden, 7006 Trondheim, Norway.
Email: Seema.Mathew@stolav.no and seemamathew.sm@gmail.com

Abstract

Aims: Some women with pelvic organ prolapse (POP) have concomitant symptoms of anal incontinence. Our aim was to assess the prevalence of anal sphincter defects and the association with incontinence in women undergoing POP surgery.

Methods: Cross-sectional study of 200 women scheduled for POP surgery. They answered yes/no and graded any symptoms of fecal and flatal incontinence on a visual analog scale (0–100). 3D/4D transperineal ultrasound was used to assess internal (IAS) and external anal sphincter (EAS) defects. A defect of $\geq 30°$ in ≥ 4 of 6 slices on tomographic imaging was regarded significant. The association between incontinence and sphincter defects was tested with multivariable logistic regression analysis.

Results: The prevalence of any sphincter defect was 50/200 (25%). Combined IAS/EAS defect was found in 19/200 (9.5%) women, 8/200 (4.0%) had isolated IAS, and 23/200 (11.5%) had isolated EAS defects. In women with defect and intact IAS, 37% and 11% reported fecal incontinence, respectively, adjusted odds ratio (aOR) 2.3 (95% confidence interval [CI], 0.7–7.0), $p = .147$ and in women with defect versus intact EAS, 36% and 9% had fecal incontinence, aOR 4.0 (95% CI, 1.5–10.8), $p = .005$. In women with defect and intact IAS, 85% versus 43% reported flatal incontinence, aOR 5.2 (95% CI, 1.6–17.2), $p = .007$ and in women with defect versus intact EAS, 71% versus 43% had flatal incontinence, aOR 1.9 (95% CI, 0.8–4.5), $p = .131$.

Conclusions: One of four women scheduled for POP surgery had an anal sphincter defect. EAS defects were associated with fecal incontinence and IAS defects were strongly associated with flatal incontinence.

KEYWORDS
anal sphincter, fecal incontinence, flatulence, pelvic organ prolapse, ultrasound imaging

1 | INTRODUCTION

Anal incontinence (AI) is defined as involuntary leakage of flatus or feces, and has a significant impact on the quality of life in affected individuals.[1,2] The prevalence of AI varies from 1.4% to 19% in various studies, and increases with age.[1,3]

Obstetric anal sphincter injury (OASI) is an important risk factor for AI.[4,5] Previous studies report incidences of 11%–22% in primiparous women diagnosed with ultrasound, whereas clinical studies state the incidence to be between 3.9% and 11%.[4–7] OASI may be underestimated, and ultrasound can diagnose injuries undetected at the time of delivery, thus rendering higher estimates of the prevalence.[7,8] In a general population of parous women, the incidence of external (EAS) and internal sphincter (IAS) defects were reported to be 15% and 3%, respectively.[8] Up to 50% of women with OASI may develop AI and even after primary repair one-half of women still exhibit mild symptoms.[5,6,9] Undiagnosed and unrepaired tears may carry an even higher risk of AI.[8]

One important risk factor for pelvic organ prolapse (POP) is levator ani muscle (LAM) injury occurring due to obstetric trauma.[10] Patients with POP may have a higher prevalence of OASI and AI than the general population.[11,12] Common risk factors during delivery, such as instrumental delivery and high infant birthweight may cause both anal sphincter and LAM injury.[10–14] The prevalence of AI in urogynecological settings is reported to be between 14% and 29%, which is higher than the prevalence in the general female population.[2,11,12,14] However, the prevalence of anal sphincter defects and AI among women with more advanced POP scheduled for surgery has not been extensively studied.[12]

Our aim was to assess the prevalence of IAS and EAS defects and to study a possible association with incontinence in women with advanced prolapse scheduled for POP surgery, who could benefit from further diagnostic workup to optimize treatment.

2 | MATERIALS AND METHODS

This was a cross-sectional study of women scheduled for POP surgery at a university hospital between 1 January 2017 and 29 June 2018. This study is a secondary analysis of women included in a randomized controlled trial (registered in ClinicalTrials.gov) designed to examine the effect of pelvic floor exercise on prolapse symptoms and LAM function in women with symptomatic POP scheduled for surgery.[15] The study was approved by the Regional Committee for Medical and Health Research

Ethics (REK 2015/1751/midt). Sample size calculation was performed for the parent study.[15] Women were recruited from the outpatient urogynecological clinic at surgical referral and examined at a preoperative consultation. Inclusion criteria were indication for POP surgery (POP stage ≥2), ≥18 years, and fluent in Norwegian or English language. Women who needed immediate surgery or had cognitive impairments were excluded. Written informed consent was obtained from all study participants.

Age, parity, delivery mode, height, and weight were registered. Women answered yes/no to questions regarding frequent involuntary leakage of stool or flatus and, if yes, marked bother on a visual analog scale (VAS) from 0 to 100, where 100 is the most bothersome. The proportion of women with any fecal and flatal incontinence (VAS > 0) was registered.

All study participants met with empty bowel and bladder; this was confirmed during the ultrasound examination. They underwent an examination in the supine position in a gynecological examination chair, with knees and hips semiflexed and abducted. We used the pelvic organ prolapse quantification system (POP-Q) for assessment of POP at maximal Valsalva, and the proportion of women with POP stage ≥ 2 in each compartment was registered.[16] 3D/4D transperineal ultrasound of the anal sphincter muscles were acquired with a GE Voluson S8 or E10 device (GE Medical Systems) using a RAB 4-8-RS abdominal 3D probe at an 85° acquisition angle, held horizontally and angled slightly caudally toward the anus. Three volumes were acquired, one at rest and two at pelvic floor muscle contraction, where the anal sphincter was clearly visualized.[12] The LAM was also assessed using 3D probe placed transperineally in the transverse plane and volumes were acquired at maximum pelvic floor contraction.[17]

Offline analysis of the ultrasound volumes was performed using 4Dview Version 14 Ext.0 (GE Healthcare) software, blinded to all clinical data. Two examiners (S. M. and R. A. G. R.) assessed all anal sphincter volumes. In the case of discordant diagnosis, the volumes were reanalyzed by a third examiner (M. Ø. N.). We used the best of the three volumes acquired at the preoperative examination. Tomographic imaging was used for the assessment of IAS and EAS defects. Interslice space was regulated according to the length of the EAS to obtain eight slices; from one slice cranial to EAS and the last slice caudal to the IAS enabling the evaluation of the entire length of the EAS on six slices. The IAS was depicted on six slices by placing the first slice cranial to the IAS and the last slice at the level of the subcutaneous portion of the EAS.[7,12] A defect of the EAS or IAS of ≥30° in at least four of six slices on tomographic ultrasound

imaging was considered a significant defect,[7,8,12] see Figures 1 and 2. The proportion of women with any defect (either EAS or IAS or both) was noted. Then, tomographic ultrasound imaging was used to identify significant LAM injury at pelvic floor muscle contraction. Offline analysis was carried out by a single examiner (M. Ø. N.). A significant LAM injury was diagnosed and registered if all three central slices; the slice in the plane of minimal hiatal dimensions and the slices 2.5 and 5.0 mm cranial to this, showed abnormal muscle insertion on one or both sides as outlined in previous studies.[13,17]

2.1 | Statistical analyses

We used IBM SPSS Statistics version 25 (SPSS Inc.) to perform statistical analyses, and a $p < .05$ was considered statistically significant. Agreement between the two examiners (S. M. and R. A. G. R.) was calculated using Cohen's kappa and the following cut-offs were used: 0.00, no agreement; 0.01–0.20, slight agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, good agreement; and 0.81–1.00, strong agreement. A possible association between incontinence and sphincter defects was tested with multivariable logistic regression analyses to calculate adjusted odds ratios (aORs) for fecal and/or flatal incontinence in the presence of either EAS or IAS defects, adjusting for age, parity, and body mass index (BMI). These possible confounders were selected based on clinical experience and previous studies.[1,2,8] In addition, IAS was entered as a confounder when testing the association between EAS and the outcome and vice versa. Mann–Whitney U test was used to assess

differences in VAS scores for fecal and flatal incontinence between women with and without EAS or IAS defect. χ^2 test was performed to determine any influence of LAM injury on sphincter defects or AI.

3 | RESULTS

In all, 272 women were referred for POP surgery during the study period. Thirty-six women declined participation, four were missed for recruitment, and 32 did not meet the eligibility criteria (one woman was excluded based on language criterion), resulting in 200 women eligible for examination. Background characteristics and anatomical findings are outlined in Table 1. All women had POP stage ≥2 in the most prominent compartment and 122 (61%) had POP stage ≥3.

Cohen's kappa between the two main examiners (S. M. and R. A. G. R.) was 0.77 for EAS defect and 0.87 for IAS defect, suggesting good to strong agreement between the two main examiners. Twenty EAS volumes and 11 volumes of IAS were discordant and evaluated by the third examiner (M. Ø. N.). The prevalence of LAM injury, EAS, and IAS defects is shown in Table 1. Anal sphincter defect was present in 50/200 (25%) and LAM injury in 100/200 (50%) women. Any AI was reported by 107 (54%) women. In a subgroup analysis of women with posterior wall POP stage ≥2, the prevalence of any anal sphincter defect and AI was similar (16/65 [25%] and 35/65 [54%], respectively). Among the 18 primiparous women, only 3 had any sphincter defect.

The distribution of incontinence and VAS scores for women with intact and defect sphincters is presented in
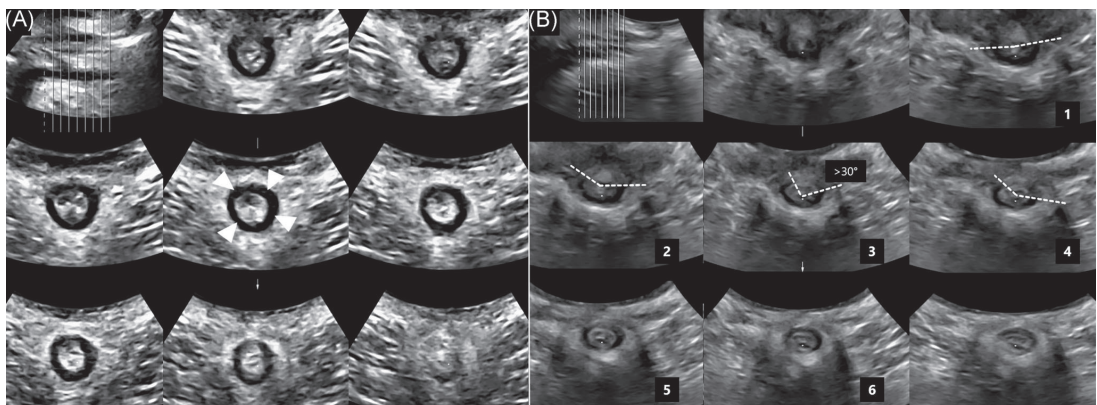

FIGURE 1 Three-dimensional transperineal ultrasound with tomographic ultrasound imaging showing (A) intact internal anal sphincter (IAS) seen as a hypoechogenic ring (white triangles) and (B) IAS defect shown as a break in echogenicity between the dotted lines involving >30° of the circumference in four of six images
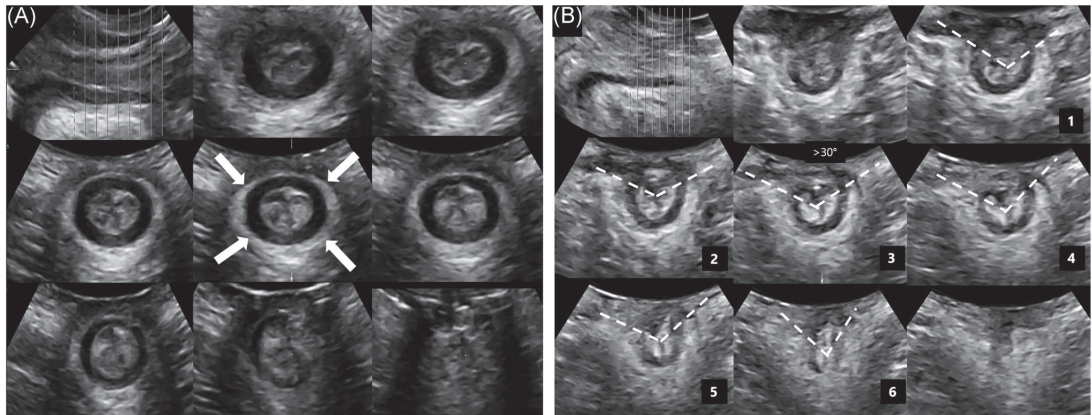
FIGURE 2 Three-dimensional transperineal ultrasound with tomographic ultrasound imaging showing (A) intact external anal sphincter (EAS) as a continuous hyperechogenic ring (white arrows) and (B) EAS defect, with the latter two showing a break (between dotted lines) in the echogenicity of involving >30° of the circumference in six of six images

Table 2. In addition, associations between EAS/IAS defects and fecal and flatal incontinence are shown in Table 2. Age, BMI, and parity were not associated with the outcome. Women with a defect EAS had aOR 4.0 (95% confidence interval [CI], 1.5–10.8) for fecal incontinence regardless of whether they had any IAS defect. After adjusting for EAS defects, women with IAS defects had aOR 5.2 (95% CI, 1.6–17.2) for flatal incontinence. Table 2 shows highly significant differences in VAS scores for women with and without EAS or IAS defects.

Any sphincter defect was present in 26/100 (26%) women with LAM injury and in 24/100 (24%) women without a LAM injury (p = 0.74). Any AI was found in 59/100 (59%) versus 48/100 (48%) in women with and without a LAM injury (p = 0.12). Eighteen (9%) women had LAM injury, anal sphincter defect, and any AI. Figure 3 illustrates the distribution of anal sphincter defects, AI, and LAM injury in a Venn diagram.

4 | DISCUSSION

The prevalence of anal sphincter defects in women scheduled for POP surgery was 25%. An EAS defect was associated with a fourfold increased risk of fecal incontinence, and a defect in the IAS increased the risk of flatal incontinence by five times. Both EAS and IAS defects correlated with higher VAS scores for fecal and flatal incontinence.

