FACULTY OF HEALTH AND MEDICAL SCIENCES
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Lifestyle advice and pelvic floor muscle training for women with pelvic organ prolapse

PhD Thesis

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Scienticic papers included in the PhD thesis

The thesis is based on the following papers/studies, which will be referred to by their number.

1. DUE U, BROSTRØM S, LOSE G. Validation of the Pelvic Floor Distress Inventory-20 and the Pelvic Floor Impact Questionnaire-7 in Danish women with pelvic organ prolapse. Acta Obstet Gynecol Scand 2013;92:1041-8 [1]
2. Due U, Brostrøm S, Lose G. Lifestyle advices with or without pelvic floor muscle training for women with pelvic organ prolapse, a single-blinded randomized controlled trial. Int Urogynecol J. 2016 Apr; 27(4):555-63 [2]
3. Due U, Brostrøm S, Lose G. The 12-month effects of structured lifestyle advice and pelvic floor muscle training for pelvic organ prolapse. Acta Obstet Gynecol Scand. 2016 Feb 22. doi: 10.1111/aogs.12884. [Epub ahead of print] [3]

Contents

Abbreviations

POP: Pelvic Organ Prolapse

HRQoL: Health Related Quality of Life

POP-Q: Pelvic Organ Prolapse Quantification system

PFDI-20: Pelvic Floor Distress Inventory - short form 20

POPDI-6: Pelvic Organ Prolapse Distress Inventory 6

CRADI-8: Colorectal-Anal Distress Inventory 8

UDI-6: Urinary Distress Inventory 6

PFIQ-7: Pelvic Floor Impact Questionnaire - short form 7

UIQ-7: Urinary Impact Questionnaire 7

CRAIQ-7: Colorectal-Anal Impact Questionnaire 7

POPIQ-7: Pelvic Organ Prolapse Impact Questionnaire 7

PISQ-12: The Pelvic organ prolapse/urinary Incontinence Sexual Questionnaire 12

PGI-I: Patient Global Index of Improvement scale

NRS: Numeric Rating Scale

PFMT: Pelvic Floor Muscle Training

LG: Lifestyle advice Group

TLG: Combined pelvic floor muscle Training and Lifestyle advice Group

ITT: Intention To Treat analysis

RR: Relative Risk

IAP: Intra-abdominal pressure

Introduction

Pelvic organ prolapse (POP) as a diagnosis is based on the presence of both symptoms and signs of POP[4]. Symptoms are defined as: *"A departure from normal sensation, structure, or function, experienced by the woman in reference to the position of her pelvic organs"* (Haylen 2010, page 6, column 2, line 9-11)[4] and it may include: *"vaginal bulging.. pelvic pressure, bleeding, discharge, infection.. splinting/digitation .. low backache"* (Haylen 2010, page 6, column 2, line 17-32[4]. Signs (anatomic findings) are defined as:" *The descent of one or more of the anterior vaginal wall, posterior vaginal wall, the uterus (cervix), or the apex of the vagina (vaginal vault or cuff scar after hysterectomy)"* (Haylen 2010, page 8, column 1, line 14-16)"[4]. "*The presence of any such sign should correlate with relevant POP symptoms".* (Haylen 2010, page 19, column 1, line 25-26)[4].

The "sign" POP has been found in 40-50% of women more than 40 years of age [5]. Most of these women do not perceive their POP, and only approximately one in ten (8 -11 %) women report POP related symptoms, which may lead to bother and impact on quality of life, including sexual life [6, 7].

Only a few years ago treatment options for symptomatic POP were described as: *"observation, pessary use, and surgery"* (Jelovsek 2007, page 1027, line 10) [8]. The lifetime risk for POP surgery has been found to be 12.6% [9]. However surgical treatment is not always successful [10] or without complications or adverse events [11] . Furthermore, the positive effect of surgical reconstruction has been found to fade in the long term[12]. Many women with POP prefer conservative treatment especially if they have minor symptoms[13, 14]. To some women with POP a supporting pessary is the solution but not all women can be fitted with a pessary[15]. Other conservative treatment options have therefore gained interest.