We found a higher prevalence of EAS and IAS defects (21% and 13.5%) compared with previous reports from a general population of parous women (15% and 3%).[8] A study from a urogynecological population found EAS and

IAS defects in 18% and 12%, respectively, which is comparable to our findings.[12] Eight women had isolated IAS defects. This can be attributed to a missed diagnosis of IAS tear during the primary repair of the EAS. In addition, some women may still show a defect even after primary repair, due to interrupted healing as demonstrated by some studies.[6,8]

Fecal incontinence was found in 15%, which is in agreement with a previous study from a similar population.[12] Flatal incontinence was found in 48%, which is lower than some studies from a general population reporting up to 60% flatal leakage.[3] One-third of that study population was over 65 years, therefore, age and chronic diseases may have influenced this finding.[2,3] In another urogynecological setting, the prevalence of fecal and flatal incontinence was 41% and 58% respectively, which correlates well with our study.[14] Any AI of 54% is higher than reported in similar studies, but can be explained because this cohort consists of patients with severe POP.[11,12] Advanced prolapse of the posterior vaginal wall may cause rectal distension and incomplete defecation resulting in reduced reservoir function which in time may cause overflow incontinence.[18] However, the prevalence of AI was similar for women with posterior wall POP in our study. A follow-up study of the population after surgical correction may shed light on any improvement in symptoms of AI. As subsequent births may aggravate symptoms, another reason for the high prevalence of AI might be the increased share of multiparous women in this study.[1,8]

Our findings of increased risk of incontinence associated with sphincter defects coincide well with results from a recent study reporting a 50% increased risk of

TABLE 1 Population characteristics, anatomical findings, and prevalence of internal (IAS), external anal sphincter (EAS) and combined defects among 200 women

Background characteristics	Mean (SD)	Median (range)
Age	61.7 (11.4)	63 (31.0–83.0)
Body mass index	26.1 (4.0)	25.8 (19.6–43.0)
Parity	2.5 (0.9)	3 (0–6)
	Number (%)	
Nullipara	2 (1.0)	
Primipara	18 (9.0)	
Multipara	180 (90.0)	
Normal vaginal delivery	145 (72.5)	
Operative vaginal delivery	40 (20.0)	
Vaginal breech or twin delivery	11 (5.5)	
Only cesarean section	2 (1.0)	
Anatomical findings		
Pelvic organ prolapse stage ≥2 in		
Anterior wall	163 (81.5)	
Posterior wall	65 (32.5)	
Mid compartment	72 (36.0)	
Any levator ani muscle injury	100 (50.0)	
Bilateral levator ani muscle injury	48 (24.0)	
Any sphincter defect	50 (25.0)	
Isolated EAS defect	23 (11.5)	
Isolated IAS defect	8 (4.0)	
Combined defect	19 (9.5)	

fecal incontinence for women with defect EAS.[8] EAS is a voluntary muscle and injury affects function and may cause incontinence.[19] We found no association between EAS defects and flatal incontinence. This is plausible, as it is the IAS that contributes to the mean anal basal pressure, and IAS injury, therefore, affects flatal incontinence as shown in this study.[19] In addition, IAS involvement may suggest a more severe injury resulting in a higher risk of incontinence.

Previous studies have found an association between anal sphincter defects and AI. Our findings emphasize this association between sphincter defects and AI in women with the most advanced POP scheduled for surgery and adds new knowledge to the association between IAS defects and flatal incontinence in women with severe POP.

One strength of this study was the use of transperineal ultrasound to assess anal sphincter defects. Transperineal ultrasound has shown good correlation to

TABLE 2 Prevalence of fecal and flatal incontinence among women with intact and defect internal anal sphincter (IAS) and external anal sphincter (EAS) with adjusted odds ratio (aOR)[a] and visual analog scale (VAS) scores

	Fecal incontinence (n = 29/199) Number (%)	aOR[a] (95% CI); p	Flatal incontinence (n = 97/199) Number (%)	aOR[a] (95% CI); p	Fecal incontinence VAS scores (n = 198) Mean score (SD); median (range)	Mann-Whitney U (p)	Flatal incontinence VAS scores (n = 198) Mean score (SD); median (range)	Mann-Whitney U (p)
IAS								
Intact (n = 173/200)	19 (10.9)	2.3 (0.7–7.0); 0.147	74 (43.0)	5.2 (1.6–17.2); 0.007	5.6 (14.3); 0.0 (0–95)	<0.001	18.8 (29.2); 0.0 (0–100)	<0.001
Defect (n = 27/200)[b]	10 (37.0)		23 (85.2)		12.5 (24.6); 0.0 (0–82.3)		39.1 (34.9); 32.6 (0–100)	
EAS								
Intact (n = 158/200)	14 (8.9)	4.0 (1.5–10.8); 0.005	67 (42.7)	1.9 (0.8–4.5); 0.131	2.8 (13.5); 0.0 (0–95)	<0.001	19.6 (29.8); 0.0 (0–100)	0.006
Defect (n = 42/200)[b]	15 (35.7)		30 (71.4)		12.2 (22.7); 0.0 (0–82.3)		28.8 (33.6); 10.9 (0–100)	

[a]Potential confounders adjusted for include the presence of either EAS or IAS defects, age, parity, and body mass index.

[b]Isolated IAS defect in 8/200 (4%) and isolated EAS defects in 23/200 (13%) were found.
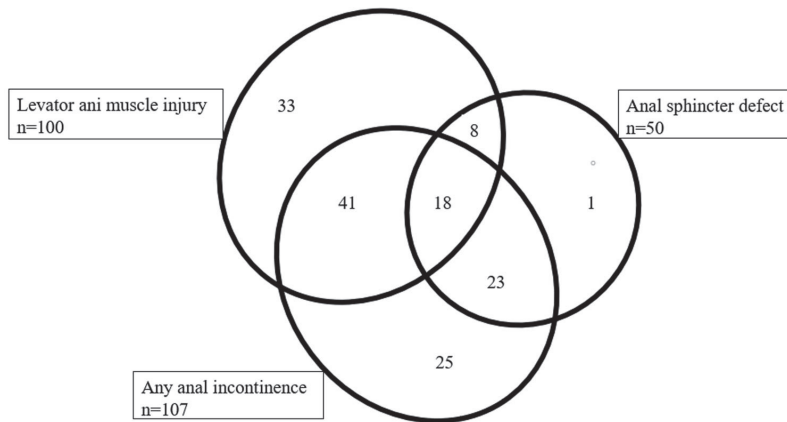
FIGURE 3   Venn diagram illustrating the distribution of anal sphincter defects, anal incontinence, and levator ani muscle injury among 200 women

symptoms, creates the least discomfort to patients and is readily available in most gynecological practices.[20,21] Another strength was that all volumes were assessed by two examiners, blinded to each other and to the patient characteristics and symptoms, and we found a good to strong agreement between the two main examiners. A third examiner evaluated all discordant findings, adding to the strength. We included women with prolapse in all compartments, therefore, the results should be representative for women with severe POP in a urogynecological practice.[8,12] Another strength was that we tested any association between LAM injury, AI, EAS, and IAS defect. We found no association between LAM injury and AI, which is in accordance with another study.[13]

A limitation of this study was that we had no information about OASI recorded at delivery and subsequent repairs. The participants were part of a larger study evaluating the LAM anatomy using a transperineal ultrasound, and the same approach was used to assess the anal sphincters. One study comparing transperineal and introital to endoanal ultrasound suggested that the endoanal ultrasound is the most accurate diagnostic imaging modality, but the transperineal approach was well tolerated and had high negative predictive value in rendering it suitable for preliminary diagnostics.[22] Another limitation was that a yes/no answer to leakage of stool or flatus does not give a nuanced picture of all aspects of AI. Still, it can be a useful screening aid in a busy clinical setting, and we used VAS score to further quantify symptoms. A study by Ulrich et al.[23] showed that a VAS is a valid tool in a urogynecological setting of POP patients. Standardized questionnaires could have improved the estimate of AI, as the questions asked in

this study did not differentiate between leakage of loose or solid stool. Our study population included women who gave birth at a time where forceps deliveries were common in Norway, and the rate of undiagnosed anal injuries may have been higher than today. The etiology for AI is multifactorial and not solely dependent on muscle damage. Neurological impairment, estrogen deficiency, degenerative processes, chronic diseases, and positional instability of the pelvic structures possibly play a role in the development of AI.[19] We did not register background information regarding any previous anorectal surgery or diseases with possible impact on AI. Data concerning the 72 excluded women were not collected, which can also be considered a limitation. Symptomatic women are more eager to participate in studies than nonsymptomatic women introducing a bias in this study.

In a urogynecological population, the likelihood of sphincter defects and AI may be high and should be addressed.[2,12] Transperineal ultrasound has a high negative predictive value and can be utilized as a tool to assess symptomatic women who may benefit from extended investigation and treatment.[20–22] Further anophysiological investigation by a colorectal surgeon might be required to evaluate ideal treatment options. Symptomatic women with sphincter defects on transperineal ultrasound may also benefit referral to physiotherapy, biofeedback, bulking agents or sacral nerve stimulation.[24,25] Patients with POP and sphincter defects have usually sustained vaginal trauma during childbirth. Studies report that 25%–30% of women with OASI had concomitant LAM injury underlining the common risk factors.[7,13] Further follow-up studies are needed to determine whether prolapse surgery may alleviate the

symptoms of AI, particularly in patients with a posterior compartment prolapse. The high prevalence of AI in this population necessitates careful discussion of patient expectations regarding the alleviation of AI postoperatively and offers proper investigation and treatment options in case of persistent symptoms.

5 | CONCLUSION

One of four women with severe POP scheduled for surgery have anal sphincter defects. In symptomatic patients scheduled for POP surgery, we suggest examining for anal sphincter defects to diagnose any major defect. This should prompt further diagnostic testing to facilitate optimal treatment for this debilitating condition.

CONFLICT OF INTERESTS
The authors declare that there are no conflict of interests.

ORCID
Seema Mathew http://orcid.org/0000-0002-5007-9322
Ingrid I. Volløyhaug http://orcid.org/0000-0001-9392-1674

REFERENCES
1. Rømmen K, Schei B, Rydning A, Sultan AH, Mørkved S. Prevalence of anal incontinence among Norwegian women: a cross-sectional study. *BMJ Open.* 2012;2(4):e001257.
2. Boreham MK, Richter HE, Kenton KS, et al. Anal incontinence in women presenting for gynecologic care: prevalence, risk factors, and impact upon quality of life. *Am J Obstet Gynecol.* 2005;192(5):1637-1642.
3. Nelson R, Norton N, Cautley E, Furner S. Community-based prevalence of anal incontinence. *JAMA.* 1995;274(7):559-561.
4. Dudding TC, Vaizey CJ, Kamm MA. Obstetric anal sphincter injury: incidence, risk factors, and management. *Ann Surg.* 2008;247(2):224-237.
5. Halle TK, Salvesen KA, Volloyhaug I. Obstetric anal sphincter injury and incontinence 15-23 years after vaginal delivery. *Acta Obstet Gynecol Scand.* 2016;95(8):941-947.
6. Laine K, Skjeldestad FE, Sanda B, Horne H, Spydslaug A, Staff AC. Prevalence and risk factors for anal incontinence after obstetric anal sphincter rupture. *Acta Obstet Gynecol Scand.* 2011;90(4):319-324.
7. Guzman Rojas RA, Shek KL, Langer SM, Dietz HP. Prevalence of anal sphincter injury in primiparous women. *Ultrasound Obstet Gynecol.* 2013;42(4):461-466.
8. Guzman Rojas RA, Salvesen KA, Volloyhaug I. Anal sphincter defects and fecal incontinence 15-24 years after first delivery: a cross-sectional study. *Ultrasound Obstet Gynecol.* 2018;51(5):677-683.
9. Zetterström J, López A, Anzén B, Norman M, Holmström B, Mellgren A. Anal sphincter tears at vaginal delivery: risk factors and clinical outcome of primary repair. *Obstet Gynecol.* 1999;94(1):21-28.
10. Volloyhaug I, Morkved S, Salvesen O, Salvesen KA. Forceps delivery is associated with increased risk of pelvic organ prolapse and muscle trauma: a cross-sectional study 16-24 years after first delivery. *Ultrasound Obstet Gynecol.* 2015;46(4):487-495.
11. Gordon D, Groutz A, Goldman G, et al. Anal incontinence: prevalence among female patients attending a urogynecologic clinic. *Neurourol Urodyn.* 1999;18(3):199-204.
12. Guzmán Rojas RA, Kamisan Atan I, Shek KL, Dietz HP. Anal sphincter trauma and anal incontinence in urogynecological patients. *Ultrasound Obstet Gynecol.* 2015;46(3):363-366.
13. Volløyhaug I, Taithongchai A, Van, Gruting I, Sultan A, Thakar R. Levator ani muscle morphology and function in women with obstetric anal sphincter injury. *Ultrasound Obstet Gynecol.* 2019;53(3):410-416.
14. Meschia M, Buonaguidi A, Pifarotti P, Somigliana E, Spennacchio M, Amicarelli F. Prevalence of anal incontinence in women with symptoms of urinary incontinence and genital prolapse. *Obstet Gynecol.* 2002;100(4):719-723.
15. Nyhus M, Mathew S, Salvesen Ø, Salvesen K, Stafne S, Volløyhaug I. The effect of preoperative pelvic floor muscle training on pelvic floor contraction, symptomatic and anatomical pelvic organ prolapse after surgery: a randomized controlled trial. *Ultrasound Obstet Gynecol.* 2020;56:28-36. https://doi.org/10.1002/uog.22007
16. Bump RC, Mattiasson A, Bø K, et al. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. *Am J Obstet Gynecol.* 1996;175(1):10-17.
17. Dietz HP, Bernardo MJ, Kirby A, Shek KL. Minimal criteria for the diagnosis of avulsion of the puborectalis muscle by tomographic ultrasound. *Int Urogynecol J.* 2011;22(6):699-704.
18. Felt-Bersma RJ, Sloots CE, Poen AC, Cuesta MA, Meuwissen SG. Rectal compliance as a routine measurement: extreme volumes have direct clinical impact and normal volumes exclude rectum as a problem. *Dis Colon Rectum.* 2000;43(12):1732-1738.
19. Rao SSC. Pathophysiology of adult fecal incontinence. *Gastroenterology.* 2004;126:S14-S22.
20. Cornelia L, Stephan B, Michel B, Antoine W, Felix K. Transperineal versus endo-anal ultrasound in the detection of anal

sphincter tears. *Eur J Obstet Gynecol Reprod Biol.* 2002;103(1): 79-82.

21. Turel F, Shek KL, Dietz HP. How valid is tomographic ultrasound imaging in diagnosing levator and anal sphincter trauma? *J Ultrasound Med.* 2019;38(4):889-894.

22. Taithongchai A, van Gruting IM, Volløyhaug I, Arendsen LP, Sultan AH, Thakar R. Comparing the diagnostic accuracy of 3 ultrasound modalities for diagnosing obstetric anal sphincter injuries. *Am J Obstet Gynecol.* 2019;221(2):134.e1-134.e9.

23. Ulrich D, Guzman Rojas R, Dietz HP, Mann K, Trutnovsky G. Use of a visual analog scale for evaluation of bother from pelvic organ prolapse. *Ultrasound Obstet Gynecol.* 2014;43(6):693-697.

24. Norton C, Cody JD. Biofeedback and/or sphincter exercises for the treatment of faecal incontinence in adults. *Cochrane Database Syst Rev.* 2012;(7):CD002111.

25. Simillis C, Lal N, Pellino G, et al. A systematic review and network meta-analysis comparing treatments for faecal incontinence. *Int J Surg.* 2019;66:37-47.

3

ORIGINAL ARTICLE

The effect of preoperative pelvic floor muscle training on urinary and colorectal-anal distress in women undergoing pelvic organ prolapse surgery—a randomized controlled trial

Seema Mathew[1,2] · Maria Øyasæter Nyhus[1,2] · Øyvind Salvesen[3] · Kjell Åsmund Salvesen[1,2] ·
Signe Nilssen Stafne[3,4] · Ingrid Volløyhaug[1,2]

Abstract

Introduction and hypothesis Pelvic floor muscle training (PFMT) improves urinary incontinence and mild pelvic organ prolapse (POP). We aimed to investigate the effect of preoperative PFMT on urinary and colorectal-anal distress and related quality of life (QoL) in women with severe POP scheduled for surgery.

Methods Randomized controlled trial of 159 women scheduled for POP surgery (intervention = 81, controls = 78). Intervention consisted of daily PFMT from inclusion to the day of surgery. Symptoms and QoL were assessed at inclusion, day of surgery and 6 months postoperatively using the Urinary Distress Inventory (UDI-6), Colorectal-Anal Distress Inventory (CRADI-8), Urinary Impact Questionnaire (UIQ) and Colorectal-Anal Impact Questionnaire (CRAIQ) (range 0–100). Mixed model statistical analyses were used.

Results One hundred fifty-one (95%) women completed the study (intervention = 75, controls = 76). Mean waiting times until surgery and follow-up were 22 and 28 weeks. There was no difference in mean postoperative symptom and QoL scores (95% CI) between the intervention and control group: UDI-6 16 (12–21) vs. 17 (13–22), CRADI-8 15 (11–18) vs. 13 (10–16), UIQ 11 (7–15) vs. 10 (6–13) and CRAIQ 5 (2–7) vs. 6 (4–9), all $p > 0.05$. Overall mean scores were reduced from baseline to postoperative follow-up: UDI-6 37 (33–41) vs. 17 (14–20), CRADI-8 22 (19–25) vs. 14 (11–16); UIQ 28 (24–32) vs. 10 (7–13) and CRAIQ 16 (12–19) vs. 5 (3–7), all $p < 0.01$.

Conclusions We found no added effect of preoperative PFMT on symptoms or QoL related to urinary and colorectal-anal distress in women scheduled for POP surgery. They achieved symptomatic improvement postoperatively regardless of PFMT.

Clinical trial registration The study was registered in clinicaltrials.gov: NCT 03,064,750.

✉ Seema Mathew
  seemamathew.sm@gmail.com; Seema.Mathew@stolav.no

1 Department of Obstetrics and Gynecology, St. Olavs University Hospital, Trondheim, Norway

2 Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway

3 Department of Public Health and Nursing, Norwegian University of Science and Technology, Trondheim, Norway

4 Clinical Services, St. Olavs University Hospital, Trondheim, Norway

Introduction

Urinary and colorectal-anal distress has a negative impact on quality of life [1–3]. These symptoms are highly prevalent in women with pelvic organ prolapse (POP) because of shared risk factors such as age, parity and pelvic floor trauma occurring during delivery [1–5]. Injury to nerves, connective tissue and muscles contributes to the pathophysiology of pelvic floor disorders [1, 6]. Strengthening the pelvic floor muscles is therefore one option to treat pelvic floor disorders [7].

Intensive pelvic floor muscle training (PFMT) is effective in treating stress urinary incontinence and symptomatic mild POP, reducing bulge sensation and frequent urination [8, 9]. PFMT is also effective in treating anal incontinence symptoms and improve quality of life, but the effect on other urinary symptoms or colorectal-anal symptoms such as emptying

difficulties is unclear [9–13]. Repeated contractions improve the strength and endurance of the pelvic floor muscles, providing better support to pelvic organs and improving urinary continence [9, 12]. However, most studies have either examined women in the immediate postpartum period or women with isolated stress urinary incontinence [10, 12]. Other studies of women undergoing POP surgery have mainly focused on the effect of peri- or postoperative PFMT on urinary and colorectal-anal symptoms, and one study found marginal effects of PFMT on quality of life [14–17]. Previous studies with < 100 participants have included women scheduled for surgery because of different conditions (POP, urinary incontinence and hysterectomy for other reasons), and it is unclear whether the positive effect of peri- and postoperative PFMT was found in women with POP [15, 16, 18]. Any additional effect of preoperative PFMT on urinary and colorectal-anal symptoms and quality of life in women with advanced POP has not been thoroughly investigated.

Our aim was therefore to examine the effect of preoperative PFMT on urinary and colorectal-anal symptoms in women scheduled for POP surgery. We also aimed to study any effect on quality of life related to these symptoms.

Materials and methods

This was a randomized controlled trial (RCT) of women scheduled for POP surgery at Trondheim University Hospital, Norway, from January 2017 through March 2019. Women were recruited from the outpatient urogynecological clinic from January 2017 through June 2018. All participants signed a written informed consent form at a preoperative consultation. Inclusion criteria were indication for POP surgery (bulge sensation and POP stage ≥ 2), age > 18 years and fluent in Norwegian or English. Women declining participation, needing immediate surgery or with cognitive impairments were excluded. The study was approved by the Regional Committee for Medical and Health Research Ethics (REK2015/1751/midt) and registered in clinicaltrials.gov with the identifier NCT 03,064,750.

Age, parity, delivery mode, height, weight, smoking habits, menopausal status, hormonal therapy, pessary use and any previous PFMT or POP surgery were registered at inclusion. Surgical procedure was determined according to the clinical practice considering age, prolapse grade, involved compartments and any previous POP surgery. Available procedures were: colporrhaphy (anterior and posterior), perineoplasty, enterocele correction, cervical amputation with shortening of the ligaments, vaginal hysterectomy, sacrospinous ligament fixation, laparoscopic robot-assisted sacrouteropexy or sacrocolpopexy. The procedures performed and any surgical complications were registered.

At inclusion, women were randomized to intervention or control with the allocation ratio of 1:1 and stratified using POP stage > or < 3 and age > or < 60 years using a web-based randomization tool (WebRAND). Participants were examined and patient-reported outcomes collected at inclusion, day of surgery (minimum 3 months later) and 6 months postoperatively by one of three authors (SM/MØN/IV). Data were registered in a web-based case report form (WebCRF) provided by the Unit of Applied Clinical Research, Norwegian University of Science and Technology. A gynecological examination was performed with the participant in the supine position with hips and knees semi-flexed and abducted. POP was assessed at maximum Valsalva according to the Pelvic Organ Prolapse Quantification (POP-Q) system [19]. Examiners were not blinded to background data or group allocation at examination. At each visit the women answered a validated Norwegian translation of the Pelvic Floor Distress Inventory (PFDI-20) and Pelvic Floor Impact Questionnaire (PFIQ-7) [20, 21]. For quantification of urinary and colorectal-anal distress and impact on quality of life, we used the PFDI-20 sub-scales: Urinary Distress Inventory (UDI-6) and Colorectal Anal Distress Inventory (CRADI-8) and PFIQ-7 subscales: Urinary Impact Questionnaire (UIQ) and Colorectal Anal Impact Questionnaire (CRAIQ), all with a range of 0–100 where 100 is the worst bother [20, 21]. The average waiting time to surgery at Trondheim University Hospital during the study period was 3 months. Waiting time was not influenced by group allocation.

Women allocated to intervention received written information regarding the correct pelvic floor exercise technique at inclusion. They were given written lifestyle advice regarding diet and proper emptying of the bladder and bowel as well as instructions on contraction of the pelvic floor muscles when sneezing, coughing or laughing [7, 9]. Vaginal examination was performed by one of the examiners (SM, MØN, IV) at inclusion and by a pelvic floor physiotherapist at visits 2 and 6 weeks after inclusion to ensure proper contraction for women in the intervention group. Women were instructed to perform intensive pelvic floor muscle exercise with 8–12 maximal contractions holding at least 6–8 s three times daily from time of inclusion until the day of surgery [22, 23]. They were informed about voluntary weekly group training sessions at the baseline examination and at the first consultation with the physiotherapist 2 weeks after inclusion. They were required to record daily exercises in a training diary, to be handed in at the day of surgery. Women who failed to deliver a training diary were interviewed by telephone regarding the number of days per week they had performed training and the number of repetitions each day. A ≥ 70% completion of daily exercise rate was defined as adherence to the protocol [24, 25]. Women in the control group received no intervention in the waiting time for

surgery. All postmenopausal women, regardless of randomization, received local estrogen therapy unless contraindicated.

Primary outcome measures of the RCT were pelvic floor muscle strength assessed by palpation and ultrasound and symptoms of pelvic floor disorders as registered in clinicaltrials.gov (NCT 03,064,750). We have previously reported results regarding muscle contraction assessed by palpation, manometry and ultrasound as well as prolapse symptoms [25]. In the present article, we report on another of the primary outcomes: symptoms of urinary and colorectal-anal distress assessed by validated PFDI sub-scales: UDI-6 and CRADI-8. A secondary outcome was patient reported quality of life related to urinary and colorectal-anal symptoms using the PFIQ sub-scales: UIQ and CRAIQ.

Sample size calculation was based on differences in pelvic floor muscle contraction. A mean modified Oxford scale of 2.6 ± 1.3 was anticipated and a clinically relevant change in modified Oxford scale at 6-month follow-up of 3.2 ± 1.3. With power 80%, $p = 0.05$ and sampling ratio 1:1, a study sample of 74 women in each group was considered sufficient.

Statistical methods

Outcomes were analyzed following an intention-to-treat principle. We used IBM SPSS Statistics version 25 (SPSS Inc., Chicago, IL) and R version 3.6.3 (R Project for Statistical Computing) to perform statistical analyses. The level of statistical significance was set at 5%. Normality of the continuous variables (UDI-6, CRADI-8, UIQ and CRAIQ) was assessed using histograms and QQ plots. Independent sample t-test was used to examine any differences between women accepting and declining randomization. Symptoms and quality of life in the intervention group versus the control group at the day of surgery and postoperative control were evaluated with mixed models analysis with a five-level combined variable for time and group status as fixed effects (baseline for total study population, day of surgery for intervention group, day of surgery for control group, postoperative follow-up intervention group and postoperative follow-up control group). The model was fitted by restricted maximum likelihood estimation and unstructured covariance for the repeated measurements of each participant. The effect of the stratification variables (POP stage > or < 3 and age > or < 60) was tested, and no effect was found. The change in the total study population with time as fixed effect (baseline for total study population, postoperative follow-up for total population) was also tested using a mixed models analysis fitted by restricted maximum likelihood estimation and unstructured covariance for the repeated measurements.

Results

During the recruitment period from January 2017 through June 2018, 272 women were referred for POP surgery. One hundred thirteen women were excluded because they refused participation, did not fulfill the inclusion criteria or declined randomization; see the flow chart (Fig. 1). Of the 159 randomized women, 151 (95%) completed the study, 75 in the intervention group and 76 in the control group. Data collection ended in June 2019.

Background characteristics and outcome variables are outlined in Table 1. Overall, 92/151 (61%) had POP stage $\geq$ 3. The proportion of women undergoing an isolated anterior or posterior compartment repair was 28/151 (19%) and 27/151 (18%), respectively. Thirty-eight (25%) women had an isolated central compartment repair. A combination of procedures involving more than one compartment was performed in 58/151 (38%) women. Sixty (80%) women in the training group achieved an adherence level of $\geq$ 70% to the intervention. None of the participants met for the voluntary weekly group training sessions. Women declining randomization were similar to study participants in POP stage $\geq$ 3, body mass index and parity, but significantly older compared to the study participants (67 vs. 61 years, $p = 0.002$).

Mean (SD) and median (range) waiting time to surgery was 22 (10) and 21(7–84) weeks, and women were examined postoperatively after mean 28 (8) and median 26 (11–79) weeks. There was no statistically significant difference in UDI-6 or CRADI-8 scores or change in scores between intervention and control groups at day of surgery or postoperatively; see Table 2. Analysis of the quality of life related to urinary and colorectal-anal distress (UIQ and CRAIQ) revealed similar findings (Table 2). Figure 2 demonstrates the linear mixed model analysis of the change in scores for the intervention and control group at each examination. Overall, there was a statistically significant decrease in symptoms and improvement in quality of life from baseline to postoperative control in the total study population (Table 3).

Two major complications were registered: an intestinovaginal fistula after laparoscopic sacrocolpopexy and one postoperative hemorrhage, both requiring further surgery. Other complications were postoperative urinary tract infection requiring treatment in 3/151 (2%) and one woman (< 1%) with persisting residual urine after 6 months.