Pelvic floor muscle training (PFMT), was introduced by Arnold Kegel in 1948 for the treatment of urinary incontinence[16]. Nowadays, PFMT is recommended as first line of therapy for women with urinary incontinence and for fecal incontinence[17] [18] . During the last decade PFMT has also gained interest in relation POP. A Cochrane review from 2006 found three randomized controlled trials using PFMT for POP [19-22]. An update of the review in 2011 found that this number had increased to six studies[23] [24-26] and subsequently three more studies have been published [26-28]. Five of these studies have compared an individual PFMT program with a lifestyle advice leaflet or a single lifestyle advice instruction. The studies have all found superior effect of PFMT on POP symptoms [22, 25, 29-31] and some have also found positive effect

on signs of POP [22, 25, 29]. PFMT has now achieved a grade A recommendation based on level 1 evidence in the treatment of POP compared to no treatment, a short lifestyle advice instruction or a lifestyle advice leaflet [32] . However, the association, between improved pelvic floor muscle (PFM) function and improvement of subjective symptoms and signs of anatomic POP remains uncertain [25]. While the improvement of POP symptoms after PFMT may be related to better muscle function[33], the added attention and the lifestyle advice provided with the PFMT may have a positive effect on the accompanying bladder and bowel symptoms, introducing a risk of bias. Although, it is unlikely that PFMT would be offered without lifestyle advice, a structured lifestyle advice program applied in the same manner as a PFMT program could hypothetically give the same effect as a PFMT program. The primary aim of the randomized controlled trial in this thesis was therefore to examine whether PFMT is more effective than lifestyle advice?

Background

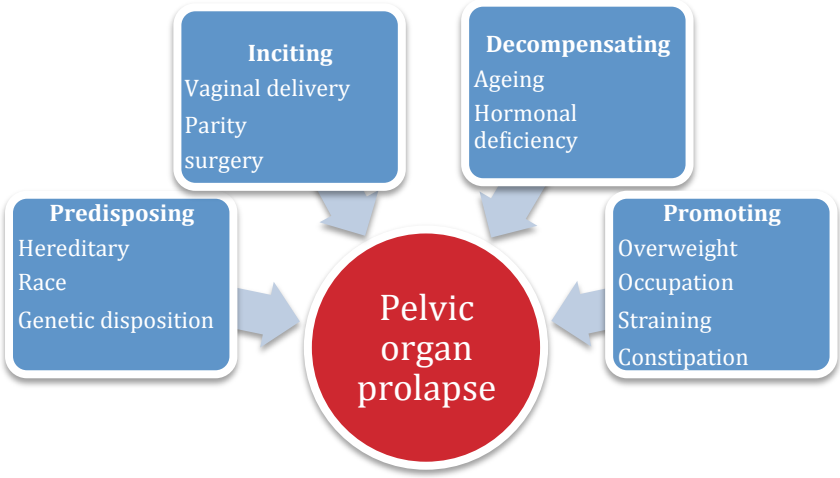
Etiology of Pelvic organ prolapse (POP)

The development of POP is believed to be multifactorial[8, 34]. In 1998 a theoretical model was developed to explain the multiple causes for the development of pelvic floor disorders including POP [35] . This model is widely accepted and it provides a theoretical framework for the understanding of the development of POP, including the possible impact of lifestyle factors.

The factors are described as *predisposing, inciting, decompensating and promoting* (figure 1)[35] Predisposing factors related to POP are the probable hereditary, racial and possible genetic disposition for POP causing differences in the collagen concentration of the connective tissue [7, 36-38]. Inciting factors most importantly include the strong connection between vaginal delivery [39-41], number of vaginal deliveries [42], increased birth weight of the child [43], more than one perineal laceration [44] and use of forceps [42, 45]. Surgery to the pelvis including hysterectomy has furthermore been found to increase the risk of POP and subsequent POP surgery[46]. A decompensating factor is the influence of ageing and the influence of female hormone deficiency described by some [47, 48] and questioned by others [49, 50] Promoting factors are overweight [36], heavy occupational work with many heavy lifts and low income jobs [51, 52],

straining during defecation and constipation [53-55]. Other factors such as chronic coughing are likely to promote the development of POP [56].