Discussion

In this randomized controlled trial of women scheduled for POP surgery, we found no effect of preoperative PFMT on urinary or colorectal-anal distress and related quality of life 6 months after surgery. Women achieved symptomatic improvement postoperatively regardless of PFMT.
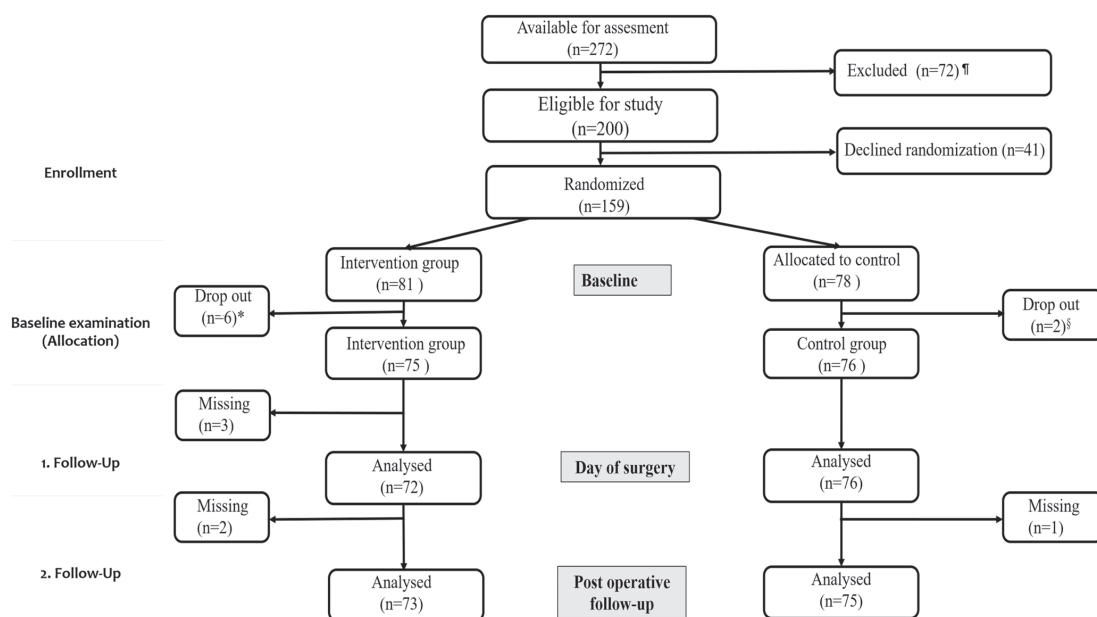
Fig. 1 Flowchart of study population. ¶Declined participation ($n = 36$), missed for recruitment ($n = 4$), did not meet eligibility criteria ($n = 32$). *Three women postponed surgery (one because of other medical conditions and two because of symptomatic improvement). Three women declined further participation. §Two women postponed surgery because of improvement of symptoms

PFMT is shown to reduce stress urinary incontinence, anal incontinence and symptoms of mild POP, but there is less evidence regarding the effect of a strong and well-functioning pelvic floor on other urinary symptoms and

Table 1 Participant demographics and main findings for the intervention and control groups

	Intervention group $N=75$	Control group $N=76$
Demographics		
	Mean (SD)	
Age (years)	60.1 (11.2)	60.6 (10.9)
Body mass index (kg/m^2)	26.3 (4.4)	25.7 (4.1)
Parity (number)	2.3 (0.8)	2.6 (0.9)
Waiting time before surgery (weeks)	21.6 (8.5)	23.2 (10.8)
Time to postoperative follow-up (weeks)	28.7 (8.0)	27.6 (7.6)
	N (%)	
Normal vaginal delivery	51 (68.0)	55 (72.4)
Operative vaginal delivery (including breech or twin delivery)	22 (29.3)	20 (26.3)
Smoking	10 (13.9)*	6 (7.9)
Postmenopausal	59 (79.7)*	59 (77.6)
Local estrogen therapy	47 (63.5)*	48 (63.2)
Previous pessary use	50 (67.6)*	60 (78.9)
Previous pelvic floor muscle training	13 (17.6)*	14 (18.4)
Previous pelvic organ prolapse surgery	7 (9.5)*	11 (14.5)
Objective findings		
Pelvic organ prolapse quantification (POPQ)≥3	44 (58.7)	48 (63.2)
Subscale scores at inclusion (range 0–100)	Mean (95% CI)	
Urinary distress inventory (UDI-6)	38.0 (32.7–43.2)*	35.5 (29.2–41.8)§
Colorectal-anal distress inventory (CRADI-8)	23.9 (20.3–27.4)	20.4 (16.1–24.6)¶
Urinary impact questionnaire (UIQ)	30.2 (24.0–36.3)	25.5 (19.5–31.6)**
Colorectal anal impact questionnaire (CRAIQ)	18.8 (13.4–24.2)	12.8 (8.0–17.6)**

* Data missing for one participant, ** data missing for two participants, ¶ data missing for four participants, § data missing for six participants

Table 2 Mean values with 95% confidence intervals (CI) at baseline, day of surgery and postoperative follow-up. Mean differences with 95% CI between intervention and control groups

| | Baseline* | Day of surgery** | | | | Postoperative follow-up*** | | | |
| | n=151 | Intervention n=72 | Control n=76 | Difference between groups¶ | p | Intervention n=73 | Control n=75 | Difference between groups¶ | p |
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)		Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	
Symptoms subscales (range 0–100)									
Urinary distress inventory (UDI-6)	37.2 (33.2-41.2)	37.4 (32.3-42.6)	40.6 (35.6-45.6)	-3.2 (-9.1-2.7)	0.284	16.3 (11.9-20.8)	17.4 (13.2-21.7)	-1.1 (-7.2-4.9)	0.718
Colorectal anal distress inventory (CRADI-8)	21.9 (19.2-24.6)	23.8 (20.1-27.5)	23.2 (19.6-26.8)	0.6 (-4.0-5.3)	0.784	14.6 (11.4-17.8)	13.1 (9.9-16.2)	1.5 (-2.7-5.8)	0.474
Quality of life subscales (range 0–100)									
Urinary impact questionnaire (UIQ)	27.7 (23.5-31.9)	24.7 (19.5-29.8)	27.0 (22.0-32.1)	-2.4 (-8.7-3.9)	0.453	10.5 (6.6-14.5)	9.5 (5.7-13.4)	1.0 (-4.2-6.2)	0.707
Colorectal anal impact questionnaire (CRAIQ)	15.8 (12.2-19.4)	14.9 (10.9-18.9)	13.8 (9.8-17.7)	1.1 (-3.7-6.0)	0.645	4.6 (1.8-7.3)	6.0 (3.5-8.6)	-1.4 (-5.2-2.2)	0.428

* Missing values UDI:7, CRADI:4, UIQ:2, CRAIQ:2

** Missing values, UDI:19, CRADI:17, UIQ:15, CRAIQ:15

*** Missing values UDI:10, CRADI:12, UIQ:8, CRAIQ:10

¶ A positive mean difference in symptoms scores (UDI-6 and CRADI-8) and quality of life parameters (UIQ and CRAIQ) indicates improvement in the control group whereas a negative mean difference indicated improvement in the intervention group

colorectal-anal distress [8, 9, 11, 12, 17]. A systematic review on fecal incontinence in adults reported conflicting results in different studies comparing PFMT to other conservative treatments such as dietary advice, medical management and PFMT with biofeedback [11]. This review included both genders and varying treatment durations from 1 to 12 months, thus making it difficult to generalize [11]. Our results are consistent with previous studies on women with severe POP where peri- and postoperative PFMT did not alter symptoms of urinary and colorectal-anal distress [14, 15]. A recent study by Duarte et al. included a preoperative intervention period of 2 weeks and reported an overall improvement in symptoms and quality of life (using PFDI-20, PFIQ-7 and subscales) for all women scheduled for POP surgery, without clear advantage from PFMT in the intervention group, which agrees with our findings [14]. The study excluded women with previous POP surgery and covered a shorter postoperative follow-up of 90 days [14]. In contrast, 10% of the women in the current study had prior POP surgery, and they were followed 6 months to observe any durable effects. Tools used for symptom assessment differ between studies, and the intervention in the current study was exclusively preoperative whereas the intervention in most prior studies was mainly postoperative PFMT [15, 16]. McClurg et al. demonstrated a postoperative reduction of prolapse symptoms in the intervention group, but no effect on incontinence symptoms, although the participants had milder prolapses and other adjuncts such as electrical stimulation and biofeedback were also applied in addition to PFMT [16]. Incontinence and POP symptoms did not improve after PFMT alone in a study by Frawley et al., although they reported less de novo stress incontinence after PFMT [15]. However, the intervention consisted of only one supervised preoperative PFMT session followed by seven sessions over 1 year, and women scheduled for hysterectomy for other indications than POP were included [15]. A study by Jarvis et al. included women scheduled for urinary incontinence or POP surgery with 12-week follow-up and found reduced stress urinary incontinence after PFMT, but it is unclear whether the positive effect of PFMT was found only in women with isolated incontinence or also in women with POP [18].

The main clinical implication of our findings is that women scheduled for POP surgery have no additional benefit of PFMT on urinary and colorectal-anal symptoms. Women with advanced POP and complex injuries to the pelvic floor may need more supervised and intensive exercise or additional treatments such as nerve stimulation to increase strength. In a previous publication from this RCT, we found no difference in muscle strength or POP symptoms between the intervention and control groups [25]. The failure to improve pelvic floor muscle strength is a possible explanation for the lack of effect also on urinary and colorectal-anal distress. They experienced improved pelvic floor muscle contraction after surgery, which may explain the results from the present study of reduced

Table 3 Mean values, median and range for total population at baseline and postoperative follow-up, showing mean difference and 95% confidence interval (95% CI) with positive values indicating reduction of symptoms and related impact on quality of life scores postoperatively

	Baseline n=151[*]	Postoperative follow-up n=148[*]	Difference between baseline and postoperative follow-up	
	Mean (95% CI)	Mean (95% CI)	Mean difference (95% CI)	p
Symptoms- subscales (range 0–100)				
Urinary distress inventory (UDI-6)	37.2 (33.3–41.2)	16.9 (13.8–20.0)	20.3 (16.0–24.6)	<0.001
Colorectal-anal distress inventory (CRADI-8)	21.9 (19.2–24.6)	13.8 (11.4–16.2)	8.1 (5.5–10.7)	<0.001
Quality of life subscale range (0–100)				
Urinary impact questionnaire (UIQ)	27.7 (23.5–31.9)	10.0 (7.2–12.9)	17.7 (13.7–21.7)	<0.001
Colorectal-anal impact questionnaire (CRAIQ)	15.7 (12.2–19.4)	5.3 (3.4–7.3)	10.4 (6.9–14.0)	<0.001

[*] Missing values UDI:16, CRADI:16, UIQ:10, CRAIQ:12

urinary and colorectal-anal distress and improved quality of life at the postoperative follow-up [25]. With 60% of women having POP stage ≥ 3, it seems likely that advanced POP poses limitations to correct muscle contraction for sufficient clinical and subjective improvement. In addition, the large reduction in symptoms and improvement of quality of life after surgery may obscure any additional minor effect of PFMT after surgery. Latent stress urinary incontinence can

appear after anterior compartment correction and may also be a reason for failing to detect any effect of PFMT on urinary distress in this cohort [26]. The etiology of urinary and colorectal-anal distress is complex and not solely dependent on weak pelvic floor muscle function [1, 4, 5, 27]. This cohort consists of women with extensive pelvic floor injuries, such as levator muscle injury, sphincter injury and nerve damage, all possibly contributing to the development and persistence of
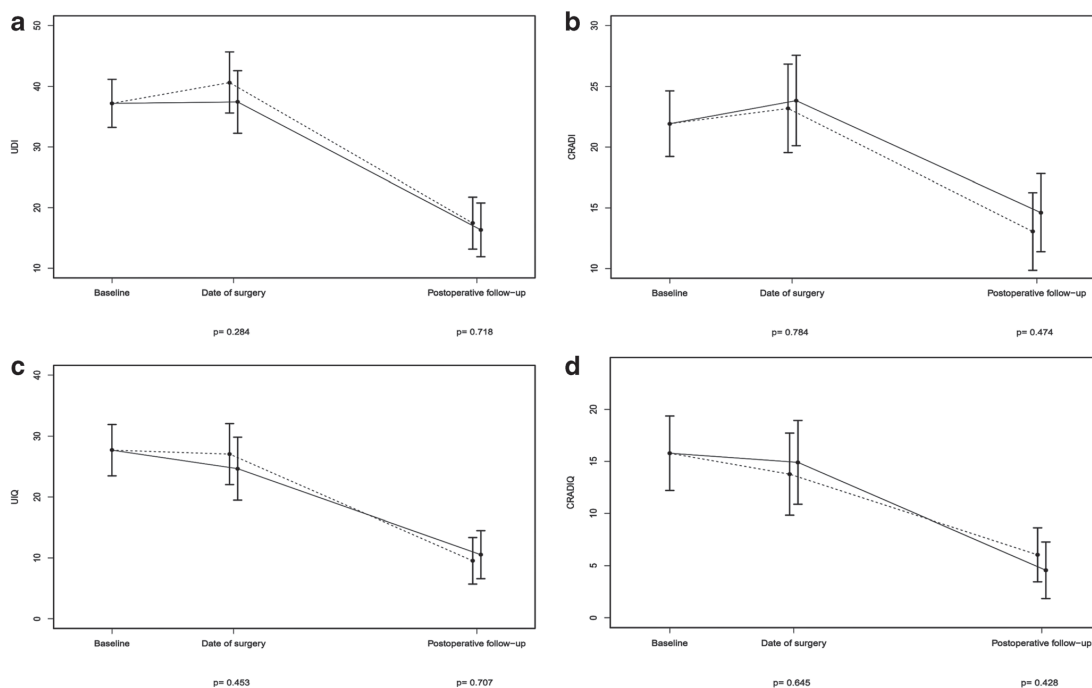

Fig. 2 Figure comparing symptoms and related quality of life in the intervention group (solid line) and the control group (dashed line) from baseline to the day of surgery and the postoperative follow-up, using linear mixed models analysis. Examination time (baseline, day of surgery and postoperative follow-up) on the x-axis and mean score with 95% confidence interval on the y-axis of the **a** urinary distress inventory (UDI-6), **b** colorectal-anal distress inventory (CRADI-8), **c** urinary impact questionnaire (UIQ) and **d** colorectal-anal impact questionnaire (CRAIQ)

urinary or colorectal-anal symptoms [1]. Other chronic diseases and lifestyle habits also contribute to symptoms [1, 2].

The main strength of the present study was the randomized controlled design and the large study size. The intervention consisted of daily PFMT and 80% of women in the intervention group maintained ≥ 70% adherence, indicating that the training program was acceptable for most women scheduled for POP surgery. We included women with advanced POP in any compartment and those with prior POP surgery, representing a heterogenous cohort commonly encountered in urogynecological practice and further increasing the clinical relevance of this study. The intervention lasted on average 22 weeks, which should be sufficient to achieve muscle hypertrophy [8, 22, 23]. No adjunctive treatments such as biofeedback or nerve stimulation were given in order to uncover the exclusive effects of PFMT. Validated questionnaires designed for evaluating distress and quality of life related to urinary and colorectal-anal symptoms were used [20, 21]. We used mixed models statistics for assessment of symptoms over time and between the groups, making it possible to use all data available also for women with missing data at the day of surgery or postoperative follow-up.

A limitation was that we did not register the number of women with previous incontinence surgery. However, the randomization ensured similar distribution to the intervention and control group for both previous surgery and other potential confounders. Another limitation was that we did not record whether women in the control group performed PFMT, and this might dilute any possible difference between the groups. Participants were not blinded to the intervention, and therefore women in the intervention group might have scored higher on quality of life because of an expectation of improvement. Examining gynecologists were not blinded to group allocation at the day of surgery or at the postoperative follow-up, but since this study only presents patient-reported outcomes, this would not be relevant to the outcome. Women declining randomization were significantly older; hence, the results may not apply to the older segment of POP patients. No power calculation was performed for these outcome measures, but the women had symptom scores between 20–40 out of 100. Hence, with 75 and 76 women in each group we would expect to find a clinical and statistically significant difference in symptom scores after intervention if there were any effect of PFMT.

Conclusion

In women with advanced POP scheduled for surgery, we found no added effect of preoperative PFMT on symptoms or quality of life related to urinary or colorectal-anal distress 6 months after surgery. Surgical prolapse correction decreased urinary and colorectal-anal symptoms and improved quality of life related to these symptoms. There is a need for long-term trials of intensive PFMT in women after corrective POP surgery in order to investigate the comprehensive effect on urinary and colorectal-anal distress and de novo incontinence.

Compliance with ethical standards

Conflict of interest None.

References

1. Wu JM, Vaughan CP, Goode PS, Redden DT, Burgio KL, Richter HE, Markland AD. Prevalence and trends of symptomatic pelvic floor disorders in US women. Obstet Gynecol. 2014;123(1):141–8. https://doi.org/10.1097/AOG.

2. Boreham MK, Richter HE, Kenton KS, Nager CW, Gregory WT, Aronson MP, Vogt VY, McIntire DD, Schaffer JI. Anal incontinence in women presenting for gynecologic care: prevalence, risk

factors, and impact upon quality of life. Am J Obstet Gynecol. 2005;192(5):1637–42.

3. Rømmen K, Schei B, Rydning A, Sultan AH, Mørkved S. Prevalence of anal incontinence among Norwegian women: a cross-sectional study. BMJ Open. 2012;2(4):e001257.

4. Guzmán Rojas RA, Kamisan Atan I, Shek KL, Dietz HP. Anal sphincter trauma and anal incontinence in urogynecological patients. Ultrasound Obstet Gynecol. 2015;46(3):363–6.

5. Wu JM, Matthews CA, Conover MM, Pate V, Jonsson Funk M. Lifetime risk of stress urinary incontinence or pelvic organ prolapse surgery. Obstet Gynecol. 2014;123(6):1201–6. https://doi.org/10.1097/aog.

6. Delancey JO, Kane Low L, Miller JM, Patel DA, Tumbarello JA. Graphic integration of causal factors of pelvic floor disorders: an integrated life span model. Am J Obstet Gynecol. 2008;199(6):610.e611-615. https://doi.org/10.1016/j.ajog.2008.04.001.

7. Bo K, Frawley HC, Haylen BT, Abramov Y, Almeida FG, Berghmans B, Bortolini M, Dumoulin C, Gomes M, McClurg D, Meijlink J, Shelly E, Trabuco E, Walker C, Wells A. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for the conservative and nonpharmacological management of female pelvic floor dysfunction. Int Urogynecol J. 2017;28(2):191–213. https://doi.org/10.1007/s00192-016-3123-4.

8. Braekken IH, Majida M, Engh ME, Bo K. Can pelvic floor muscle training reverse pelvic organ prolapse and reduce prolapse symptoms? An assessor-blinded, randomized, controlled trial. Am J Obstet Gynecol. 2010;203(2):170.e171-177. https://doi.org/10.1016/j.ajog.2010.02.037.

9. Dumoulin C, Cacciari LP, Hay-Smith EJC (2018) Pelvic floor muscle training versus no treatment, or inactive control treatments, for urinary incontinence in women. Cochrane Database Syst Rev (10): CD005654. https://doi.org/10.1002/14651858.CD005654.pub4

10. Sigurdardottir T, Steingrimsdottir T, Geirsson RT, Halldorsson TI, Aspelund T, Bo K. Can postpartum pelvic floor muscle training reduce urinary and anal incontinence?: an assessor-blinded randomized controlled trial. Am J Obstet Gynecol. 2019. https://doi.org/10.1016/j.ajog.2019.09.011.

11. Simillis C, Lal N, Pellino G, Baird D, Nikolaou S, Kontovounisios C, Smith JJ, Tekkis PP. A systematic review and network meta-analysis comparing treatments for faecal incontinence. Int J Surg. 2019;66:37–47. https://doi.org/10.1016/j.ijsu.2019.04.007.

12. Woodley SJ, Lawrenson P, Boyle R, Cody JD, Mørkved S, Kernohan A, Hay-Smith EJC. Pelvic floor muscle training for preventing and treating urinary and faecal incontinence in antenatal and postnatal women. Cochrane Database Syst Rev. 2020;5(5):Cd007471. https://doi.org/10.1002/14651858.CD007471.pub4.

13. Mazur-Bialy AI, Kołomańska-Bogucka D, Opławski M, Tim S. Physiotherapy for prevention and treatment of fecal incontinence in women—systematic review of methods. J Clin Med. 2020;9(10):3255.

14. Duarte TB, Bo K, Brito LGO, Bueno SM, Barcelos TM, Bonacin MA, Ferreira CH. Perioperative pelvic floor muscle training did not improve outcomes in women undergoing pelvic organ prolapse surgery: a randomised trial. J Physiother. 2020;66(1):27–32. https://doi.org/10.1016/j.jphys.2019.11.013.

15. Frawley HC, Phillips BA, Bø K, Galea MP. Physiotherapy as an adjunct to prolapse surgery: an assessor-blinded randomized controlled trial. Neurourol Urodyn. 2010;29(5):719–25. https://doi.org/10.1002/nau.20828.

16. McClurg D, Hilton P, Dolan L, Monga A, Hagen S, Frawley H, Dickinson L. Pelvic floor muscle training as an adjunct to prolapse surgery: a randomised feasibility study. Int Urogynecol J. 2014;25(7):883–91. https://doi.org/10.1007/s00192-013-2301-x.

17. Haya N, Feiner B, Baessler K, Christmann-Schmid C, Maher C. Perioperative interventions in pelvic organ prolapse surgery. Cochrane Database Syst Rev. 2018;8(8):Cd013105. https://doi.org/10.1002/14651858.Cd013105.

18. Jarvis SK, Hallam TK, Lujic S, Abbott JA, Vancaillie TG. Peri-operative physiotherapy improves outcomes for women undergoing incontinence and or prolapse surgery: results of a randomised controlled trial. Aust N Z J Obstet Gynaecol. 2005;45(4):300–3. https://doi.org/10.1111/j.1479-828X.2005.00415.x.

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

20. Barber MD, Walters MD, Bump RC. Short forms of two condition-specific quality-of-life questionnaires for women with pelvic floor disorders (PFDI-20 and PFIQ-7). Am J Obstet Gynecol. 2005;193(1):103–13. https://doi.org/10.1016/j.ajog.2004.12.025.

21. Teig CJ, Grotle M, Bond MJ, Prinsen CAC, Engh MAE, Cvancarova MS, Kjollesdal M, Martini A. Norwegian translation, and validation, of the Pelvic Floor Distress Inventory (PFDI-20) and the Pelvic Floor Impact Questionnaire (PFIQ-7). Int Urogynecol J. 2017;28(7):1005–17. https://doi.org/10.1007/s00192-016-3209-z.

22. Garcia-Sanchez E, Avila-Gandia V, Lopez-Roman J, Martinez-Rodriguez A, Rubio-Arias JA (2019) What pelvic floor muscle training load is optimal in minimizing urine loss in women with stress urinary incontinence? A systematic review and meta-analysis. Int J Environ Res Public Health 16 (22). https://doi.org/10.3390/ijerph16224358

23. Bø K, Talseth T, Holme I. Single blind, randomised controlled trial of pelvic floor exercises, electrical stimulation, vaginal cones, and no treatment in management of genuine stress incontinence in women. BMJ. 1999;318(7182):487–93. https://doi.org/10.1136/bmj.318.7182.487.

24. Dumoulin C, Hay-Smith J, Frawley H, McClurg D, Alewijnse D, Bo K, Burgio K, Chen S-Y, Chiarelli P, Dean S, Hagen S, Herbert J, Mahfooza A, Mair F, Stark D, Van Kampen M. 2014 consensus statement on improving pelvic floor muscle training adherence: international continence society 2011 state-of-the-science seminar. NeurourolUrodyn. 2015;34(7):600–5. https://doi.org/10.1002/nau.22796.

25. Nyhus M, Mathew S, Salvesen Ø, Salvesen K, Stafne S, Volløyhaug I. The effect of preoperative pelvic floor muscle training on pelvic floor contraction, symptomatic and anatomical pelvic organ prolapse after surgery: a randomized controlled trial. Ultrasound Obstet Gynecol. 2020. https://doi.org/10.1002/uog.22007.

26. Davenport MT, Sokol ER, Comiter CV, Elliott CS. Does the degree of cystocele predict de novo stress urinary incontinence after prolapse repair? Further analysis of the colpopexy and urinary reduction efforts trial. Female Pelvic Med Reconstr Surg. 2018;24(4):292–4. https://doi.org/10.1097/spv.

27. Mathew S, Guzmán Rojas RA, Salvesen KA, Volløyhaug I. Levator ani muscle injury and risk for urinary and fecal incontinence in parous women from a normal population, a cross-sectional study. Neurourol Urodyn. 2019;38(8):2296–302. https://doi.org/10.1002/nau.24138.

12.0 APPENDICES

1	UROPRO	
		Patient information and consent form
		Questionnaires
2	CONTRAPOP	
		Patient information and consent form
3	CONTRAPOP	
		Questionnaires
4	CONTRAPOP	
		Information on pelvic floor muscle exercise and lifestyle advice
5	CONTRAPOP	
		Training diary and supplementary form

Appendix 1

UROPRO

Patient information and consent form

Questionnaires

INFORMASJONSHEFTE

Forespørsel om deltakelse i studie

Detalj fra "du sang I" May Bente Aronsen

UROPRO
-en studie om
underlivsfremfall og lekkasje
hos kvinner

NTNU
Det skapende universitet

ST. OLAVS HOSPITAL
UNIVERSITETSSYKEHUSET I TRONDHEIM

Norske Kvinners Sanitetsforening

ExtraStiftelsen
Helse og Rehabilitering

DELTAKELSE I STUDIEN ER FRIVILLIG

Vi ber om at du returnerer samtykkeerklæring og spørreskjema i vedlagte svarkonvolutt innen to uker.

eller

Du kan besvare samtykke og spørreskjema ved å gå inn på www.nsfm.no/uropro

BLANT STUDIEDELTAKERNE TREKKER VI UT EN VINNER AV EN iPad

HVA INNEBÆRER STUDIEN FOR DEG?

Alle som deltar i studien fyller ut et **spørreskjema** om symptomer på underlivsfremfall og lekkasje

Noen av studiedeltakerne, som på forhånd samtykker til det, møter til **undersøkelse** ved St. Olavs Hospital i Trondheim

-Vi undersøker styrke i bekkenbunnsmuskler, og måler grad av fremfall

-Vi undersøker bekkenbunnsmusklene med ultralyd

Mer informasjon om studien finner du i vedlagte informasjonshefte

Forsidebilde: Detalj fra "du sang I" May Bente Aronsen

INVITASJON TIL Å DELTA I STUDIE

Vi vil undersøke om ulike fødselsmåter har innvirkning på utvikling av fremfall fra underlivet.

Vi innhenter opplysninger fra en gruppe kvinner som fødte sitt første barn i perioden 1990-1997.

Du er valgt ut til å kunne delta fordi du fødte ved St. Olavs Hospital i denne perioden.

UROPRO – en studie om underlivsfremfall og lekkasje hos kvinner

NTNU
Det skapende universitet

Foto: NTNU

Studien gjennomføres i regi av Kvinneklinikken ved St. Olavs Hospital og NTNU

Studien er godkjent av Regional komite for medisinsk og helsefaglig forskningsetikk Midt-Norge.

Studien er finansiert med midler fra Extrastiftelsen og Norske Kvinners Sanitetsforening.

KONTAKTINFORMASJON

Prosjektleder: Professor Kjell Å salvesen, Institutt for laboratoriemedisin, barne- og kvinnesykdommer, NTNU

Studieleder: Overlege Ingrid Volløyhaug, Kvinneklinikken, St. Olavs Hospital

Har du spørsmål?