Figure 1: The multifactorial etiology in the development of POP (adapted from Bump 1998)



Suspension of the pelvic organs and POP

The pelvic organs are attached to the pelvic walls through the endopelvic fascia and the attachments are functionally divided into three levels[57]. At level I, the upper most level, the vagina is suspended by the cardinal and utero sacral ligaments and injuries at this level can result in an apical POP of the uterus, the cervix or the vaginal vault after hysterectomy. At level II the vaginal walls are attached directly to the arcus tendineus fascia pelvis, and to the superior fascia of the pelvic floor muscles (PFM). At level III, most distally, the vaginal walls are fused with the urethra, the perineal body and the pelvic floor muscles (PFM)[58, 59]. Injuries to the vaginal walls at level II or III result in an anterior or a posterior POP[57].

Signs of POP can be objectively evaluated through clinical examination using the hymen as a landmark. The Pelvic Organ Quantification system (POP-Q) is a system that divides signs of POP into stages using the hymen as reference line[4, 60]. The POP stages are numbered from 0 to IV. A POP-Q stage of 0 indicates normal suspension of the organs, while a POP-Q stage IV indicate a total eversion of the genital tract (table 1).

Table 1: POP-Q stages adapted from the terminology report developed by the International Continence Society (ICS) and the International Urogynecological Association (IUGA), 2010[4]

Stage 0:	No prolapse is demonstrated.
Stage I:	Most distal portion of the prolapse is more than 1 cm above the level of the hymen.
Stage II:	Most distal portion of the prolapse is 1 cm or less proximal to or distal to the plane of the hymen.
Stage III:	The most distal portion of the prolapse is more than 1 cm below the plane of the hymen
Stage IV:	Complete eversion of the total length of the lower genital tract is demonstrated.

Symptoms related to POP

A cardinal symptom of POP is a perceptible or visible bulge in the vaginal opening[8, 61, 62]. A vaginal bulge is the only symptom considered to be specific for POP, but mechanical symptoms are not the only symptoms related to the descending of the organs[8, 57, 58]. POP is associated with a number of symptoms such as urinary incontinence, voiding difficulties, bowel problems and sexual problems [6, 60, 63, 64]. Both urinary and anal incontinence are prevalent symptoms among women with POP[63]. Obstructive symptoms are also common either alone or concomitant with incontinence[6, 59-61].

A study using the POP-Q to evaluate 237 consecutive patients with symptomatic POP found that while 73% reported some urinary incontinence, 50% reported difficulty with bladder emptying with 62% having a sensation of incomplete bladder emptying[63]. Furthermore, 31% reported fecal incontinence, 67% had complaints of constipation and 52% described incomplete defecation[63]. It seems that a worsening of symptoms and an increased number of symptoms correlate with more advanced POP. However some symptoms have been found to be inversely correlated with POP stage[60, 63, 65, 66]. Thus, women with less advanced POP have been found to have more stress urinary incontinence (SUI) while voiding difficulties and symptoms of obstructed defecation increase with in increase in the signs of anatomic POP [63] [64, 67].

POP may affect sexual life negatively because of the mechanical difficulties caused by the bulge and because of the other symptoms such as incontinence co-existing in POP[63, 68, 69].

Outcome measures and POP

According to generally accepted standardization papers: "*Functional outcomes* (related to POP) *are best reported using valid, reliable and responsive symptom questionnaires and condition-specific HRQOL* (health related quality of life) *instruments* (Barber 2013, page 1783, column 2, line 21-24) [70]. It is recommended that signs of anatomic POP should be graded into stages using the Pelvic Organ Prolapse Quantification system (POP-Q)[4, 70 71 72]. The POP-Q has been shown to have good intra-tester and inter-tester reliability and it is considered to be a standardized and transparent tool to document signs of POP[4, 71].

In the International Consultation on Incontinence (ICI) book from 2013, (page 389-391) it is described that when choosing a patient reported outcome (PRO) for clinical trials or for clinical practice: *"it is important to choose a questionnaire that has been scientifically developed and validated,"* (ICI 2013, page 391, column 1, line 5-7)[73]. The chosen PRO must furthermore fit both the target group and the purpose of measuring. The symptom score: The Pelvic Floor Distress Inventory- 20 (the PFDI-20) and the matching health related quality of life score (HRQoL), the Pelvic Floor Impact Questionnaire-7 (the PFIQ-7)[74] have both reached grade A recommendation as PROs for women with POP (ICI 2013, page 403, column 1, table 9) [73].