-Skriv mail til: uropro@stolav.no

-Telefon: 90 25 45 39

NTNU
Det skapende universitet

ST. OLAVS HOSPITAL
UNIVERSITETSSYKEHUSET I TRONDHEIM

ExtraStiftelsen
helse og rehabilitering

Norske Kvinners Sanitetsforening

"Fødselstype og risiko for underlivsfremfall"
*Delivery method and risk for **uro**genital **pro**lapse*
UROPRO

Bakgrunn og hensikt
Dette er et spørsmål til deg om å delta i en forskningsstudie for å undersøke om fødsel med tang eller vakuum/sugekopp har innvirkning på utvikling av fremfall fra underlivet. Vi undersøker fire grupper av kvinner som fødte sitt første barn i perioden 1990-1997: Gruppe1: Tangfødsel, gruppe 2: fødsel med vakuum/sugekopp, gruppe3: vanlig fødsel og gruppe 4: keisersnitt. Du er valgt ut til å delta fordi du var førstegangsfødende i perioden 1990-1997 og tilhører en av de fire gruppene. Studien gjennomføres i regi av Kvinneklinikken ved St. Olavs Hospital og NTNU (Norges Teknisk Naturvitenskapelige Universitet)

Hva innebærer studien?
Studien er todelt.
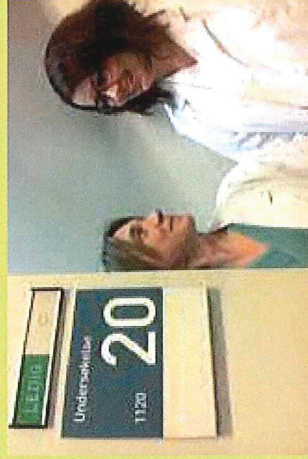Del 1: Alle studiedeltakere blir bedt om å fylle ut et spørreskjema. Dette kan fylles ut i vedlagt papirutgave og sendes i vedlagte konvolutt, eller besvares elektronisk ved å gå inn på websiden: www.nsfm.no/uropro og logge inn med deltakernummer, som du finner i øverste høyre hjørne på spørreskjemaet.
Spørreskjemaet inneholder spørsmål om fødsler og operasjoner i underlivet, inkontinens for urin og avføring og symptomer på fremfall fra underlivet. Utfylling av spørreskjema tar ca. 30 minutter.
Det er mulig å delta bare på del 1, uten å samtykke til å delta i del 2 av studien.

Del 2: Et utvalg av studiedeltakere, som på forhånd har samtykket til det, blir invitert til klinisk undersøkelse. Dette innebærer oppmøte ved Kvinneklinikken, St. Olavs Hospital i Trondheim. Det blir gjennomført en gynekologisk undersøkelse, der vi også undersøker styrke i bekkenbunnsmuskler, og måler grad av fremfall (hos dem som har denne tilstanden). I tillegg undersøker vi bekkenbunnsmusklene med ultralyd ved hjelp av en ultralydprobe som settes mot huden på utsiden av skjedeåpningen (ikke inne i skjeden). Undersøkelsen tar ca. 30-45 minutter.

Mulige fordeler og ulemper
Del 1: Det er ingen spesielle fordeler for studiedeltakeren med å utfylle spørreskjema. Ulempen er tiden det tar å fylle ut skjemaet.

Del 2: Fordelen med den kliniske undersøkelsen er at man får en grundig undersøkelse av bekkenbunnsmuskler og eventuelt fremfall, og at det er mulig å fange opp problemer hos den enkelte studiedeltaker og henvise til videre undersøkelser og behandling dersom det er ønskelig. Det er imidlertid ingen fullstendig gynekologisk undersøkelse med celleprøvetaking og ultralyd av eggstokker og livmor. Ulempene er tiden det tar å reise til sykehuset for å bli undersøkt, og noen vil kunne oppleve undersøkelsen som litt ubehagelig. Det er ingen risiko forbundet med undersøkelsen.

Blant de som samtykker til deltakelse i studien vil det bli trukket ut en heldig vinner av en iPad.

Kapittel A- utdypende forklaring av hva studien innebærer

Kriterier for deltakelse
Førstegangsfødende ved RiT/St.Olavs Hospital i perioden 1990-1997
Vaginal fødsel; enten vanlig (normal) eller med tang eller vakuum/sugekopp, eller keisersnitt.
Bostedsadresse i en av følgende kommuner på det tidspunkt fødselen fant sted: Klæbu, Malvik, Melhus, Midtre Gauldal, Rissa, Selbu, Trondheim, Tydal, Åfjord
Studiedeltaker må kunne forstå norsk og være i stand til å fylle ut spørreskjema.

Bakgrunnsinformasjon om studien
Mange kvinner opplever plager av urinlekkasje og underlivsfremfall. En av ti kvinner vil ha behov for operasjon for disse plagene innen de fyller 80 år. Vi ønsker å finne ut mer om årsaken til at enkelte kvinner utvikler slike plager og andre ikke gjør det. Studier fra andre land har vist at visse forhold under fødsel kan ha innvirkning på utvikling av fremfall, men studiene er utført i land som driver fødselshjelp på en annen måte enn hva vi gjør i Norge. Vi vet at skader på bekkenbunnsmuskulaturen og styrke i bekkenbunnsmuskulaturen har betydning for utvikling av lekkasje og fremfall. Det er mangel på studier som undersøker kvinner så lenge som 15-20 år etter at de fødte sitt første barn.
Vi håper at resultatene fra studien kan gi oss informasjon som gjør at vi i større grad kan forebygge utvikling av urinlekkasje og underlivsfremfall i fremtiden.

Spørreskjema
Studien innebærer utfylling av spørreskjema med spørsmål om operasjoner i underlivet, overgangsalder, hormonbruk, røyking, høyde og vekt. Deretter følger spørsmål om urinlekkasje, symptomer på fremfall fra underlivet og avføringslekkasje, samt i hvilken grad slike symptomer eventuelt påvirker hverdagen din. Grunnen til at vi stiller spørsmål også om urinlekkasje og avføringslekkasje er at disse plagene ofte har sammenheng med symptomer på underlivsfremfall. Se vedlagt spørreskjema for detaljer.
Spørreskjemaet kan besvares enten ved å fylle ut vedlagte skjema og returnere i svarkonvolutt, eller ved å gå inn på websiden: nsfm.no/uropro og logge inn med din personlige kode som du finner i øverste høyre hjørne på spørreskjemaet. Når skjemaet besvares elektronisk og du trykker send inn, har du samtidig gitt ditt samtykke til å delta i studien.

Undersøkelser
Et utvalg av de som samtykker til deltakelse i del 2 av studien blir innkalt til klinisk undersøkelse. Dette er en gynekologisk undersøkelse som utføres av en erfaren kvinnelig gynekolog. Under undersøkelsen må du være avkledd nedentil, og du må ligge i gynekologisk undersøkelsesstol.
Gynekologen starter med å undersøke muskulaturen i bekkenbunnen med en finger i skjeden. Du vil bli bedt om å stramme bekkenbunnsmuskulaturen, og du får instruksjon om hvordan du skal gjøre dette. Når den som undersøker kjenner at du kniper riktig, vil det bli ført inn et lite ballongkateter i skjeden. Dette er på tykkelse med en finger, og du blir bedt om å knipe rundt ballongkateteret, slik at måling av muskelstyrken vises direkte på en dataskjerm.
Deretter vil du bli bedt om å slappe av i bekkenbunnsmusklene og trykke/presse nedover. Mens du gjør dette, blir det gjort mål med en målepinne i skjeden for å måle tendens til fremfall.

Til slutt gjennomføres en ultralydundersøkelse av bekkenbunnsmusklene. Gynekologen setter en ultralydprobe mot skjedeåpningen, og du vil bli bedt om å stramme bekkenbunnsmusklene og deretter å slappe av og trykke/presse nedover.

Tidsskjema
Del 1: Samtykkeerklæring og spørreskjema er vedlagt og returneres så snart som mulig og senest innen to uker etter at du har mottatt dette brevet. Alternativt kan samtykkeerklæring og spørreskjema fylles ut og leveres elektronisk på nsfm.no/uropro.

Del 2: Etter at vi har fått inn alle spørreskjema og samtykkeerklæringer, vil et utvalg av dem som har gitt sitt samtykke, bli innkalt til klinisk undersøkelse. Dette skjer i løpet av 2013. Du får beskjed i god tid (ca 3-4 uker) før den oppsatte timen.

Mulige fordeler
Det blir utført en grundig undersøkelse av bekkenbunnsmusklene og tendens til fremfall hos studiedeltakerne. Dersom det gjøres funn som tilsier videre utredning eller behandling, vil det bli gitt kontrolltime eller henvisning til riktig instans.

Mulige bivirkninger
Vi kjenner ikke til mulige bivirkninger av undersøkelsen

Mulige ubehag/ulemper
Ulempen er den enkelte studiedeltakers tidsbruk i forbindelse med utfylling av spørreskjema og fremmøte til klinisk undersøkelse.

Den kliniske undersøkelsen kan av enkelte oppleves som ubehagelig, men undersøkelsen er ikke smertefull.

Pasientens/studiedeltakerens ansvar
De som har sagt seg villig til å delta i del 2 av studien, er ansvarlige for å møte opp til undersøkelse til oppsatt tidspunkt eller varsle studieleder eller sekretær dersom tidspunktet ikke passer.

Dersom situasjoner gjør at din deltagelse i studien blir avsluttet tidligere enn planlagt, vil du få beskjed om dette.

Kapittel B - Personvern, biobank, økonomi og forsikring

Personvern
Opplysninger som registreres om deg er:
Del 1:
1) Opplysninger knyttet til din første fødsel. Dette er opplysninger vi finner i sykehusets Pasientadministrative System, PAS, og som kontrolleres opp mot journalopplysninger.
2) Opplysninger om operasjoner i underlivet, overgangsalder, hormonbruk, røyking, høyde og vekt. Opplysninger om urinlekkasje, avføringslekkasje og symptomer å fremfall fra underlivet. Dette er opplysninger du gir oss ved å besvare spørreskjemaet.
Del 2:
3) Opplysninger om styrke i bekkenbunnsmuskulaturen, objektive mål på fremfall, ultralydundersøkelse av bekkenbunnsmuskulaturen. Dette er opplysninger vi samler inn ved den kliniske undersøkelsen

Det kan bli aktuelt at studieleder går inn i journalen din for å kontrollere at studieopplysningene stemmer overens med tilsvarende opplysninger i din journal. Alle som får innsyn har taushetsplikt.

Andre forskere enn de som er tilknyttet den aktuelle studien vil ikke ha tilgang til opplysningene om deg.

St. Olavs hospital ved administrerende direktør er databehandlingsansvarlig.

Rett til innsyn og sletting av opplysninger om deg og sletting av prøver
Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra studien, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.

Økonomi og NTNU/ St. Olavs rolle
Ingen person, institusjon eller firma med interesse av egen økonomisk gevinst er involvert i studien.

Studien er finansiert gjennom forskningsmidler fra NTNU, St. Olavs Hospital, Norske Kvinners Sanitetsforening og Extrastiftelsen. Studieleder er lønnet av NTNU, St. Olavs Hospital, Norske Kvinners Sanitetsforening og Extrastiftelsen. Vi kjenner ikke til mulige interessekonflikter.

Forsikring
Vanlig pasientskadeforsikring gjelder for deltakerne i studien.

Informasjon om utfallet av studien
Som studiedeltager har du rett til å få informasjon om utfallet av studien.

Studien er godkjent av Regional komite for medisinsk og helsefaglig forskningsetikk Midt-Norge.

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 prøver gjennom en navneliste.
Det er kun autorisert personell knyttet til prosjektet som har adgang til navnelisten og som kan finne tilbake til deg.
Informasjonen om deg blir slettet etter at resultatene av studien foreligger.
Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres.

Frivillig deltakelse
Det er frivillig å delta i studien. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke til å delta i studien. Dette vil ikke få konsekvenser for din videre behandling. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Om du nå sier ja til å delta, kan du senere trekke tilbake ditt samtykke uten at det påvirker din øvrige behandling. Dersom du senere ønsker å trekke deg eller har spørsmål til studien, kan du kontakte:

Studieleder:
Overlege Ingrid Volløyhaug, Kvinneklinikken, St. Olavs Hospital, Postboks 3250 Sluppen, N-7006 Trondheim
Telefon: 90 25 45 39
e-mail: uropro@stolav.no

Prosjektansvarlig:
Professor Kjell Å. Salvesen, Institutt for laboratoriemedisin, barne- og kvinnesykdommer, NTNU, N-7489 Trondheim

Ytterligere informasjon om studien finnes i kapittel A – *utdypende forklaring av hva studien innebærer.*
Ytterligere informasjon om biobank, personvern og forsikring finnes i kapittel B – *Personvern, biobank, økonomi og forsikring.*

Samtykkeerklæring følger med spørreskjemaet enten du svarer i vedlagt papirutgave eller elektronisk

UROPRO

Samtykke til deltakelse i studien

Jeg er villig til å delta i studien

Del 1 spørreskjema ☐ Ja   ☐ Nei

Del 2 klinisk undersøkelse ☐ Ja   ☐ Nei

(Signert av prosjektdeltaker, dato)

Jeg bekrefter å ha gitt informasjon om studien

25.01.2013 _____ _Vollajnag_ _____

(Signert, prosjektleder, dato)

25138

Generell del

1) Fødsler

a) Hvor mange barn har du født totalt?   Antall ☐☐

b) Ditt første barn ble forløst med: (Kryss av i en rute)

☐ Vanlig/normal fødsel

☐ Tangfødsel

☐ Fødsel med vakumsug

☐ Keisersnitt

☐ Husker ikke   Fødselsvekt på ditt første barn (g) ☐☐☐☐

c) Hvilken type fødsel hadde du for dine påfølgende barn?
(Kryss av i en rute for hver fødsel, og fyll inn fødselsvekt dersom du husker det)

Fødselsvekt (g)

Barn nr 2   Type fødsel:
☐ Vanlig/normal fødsel   ☐ Vakum/ sugekopp   ☐ Husker ikke   ☐☐☐☐
☐ Tangfødsel   ☐ Keisersnitt

Barn nr 3   Type fødsel:
☐ Vanlig/normal fødsel   ☐ Vakum/ sugekopp   ☐ Husker ikke   ☐☐☐☐
☐ Tangfødsel   ☐ Keisersnitt

Barn nr 4   Type fødsel:
☐ Vanlig/normal fødsel   ☐ Vakum/ sugekopp   ☐ Husker ikke   ☐☐☐☐
☐ Tangfødsel   ☐ Keisersnitt