A Danish-language PRO-score revealing POP related symptoms and bother exists [68]. Unfortunately it has never gained national interest and has not been implemented for clinical use. No specific PROs for women with POP have been recommended by the Danish gynecological societies (DSOG.dk (POP guideline), DUGS.dk). In order to perform the randomized controlled study included in this thesis it was therefore decided to translate the PFDI-20 and the PFIQ-7 into Danish and to validate them in Danish women with POP[1].

The pelvic floor muscles and POP

The pelvic floor muscles (PFM) close the pelvic outlet most caudally. The PFM can be divided into an anterior and into a posterior part. The anterior part originating from the arcus tendinius fascia pelvis forms the pubovisceral and the puborectal muscle. Fibers of the puboviseral muscle insert into the lower part of the vaginal walls, into the perineal body and that fibers insert close to the anus, while the puborectal muscle forms a sling behind the rectum just above the external anal sphincter[59]. The most posterior part of the PFM, the ilieococcygeal muscles, forms a flat sheet closing the posterior part of the pelvis[59,75]. The

urethra, the vagina and the anus pass through the medial opening of the PFM, the urogenital hiatus or most often called the genital hiatus.

Figure 2: The pelvic floor muscles seen from below showing the U-shaped muscle slings defining the genital hiatus

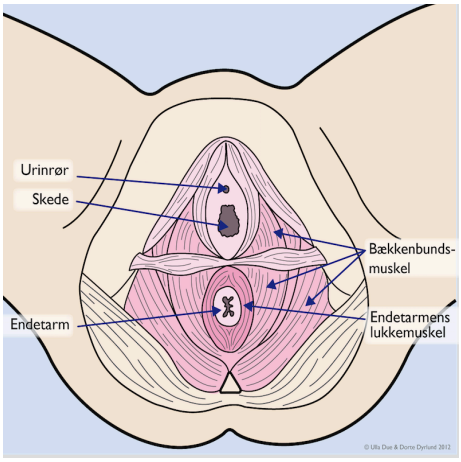
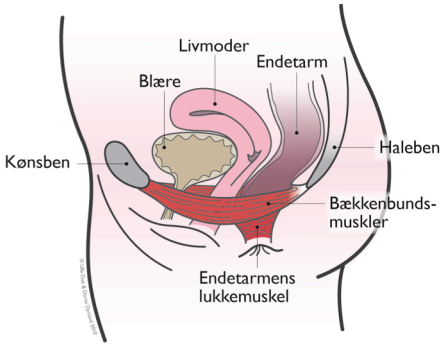
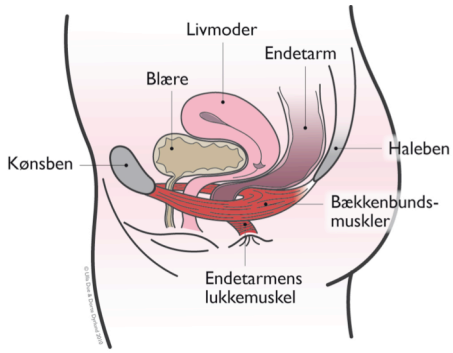


Figure 3: The PFM in relaxed position (left side) and during contraction (right side)



Bækkenbundsmusklerne i hvile



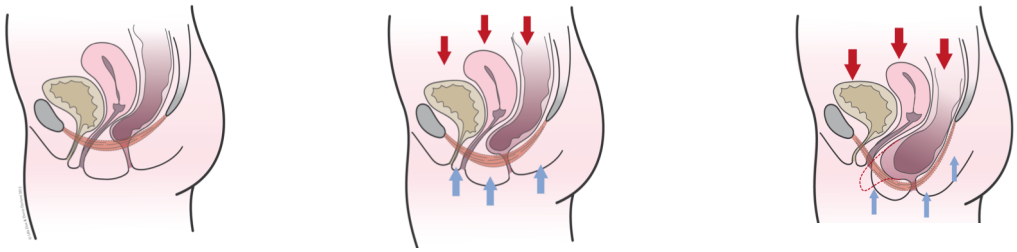
Bækkenbundsmusklerne ved knib

During a voluntary or an involuntary contraction of the PFM, the anterior part of the PFM shortens in an anterior direction causing closure of the genital hiatus and compression of the urethra, the vagina, and the rectum against the pubic bone. This movement also causes a slight lift of the organs[59].