Barn nr 5   Type fødsel:
☐ Vanlig/normal fødsel   ☐ Vakum/ sugekopp   ☐ Husker ikke   ☐☐☐☐
☐ Tangfødsel   ☐ Keisersnitt

Barn nr 6   Type fødsel:
☐ Vanlig/normal fødsel   ☐ Vakum/ sugekopp   ☐ Husker ikke   ☐☐☐☐
☐ Tangfødsel   ☐ Keisersnitt

2) Overgangsalder

a) Har du kommet i overgangsalder (dvs. mer enn ett år siden siste menstruasjon)?
☐ Ja   ☐ Nei   ☐ Vet ikke

b) Hvis ja, hvilket år var siste menstruasjon? ☐☐☐☐

c) Har du tidligere brukt hormoner, enten tabletter eller i skjeden? ☐ Ja   ☐ Nei

d) Bruker du hormontabletter nå? ☐ Ja   ☐ Nei

e) Bruker du krem/tabletter/vagitorier som inneholder østrogen i skjeden nå?
☐ Ja   ☐ Nei

25138

3) Operasjoner

a) Har du fjernet livmoren? ☐ Ja   ☐ Nei

Hvis ja, hva var årsaken til at livmoren ble fjernet?
(Vennligst kryss av alt som passer for deg):

☐ Muskelknuter
☐ Blødningsforstyrrelser
☐ Smerter
☐ Fremfall/descens/nedsunken livmor
☐ Kreft
☐ Annet _____

b) Er du operert for urinlekkasje? ☐ Ja   ☐ Nei

Hvis ja, hvor mange ganger? ☐

c) Er du operert for avføringslekkasje? ☐ Ja   ☐ Nei

Hvis ja, hvor mange ganger? ☐

d) Er du operert for fremfall av skjedevegg/urinblære/ livmor/tarm? ☐ Ja   ☐ Nei

Hvis ja, hvor mange ganger? ☐

e) Har du brukt ringpessar for fremfall? ☐ Ja   ☐ Nei

f) Bruker du ringpessar nå? ☐ Ja   ☐ Nei

4) Er du seksuelt aktiv? *(Kryss av i en rute)*
☐ Ja
☐ Nei, pga symptomer fra underlivet (fremfall, lekkasje av urin, luft eller avføring)
☐ Nei, av annen årsak

5) Høyde/vekt

Oppgi så nøyaktig som mulig din aktuelle høyde og vekt

Høyde ☐☐☐ cm   Vekt ☐☐☐ kg

6) Røyk

Røyker du? ☐ Ja   ☐ Nei

Hvis ja, hvor mange sigaretter per dag? ☐☐

7) Hoste

Har du kronisk hoste/ astma/KOLS? ☐ Ja   ☐ Nei

Kartlegging av besvær fra bekkenbunnen.   Deltaker | 130001 |

Instruksjoner
Vær så snill og svar på spørreskjema så fullstendig som mulig. Spørsmålene viser om du har symptomer fra urinblære, tarm eller underliv og i så fall hvor mye disse plager deg. Sett en X i passende boks. Når du svarer skal du gå ut i fra dine symptomer de siste 3 måneder.

Eksempel

For det følgende spørsmål

Om du vanligvis ikke har hodepine, kryss bare i "Nei"-boks

Har du vanligvis hodepine?

☒ Nei   ☐ Ja   Hvis ja, hvor mye det plager det deg?
                ☐ Ingenting   ☐ Lite   ☐ Middels   ☐ Mye

Om du vanligvis har hodepine, kryss i "Ja"-boks og angi hvor mye hodepinen plager deg. I dette eksempelet er hodepinen middels plagsom.

Har du vanligvis hodepine?

☐ Nei   **☒ Ja**   Hvis ja, hvor mye plager det deg?
                ☐ Ingenting   ☐ Lite   **☒ Middels**   ☐ Mye

8. Opplever du vanligvis trykk i nedre del av buken?

    ☐ Nei   ☐ Ja   **Hvis ja, hvor mye plager det deg?**
                ☐ Ingenting   ☐ Lite   ☐ Middels   ☐ Mye

9. Har du vanligvis tyngdefølelse i underlivet?

    ☐ Nei   ☐ Ja   **Hvis ja, hvor mye plager det deg?**
                ☐ Ingenting   ☐ Lite   ☐ Middels   ☐ Mye

10. Har du vanligvis en kul i skjeden som du kan se eller kjenne i skjedeåpningen?

    ☐ Nei   ☐ Ja   **Hvis ja, hvor mye plager det deg?**
                ☐ Ingenting   ☐ Lite   ☐ Middels   ☐ Mye

11. Må du dytte av og til rundt endetarmen eller skjedeåpningen for å få tømt tarmen?

    ☐ Nei   ☐ Ja   **Hvis ja, hvor mye plager det deg?**
                ☐ Ingenting   ☐ Lite   ☐ Middels   ☐ Mye

12. Kan det vanligvis kjennes ut som om urinblæren ikke blir skikkelig tømt?

    ☐ Nei   ☐ Ja   **Hvis ja, hvor mye plager det deg?**
                ☐ Ingenting   ☐ Lite   ☐ Middels   ☐ Mye

25138

13. Har du noen gang trengt å dytte opp en kul i skjeden for å få tømt urinblæren fullstendig?

☐ Nei   ☐ Ja   **Hvis ja, hvor mye plager det deg?**
☐ Ingenting   ☐ Lite   ☐ Middels   ☐ Mye

14. Må du trykke mye for å ha avføring?

☐ Nei   ☐ Ja   **Hvis ja, hvor mye plager det deg?**
☐ Ingenting   ☐ Lite   ☐ Middels   ☐ Mye

15. Føler du at tarmen ikke blir fullstendig tømt når du har avføring?

☐ Nei   ☐ Ja   **Hvis ja, hvor mye plager det deg?**
☐ Ingenting   ☐ Lite   ☐ Middels   ☐ Mye

16. Lekker du vanligvis avføring når den er fast?

☐ Nei   ☐ Ja   **Hvis ja, hvor mye plager det deg?**
☐ Ingenting   ☐ Lite   ☐ Middels   ☐ Mye

17. Lekker du vanligvis avføring når den er løs?

☐ Nei   ☐ Ja   **Hvis ja, hvor mye plager det deg?**
☐ Ingenting   ☐ Lite   ☐ Middels   ☐ Mye

18. Har du vanligvis problemer med å holde på luft?

☐ Nei   ☐ Ja   **Hvis ja, hvor mye plager det deg?**
☐ Ingenting   ☐ Lite   ☐ Middels   ☐ Mye

19. Har du vanligs smerte når du har avføring?

☐ Nei   ☐ Ja   **Hvis ja, hvor mye plager det deg?**
☐ Ingenting   ☐ Lite   ☐ Middels   ☐ Mye

20. Opplever du iblant en så sterk trang til å ha avføring at du må skynde deg til toalettet?

☐ Nei   ☐ Ja   **Hvis ja, hvor mye plager det deg?**
☐ Ingenting   ☐ Lite   ☐ Middels   ☐ Mye

21. Opplever du iblant at noe tarm kan komme ut av endetarmen under eller etter avføring?

☐ Nei   ☐ Ja   **Hvis ja, hvor mye plager det deg?**
☐ Ingenting   ☐ Lite   ☐ Middels   ☐ Mye

22. Må du tisse ofte?

☐ Nei   ☐ Ja   **Hvis ja, hvor mye plager det deg?**
☐ Ingenting   ☐ Lite   ☐ Middels   ☐ Mye

23. Lekker du vanligvis urin når du får slik sterk vannlatningstrang?

☐ Nei ☐ Ja **Hvis ja, hvor mye plager det deg?**
☐ Ingenting ☐ Lite ☐ Middels ☐ Mye

24. Lekker du vanligvis urin ved hoste, nysing eller når du ler?

☐ Nei ☐ Ja **Hvis ja, hvor mye plager det deg?**
☐ Ingenting ☐ Lite ☐ Middels ☐ Mye

25. Lekker du vanligvis urin dråpevis?

☐ Nei ☐ Ja **Hvis ja, hvor mye plager det deg?**
☐ Ingenting ☐ Lite ☐ Middels ☐ Mye

26. Opplever du vanligvis vanskeligheter med å få tømt urinblæren?

☐ Nei ☐ Ja **Hvis ja, hvor mye plager det deg?**
☐ Ingenting ☐ Lite ☐ Middels ☐ Mye

27. Har du vanligvis smerte elle ubehag i nedre del av buken eller i underlivet?

☐ Nei ☐ Ja **Hvis ja, hvor mye plager det deg?**
☐ Ingenting ☐ Lite ☐ Middels ☐ Mye

Bekkenbunnbesvær og innvirkning av det i din hverdag

En del kvinner synes at symptomene fra urinblære, tarm eller skjede påvirker deres aktiviteter, relasjoner og følelser. Marker med en X det svar som best beskriver hvor mye din hverdag blir påvirket av symptomer eller plager fra urinblære, tarm eller skjede de siste 3 måneder. Vær så snill å kontroller at du markerer ett svar i alle 3 kolonnene for hvert spørsmål

Hvordan bruker vanligvis symptomer eller besvær fra <u>urinblære eller urin (blærekontroll)</u> påvirke din

28. Evne til å gjøre husarbeid?
☐ Ikke i det hele tatt ☐ Lite ☐ Middels ☐ Mye

29. Mulighet for fysisk aktivitet som f.eks. å gå turer, svømming, osv?
☐ Ikke i det hele tatt ☐ Lite ☐ Middels ☐ Mye

30. Mulighet til å gå på kino, konserter eller annen underholdning?
☐ Ikke i det hele tatt ☐ Lite ☐ Middels ☐ Mye

31. Evnen til å reise med bil eller buss lenger enn 30 min. hjemmefra?
☐ Ikke i det hele tatt ☐ Lite ☐ Middels ☐ Mye

32. Deltagelse i sosiale arrangement utenfor hjemmet?
☐ Ikke i det hele tatt ☐ Lite ☐ Middels ☐ Mye

25138

33. Mentale helse (nervøsitet, depresjon osv)?
☐ Ikke i det hele tatt   ☐ Lite   ☐ Middels   ☐ Mye

34. Følelse av frustrasjon?
☐ Ikke i det hele tatt   ☐ Lite   ☐ Middels   ☐ Mye

Hvordan bruker vanligvis symptomer eller besvær fra <u>tarm eller endetarm</u> påvirke din

35. Evne til å gjøre husarbeid?
☐ Ikke i det hele tatt   ☐ Lite   ☐ Middels   ☐ Mye

36. Mulighet for fysisk aktivitet som f.eks. å gå turer, svømming, osv?
☐ Ikke i det hele tatt   ☐ Lite   ☐ Middels   ☐ Mye

37. Mulighet til å gå på kino, konserter eller annen underholdning?
☐ Ikke i det hele tatt   ☐ Lite   ☐ Middels   ☐ Mye

38. Evnen til å reise med bil eller buss lenger enn 30 min. hjemmefra?
☐ Ikke i det hele tatt   ☐ Lite   ☐ Middels   ☐ Mye

39. Deltagelse i sosiale arrangement utenfor hjemmet?
☐ Ikke i det hele tatt   ☐ Lite   ☐ Middels   ☐ Mye

40. Mentale helse (nervøsitet, depresjon osv)?
☐ Ikke i det hele tatt   ☐ Lite   ☐ Middels   ☐ Mye

41. Følelse av frustrasjon?
☐ Ikke i det hele tatt   ☐ Lite   ☐ Middels   ☐ Mye

Hvordan bruker vanligvis symptomer eller besvær fra <u>skjede eller bekken</u> påvirke

42. Evne til å gjøre husarbeid?
☐ Ikke i det hele tatt   ☐ Lite   ☐ Middels   ☐ Mye

43. Mulighet for fysisk aktivitet som f.eks. å gå turer, svømming, osv?
☐ Ikke i det hele tatt   ☐ Lite   ☐ Middels   ☐ Mye

44. Mulighet til å gå på kino, konserter eller annen underholdning?
☐ Ikke i det hele tatt   ☐ Lite   ☐ Middels   ☐ Mye

45. Evnen til å reise med bil eller buss lenger enn 30 min. hjemmefra?
☐ Ikke i det hele tatt   ☐ Lite   ☐ Middels   ☐ Mye

46. Deltagelse i sosiale arrangement utenfor hjemmet?
☐ Ikke i det hele tatt   ☐ Lite   ☐ Middels   ☐ Mye

47. Mentale helse (nervøsitet, depresjon osv)?
☐ Ikke i det hele tatt   ☐ Lite   ☐ Middels   ☐ Mye

48. Følelse av frustrasjon?
☐ Ikke i det hele tatt   ☐ Lite   ☐ Middels   ☐ Mye

25138

Appendix 2

CONTRAPOP

Patient information and consent form

Anatomi og muskelstyrke i bekkenbunnen hos kvinner

CONTRAPOP

ST. OLAVS HOSPITAL
UNIVERSITETSSYKEHUSET I TRONDHEIM

NTNU
Kunnskap for en bedre verden

Maria Øyasæter Nyhus

St Olavs hospital / NTNU

01.01.2017

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:

Maria Øyasæter, stipendiat og overlege ved gynekologisk avdeling St. Olavs hospital
Maria.oyaseter@stolav.no. Tlf: 72576820/ 41646649
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

Appendix 3

CONTRAPOP

Visual Analogue Scale (VAS)

Pelvic Floor Distress Inventory (PFDI-20)

Pelvic Floor Impact Questionnaire (PFIQ-7)

☐ ☐ ☐ ■

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

12374

Spørreskjema om bekkenbunnsplager og innvirkning på dagliglivet (PFIQ-7)

Veiledning

Noen kvinner opplever at symptomer fra blæren, endetarmen eller skjeden påvirker deres gjøremål, forhold og følelser. For hvert av spørsmålene ber vi deg krysse av for svaret som best beskriver hvordan dine gjøremål, forhold eller følelser har blitt påvirket av symptomer eller plager fra blære, endetarm eller skjede **de tre siste månedene**.