Weakening or damage to the striated pelvic floor muscles (PFM) is believed to play a major role in the development of POP[59]. When the PFMs are intact a constant tonic activity of the muscles will keep the genital hiatus closed offering support for the pelvic organs during rest

reducing stress on the endopelvic fascia and the ligaments supporting the pelvic organs[59]. During an increased intra-abdominal pressure (IAP) the PFM must automatically contract to close the genital hiatus and thereby prevent incontinence and any downward moving of the pelvic organs [59].

Figure 4: The pelvic floor during before and during an increased intra-abdominal pressure



A *B* *C*

The Illustrations show the PFM and the position of the pelvic organs during rest (A), during an an increased intra-abdominal pressure (red arrows) with a pre-contraction (thick blue arrows) of the PFM offering some protection against downward movement of the pelvic organs (B) and (C) showing the descent and protrusion of the posterior vaginal wall during an increased intra-abdominal pressure when there is no pre-contraction (thin blue arrows)

Ageing has been found to reduce the number of striated muscle fibers and the nerve density in the urethra resulting in both decreased muscle strength and speed of contraction [59, 76, 77]. This effect is most likely global for all striated muscles including the PFM. Adding to this, vaginal delivery has been found to cause an excessive stretch of the PFM A three-dimensional computer model simulating vaginal delivery could demonstrate a 217% strain of the anterior and most medial part of the PFM during second stage of delivery. The same study group later demonstrated a simultaneous 35% stretch of the pudendal nerves during vaginal delivery, which exceeds the 15% considered to be the threshold for permanent injuries [78, 79].
The consequence of this excessive strain during vaginal delivery can be injuries on the pelvic floor (connective tissue, nerve fibers and muscles) and parous women have been found to have an increased hysteresis with a reduced stiffness of their PFM during an increased IAP[80]. Furthermore, it has been found that vaginal delivery delays and reduces the automatic response from the PFM before an increase of the IAP indicating affection of the nerve supply[81]. One in five women will sustain an avulsion of their PFM from the pelvic wall during

vaginal delivery and women with POP are more likely to have these avulsions of their PFM than women without POP [82, 83] [84]. The avulsions reduce PFM strength and cause the genital hiatus to enlarge, thereby reducing the support for the organs [85, 86]increasing the risk of POP by a two- to a three-fold [84] [83, 84].

While deterioration because of ageing and vaginal delivery are known to affect PFM function negatively it has been suggested that the effect of age and vaginal delivery combined with predisposing and promoting factors (Figure 1) can increase the risk of pelvic floor dysfunction even further, which eventually will lead to pelvic floor disorders including POP[34]. Women with POP have been shown to have impairment of their PFM function and they have been found to have reduced PFM muscle strength; endurance and resting tone[87] [52]. One study found that women with POP had normal muscle strength but lacked involuntary contraction of the PFM before an increased IAP [88]. Two studies reported that more than one in ten women with POP or urinary incontinence were straining when attempting to perform a PFM contraction [87, 89].

Pelvic floor muscle training and POP

Pelvic floor muscle training has been found to improve PFM function in women with POP [25, 33]. Women offered PFMT for six months achieved increased muscle thickness, a decreased genital hiatus and a more elevated bladder and rectum at rest. They furthermore had increased stiffness of their PFM reducing descent of the organs during straining.

Two aspects of PFMT have been described to hypothetically improve POP[90]; 1) ”Conscious contractions” (the Knack) are conscious pre-contractions of the PFM in order to close the genital hiatus, to lift and stabilize the pelvic organs before and during an increased IAP [91] 2)”Regular strength training” aiming to create hypertrophy to increase the cross-sectional area and thereby the stiffness of the PFM, with the purpose of lifting the organs, reducing the genital hiatus and resisting downward movement of the organs during increased IAP [90]. While PFMT mainly acts on the pelvic floor muscles (PFM), it is possible that a strong PFM could potentially reduce strain on the pelvic floor[34]. It has been suggested that strength training also has the ability to improve strength of the connective tissue, which could be beneficial in relation to POP[34, 90]. Finally, strength training already in the early training cause an increase in number of satellite cells (stem cells) by up till 46%[92]. These satellite cells are a prerequisite

for the hypertrophic reaction to strength training because of their ability to create more myonuclei in the muscle fiber[93].

Lifestyle advice and POP

While the overall evidence on lifestyle modifications for pelvic floor disorders is limited clinical trials have shown some beneficial effect: Weight loss in obese women and reduction of constipation has been shown to reduce urinary incontinence[94 95]. In patients with fecal incontinence, especially the use of fiber supplements has been shown to have a positive effect on number of incontinence episodes [96].

Studies comparing women with symptomatic POP to a control group have found that women with symptomatic POP have a higher risk of being constipated and straining during defecation (odds ratio 2.1-4.0)[36, 97, 98], for being overweight (odds ratio 1.9-5.0)[36, 52] and are more likely to be exposed to repetitive heavy lifting (odds ratio 2.0-9.6)[36, 52]. Minimizing the effect of some of these known promoting factors for POP could therefore potentially be relevant in the treatment of POP [34, 35]. Unfortunately prospective randomized controlled trials are missing. It is therefore largely unknown whether reducing any promoting factors including specific lifestyle modifications and change of habits could improve POP[36, 52, 99].

In the published studies on PFMT for POP, lifestyle advice has been used as a comparison to an active PFMT program. The lifestyle advice has been offered as a leaflet or a single instruction, with minimal contact with a health care professional. Presumably, the participants offered individual PFMT have been verbally guided in the use of different lifestyle modifications but the content of these lifestyle advice leaflets or instructions have not been described in details. Based on published studies it is therefore not possible to separate the effect of PFMT from the effect of lifestyle advice. With the multifactorial etiology of POP in mind it is possible that an educational program without PFMT, providing thorough information about lifestyle modifications could improve both subjective and objective POP[34, 35].

Aims

The aims of the included studies in this thesis were:

Study 1

- To translate and to validate condition specific questionnaires for Danish women with POP

Study 2

- To examine the effect of a structured lifestyle advice program with or without PFMT for women with symptomatic POP stage ≥ II

Study 3

- To examine the 12-month effects of a structured lifestyle advice program with or without PFMT for women with symptomatic POP stage ≥ II.

Hypotheses for the randomized controlled study included in the thesis were:

Study 2

- PFMT in combination with a structured lifestyle advice program has better effect on symptoms, quality of life and objective POP than a structured lifestyle advice program alone
- Background variables (age, BMI, parity, work, surgery, POP-Q stage, POP position, symptoms- and HRQoL total and subscale scores) can predict effect of PFMT
- PFMT has little or no side effects.

Study 3

- Women receiving a combination of PFMT and structured lifestyle advice will experience better effects at a 12-month follow-up compared to women receiving a structured lifestyle advice program alone.

Materials and Methodology

Materials and methodology – study 1

Women referred to our hospital for POP evaluation were included if they were fluent in Danish and willing to participate. The women were recruited either from the hospital referral list, from the ward or contacted in the waiting room at the outpatient clinic. Furthermore, women scheduled for POP surgery were recruited in the waiting room at operating theater. As per Danish regulations, the study was reported to Danish Data Protection Agency. The primary investigator mainly recruited participants and all participants were given written information about the study. The women signed consent forms permitting access to their patient files regarding their objective POP.

In the study the Pelvic Floor Distress Inventory-20 (PFDI-20) and the Pelvic Floor Impact Questionnaire-7 (PFIQ-7) were translated and validated [74]. The PFDI-20 has twenty items and the PFIQ-7 has 21 items. Both questionnaires are divided into three subscales; The PFDI-20 reveals POP (POPDI-6), bowel (CRADI-8) and bladder (UDI-6) symptoms and bother while the PFIQ-7 reveals impact on health related quality of life (HRQoL) related to bladder (UIQ-7), bowel (CRAIQ-7) and POP (POPIQ-7) symptoms. Single item scores, subscale and total scores can be calculated from both the PFDI-20 and PFIQ-7 with higher scores indicating more bother and impact on HRQoL.