Du kan ha, eller ikke ha symptomer innenfor hvert av disse tre områdene, men husk å svare i **alle tre kolonner** for hvert spørsmål. Hvis du ikke har symptomer på et av områdene, svarer du "ikke i det hele tatt" i den aktuelle kolonnen.

EKSEMPEL

Ved følgende spørsmål:
Hvis blærefunksjonen påvirker evnen din til å kjøre bil i noen grad, mens tarmfunksjonen bare påvirker evnen til å kjøre bil litt, og symptomer knyttet til skjede eller bekkenbunn ikke påvirker evnen til å kjøre bil i det hele tatt, skal du sette kryss (X) i boksene som vist nedenfor:

Hvordan pleier symptomer eller plager fra →→→→ å påvirke ↓	Blære eller urin	Tarm eller endetarm	Skjede eller bekkenbunn
1. din evne til å kjøre bil	☐ Ikke i det hele tatt ☐ Litt ☒ I noen grad ☐ Ganske mye	☒ Ikke i det hele tatt ☐ Litt ☐ I noen grad ☐ Ganske mye	☐ Ikke i det hele tatt ☒ Litt ☐ I noen grad ☐ Ganske mye

12374

Veiledning: Noen kvinner opplever at symptomer fra blæren, endetarmen eller skjeden påvirker deres gjøremål, forhold og følelser. For hvert av spørsmålene ber vi deg krysse av for svaret som best beskriver hvordan dine gjøremål, forhold eller følelser har blitt påvirket av symptomer eller plager fra blære, endetarm eller skjede **de tre siste månedene**. Husk å krysse av i **alle de tre kolonnene** for hvert spørsmål.

Hvordan pleier symptomer eller plager fra →→→→ å påvirke ↓	Blære eller urin	Tarm eller endetarm	Skjede eller bekkenbunn
1. din evne til å gjøre husarbeid (matlaging, rengjøring, klesvask)?	☐ Ikke i det hele tatt ☐ Litt ☐ I noen grad ☐ Ganske mye	☐ Ikke i det hele tatt ☐ Litt ☐ I noen grad ☐ Ganske mye	☐ Ikke i det hele tatt ☐ Litt ☐ I noen grad ☐ Ganske mye
2. din fysiske aktivitet, som turgåing, svømming eller annen mosjon?	☐ Ikke i det hele tatt ☐ Litt ☐ I noen grad ☐ Ganske mye	☐ Ikke i det hele tatt ☐ Litt ☐ I noen grad ☐ Ganske mye	☐ Ikke i det hele tatt ☐ Litt ☐ I noen grad ☐ Ganske mye
3. dine fritidsaktiviteter som å gå på kino eller konsert?	☐ Ikke i det hele tatt ☐ Litt ☐ I noen grad ☐ Ganske mye	☐ Ikke i det hele tatt ☐ Litt ☐ I noen grad ☐ Ganske mye	☐ Ikke i det hele tatt ☐ Litt ☐ I noen grad ☐ Ganske mye
4. din mulighet til å reise med bil eller buss i mer enn 30 minutter hjemmefra?	☐ Ikke i det hele tatt ☐ Litt ☐ I noen grad ☐ Ganske mye	☐ Ikke i det hele tatt ☐ Litt ☐ I noen grad ☐ Ganske mye	☐ Ikke i det hele tatt ☐ Litt ☐ I noen grad ☐ Ganske mye
5. din deltakelse i sosiale aktiviteter utenfor hjemmet?	☐ Ikke i det hele tatt ☐ Litt ☐ I noen grad ☐ Ganske mye	☐ Ikke i det hele tatt ☐ Litt ☐ I noen grad ☐ Ganske mye	☐ Ikke i det hele tatt ☐ Litt ☐ I noen grad ☐ Ganske mye
6. din psykiske helsetilstand (nervøsitet, depresjon osv)?	☐ Ikke i det hele tatt ☐ Litt ☐ I noen grad ☐ Ganske mye	☐ Ikke i det hele tatt ☐ Litt ☐ I noen grad ☐ Ganske mye	☐ Ikke i det hele tatt ☐ Litt ☐ I noen grad ☐ Ganske mye
7. din følelse av frustrasjon?	☐ Ikke i det hele tatt ☐ Litt ☐ I noen grad ☐ Ganske mye	☐ Ikke i det hele tatt ☐ Litt ☐ I noen grad ☐ Ganske mye	☐ Ikke i det hele tatt ☐ Litt ☐ I noen grad ☐ Ganske mye

12374

Spørreskjema om bekkenbunnsplager - PFDI-20

Veiledning

Vennligst svar på alle spørsmålene i spørreskjemaet. Spørsmålene dreier seg om hvorvidt du har visse symptomer i tarmen, blæren eller bekkenregionen, og i så fall hvor mye de plager deg. Svar på spørsmålene ved å krysse av i den eller de boksene som passer for deg. Hvis du er usikker på hva du skal svare, svarer du så godt du kan. Vær snill og svar på spørsmålene ut fra de symptomer du har hatt gjennom de siste tre månedene.

EKSEMPEL

Ved følgende spørsmål:

Hvis du ikke pleier å ha hodepine, setter du X i "Nei"- ruten.

Har du ofte hodepine? ☒ Nei   ☐ Ja
Hvis svaret er ja, hvor mye plager det deg?
☐ Ikke i det hele tatt   ☐ Litt   ☐ I noen grad   ☐ Ganske mye

Hvis du pleier å ha hodepine, setter du X i "Ja"-boksen og angir hvor mye hodepinen plager deg. (I dette eksemplet plages vedkommende av hodepinen i noen grad)

Har du ofte hodepine? ☐ Nei   ☒ Ja
Hvis svaret er ja, hvor mye plager det deg?
☐ Ikke i det hele tatt   ☐ Litt   ☒ I noen grad   ☐ Ganske mye

12374

1. Kjenner du ofte trykk i nedre del av magen? ☐ Nei ☐ Ja

Hvis ja, hvor mye plager det deg?
☐ Ikke i det hele tatt ☐ Litt ☐ I noen grad ☐ Ganske mye

2. Har du ofte tyngdefølelse i bekkenet? ☐ Nei ☐ Ja

Hvis ja, hvor mye plager det deg?
☐ Ikke i det hele tatt ☐ Litt ☐ I noen grad ☐ Ganske mye

3. Kjenner eller ser du ofte noe som buler eller faller ut i skjeden? ☐ Nei ☐ Ja

Hvis ja, hvor mye plager det deg?
☐ Ikke i det hele tatt ☐ Litt ☐ I noen grad ☐ Ganske mye

4. Må du ofte presse med fingre i skjeden eller rundt endetarmsåpningen ☐ Nei ☐ Ja
for å få ut avføring eller få tømt tarmen helt?

Hvis ja, hvor mye plager det deg?
☐ Ikke i det hele tatt ☐ Litt ☐ I noen grad ☐ Ganske mye

5. Føler du ofte at du ikke får tømt blæren helt? ☐ Nei ☐ Ja

Hvis ja, hvor mye plager det deg?
☐ Ikke i det hele tatt ☐ Litt ☐ I noen grad ☐ Ganske mye

6. Hender det at du må trykke inn med fingrene noe som ☐ Nei ☐ Ja
buler i skjeden, for å få tisset eller tømt blæren helt?

Hvis ja, hvor mye plager det deg?
☐ Ikke i det hele tatt ☐ Litt ☐ I noen grad ☐ Ganske mye

7. Føler du at du må presse for hardt for å få ut avføringen? ☐ Nei ☐ Ja

Hvis ja, hvor mye plager det deg?
☐ Ikke i det hele tatt ☐ Litt ☐ I noen grad ☐ Ganske mye

8. Føler du at du ikke har tømt tarmen helt, når du har hatt avføring?

Hvis ja, hvor mye plager det deg? ☐ Nei ☐ Ja

☐ Ikke i det hele tatt ☐ Litt ☐ I noen grad ☐ Ganske mye

9. Har du ofte avføringslekkasje når avføringen er fast? ☐ Nei ☐ Ja

Hvis ja, hvor mye plager det deg?
☐ Ikke i det hele tatt ☐ Litt ☐ I noen grad ☐ Ganske mye

10. Har du ofte avføringslekkasje når avføringen er løs eller flytende? ☐ Nei ☐ Ja

Hvis ja, hvor mye plager det deg?
☐ Ikke i det hele tatt ☐ Litt ☐ I noen grad ☐ Ganske mye

12374

11. Har du ofte ufrivillig lekkasje av luft fra tarmen? ☐ Nei ☐ Ja

Hvis ja, hvor mye plager det deg?
☐ Ikke i det hele tatt ☐ Litt ☐ I noen grad ☐ Ganske mye

12. Har du ofte smerter når du har avføring? ☐ Nei ☐ Ja

Hvis ja, hvor mye plager det deg?
☐ Ikke i det hele tatt ☐ Litt ☐ I noen grad ☐ Ganske mye

13. Opplever du så sterk avføringstrang at du må løpe til toalettet? ☐ Nei ☐ Ja

Hvis ja, hvor mye plager det deg?
☐ Ikke i det hele tatt ☐ Litt ☐ I noen grad ☐ Ganske mye

14. Hender det at en del av tarmen følger med ut gjennom ☐ Nei ☐ Ja
endetarmsåpningen under eller etter avføring?

Hvis ja, hvor mye plager det deg?
☐ Ikke i det hele tatt ☐ Litt ☐ I noen grad ☐ Ganske mye

15. Har du vanligvis hyppig vannlating? ☐ Nei ☐ Ja

Hvis ja, hvor mye plager det deg?
☐ Ikke i det hele tatt ☐ Litt ☐ I noen grad ☐ Ganske mye

16. Opplever du så sterk vannlatingstrang at du ☐ Nei ☐ Ja
ikke rekker til toalettet før du får lekkasje?

Hvis ja, hvor mye plager det deg?
☐ Ikke i det hele tatt ☐ Litt ☐ I noen grad ☐ Ganske mye

17. Har du ofte urinlekkasje når du hoster, nyser eller ler? ☐ Nei ☐ Ja

Hvis ja, hvor mye plager det deg?
☐ Ikke i det hele tatt ☐ Litt ☐ I noen grad ☐ Ganske mye

18. Har du ofte små urinlekkasjer (dvs. dråper)?

Hvis ja, hvor mye plager det deg? ☐ Nei ☐ Ja
☐ Ikke i det hele tatt ☐ Litt ☐ I noen grad ☐ Ganske mye

19. Har du ofte problemer med å tømme blæren? ☐ Nei ☐ Ja

Hvis ja, hvor mye plager det deg?
☐ Ikke i det hele tatt ☐ Litt ☐ I noen grad ☐ Ganske mye

20. Har du ofte smerte eller ubehag i nedre del ☐ Nei ☐ Ja
av magen eller underlivet?

Hvis ja, hvor mye plager det deg?
☐ Ikke i det hele tatt ☐ Litt ☐ I noen grad ☐ Ganske mye

12374

Appendix 4

CONTRAPOP

Information on pelvic floor muscle exercise and lifestyle advice

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:

Mageliggende:

Ryggliggende:

Froskestilling:

Stående opreist:

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.

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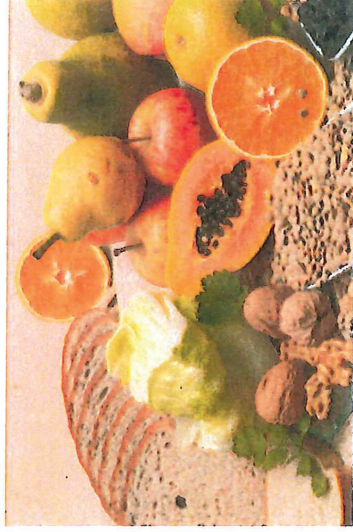
- Fiber: Kostfiber gjør avføringen fyldigere og mykere, finnes i helkornsprodukter og plantemat
- Mosjon: Det er vist at mindre til moderat mengde trening kan forebygge forstoppelse. Dette kan for eksempel være å gå eller løpe en tur daglig.
- Væske: Inntak av væske kan gjøre avføringen tyngre og glattere.

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!

Kilder:
St Olavs hospital:
https://stolav.no/behandlinger/bekkenbunnstrening
Helsenorge:
https://helsenorge.no/sykdom/mage-og-tarm/forstoppelse
Kompetanseportal for inkontinens og bekkenbunnssykdom:
http://kurs.helsekompetanse.no/kib-pasient/55567
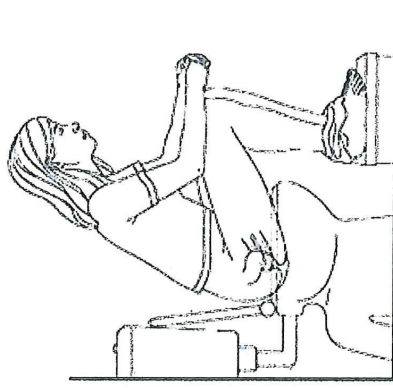
Appendix 5

CONTRAPOP

Training diary and supplementary form for women who did not submit training diary

Måned																		
Dato	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C
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																		

Telefonscreening for CONTRAPOP pasienter randomisert til bekkenbunnstrening

Dato

Studienummer: Pasient ID:

Inklusjonsdato: Operasjondato:

Spørsmål

1. Det gikk ……… uker fra inklusjon til operasjon, trente du hver dag?   Ja ☐   Nei ☐
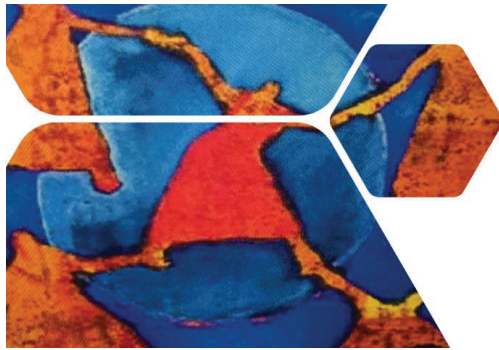
2. Hvor mange dager i uken trente du i gjennomsnitt? ☐

         Trente du mer eller mindre enn 5 dager i uken?   0-4 ☐   ≥5 ☐

3. Dersom du trente, hvor mange ganger pr dag trente du?   0 ☐   1 ☐   2 ☐   3 ☐

NTNU
Norwegian University of
Science and Technology