A panel of independent translators translated the PFDI-20 and the PFIQ-7. Patient interviews were performed based on the translated versions[100]. The interviews were followed by revisions and further pre-testings of the translated questionnaires.

The psychometric analyses included examination of construct and content validity to assure that the questionnaires were relevant for women with POP [101]and to assure that they covered all relevant aspects of POP. Convergent validity was examined by comparing questionnaire scores with objective POP [101]. Internal consistency of total and subscales was examined to evaluate if items in the two questionnaires were correlated relevantly with each other. Test-retest reliability was examined to confirm that the questionnaires would be stable if the condition was unchanged. Finally we examined if the questionnaire were sensitive to change and we tried to determine responsiveness of the questionnaires [74, 101 102, 103].

Methodological considerations - study 1

Materials

Women with POP were included because a PROM should be psychometrically evaluated on the target group to ensure validity, reliability and responsiveness[101].

Study design

We emphasized understanding and interpretability of the Danish versions of the translated questionnaires[1]. It has been shown that women find vocabulary related to pelvic floor disorders difficult to comprehend[104]. We therefore performed patient interviews on the Danish version of the questionnaires with the use of a probe technique as proposed by Guillemin 1993[100]. This technique meant that the women were continuously asked to vocalize how they understood each item of the questionnaires. Furthermore, we used an iterative process; if an interviewee found an item difficult to understand the following interviewees would be asked how they understood the item. In some cases the interviewees were presented to different formulations of the same item and asked to explain their conception of the content. Hence, the final version of each item was based on consensus between the interviewed women and the primary investigator.

Earlier studies translating the chosen questionnaires have used classical test theory and we decided to use the same psychometrical analyses[74, 101].

Materials and methodology - Study 2

Materials

Women with symptomatic POP stage ≥ II (table 1) were included if they had at least one of three symptoms: seeing or feeling a bulge in the vaginal opening, voiding disorders or defecation problems, or feeling vaginal heaviness. Fluency in Danish language was required. Exclusion criteria were dementia, symptomatic neurological disease, including serious back problems, PFMT within the last two years, childbirth within the last year, more than one surgical treatment for POP or urinary incontinence.

The study was approved by the Danish Scientific Ethical Committee (H-4-2011-072) and by the Danish Data Protection Agency. The study was reported to Clinical.Trials.gov (NCT01612637).

Primary investigator was blinded to all outcome data throughout the whole study. The research nurse performed randomization and collected all data. A statistician not involved in the study provided computer generated random numbers and each woman drew one envelope. Each envelope contained a paper describing group allocation and a patient number. The patient number was used for the research nurse to enter data into a database. Stratification was made for age ± 60 years.

The women were randomized to the structured lifestyle advice program (LG) alone or in combination with PFMT (TLG). The six group sessions should be attended with a two-week interval between sessions within 12 weeks (Figure 5).

Figure 5: Timeline and headlines for each of the six group sessions in the LG and in the TLG (see table 2 for further explanation of the lifestyle advice program)

Timeline

Week number		2	4	6	8	10	12
Session number		1	2	3	4	5	6
LG		Intro	Bladder	Bowel	Diet	Quality of life	Sports/ exercise
TLG		Intro	Bladder	Bowel	Diet	Quality of life	Sports/ exercise
	Individual PFMT	Group PFMT	Group PFMT	Group PFMT	Group PFMT	Group PFMT	Group PFMT

LG: *Lifestyle advice Group;* ***TLG****: Combined pelvic floor muscle Training and Lifestyle advice Group; PFMT: Pelvic Floor Muscle Training*

The pelvic floor muscle training program

The women in the combined lifestyle advice and PFMT group (TLG) received an individual assessment of their PFM function by a specialist pelvic floor physiotherapist (figure 5) before starting the group sessions. [105, 106]. Women unable to perform PFMT correctly were offered

more individual sessions. During the sessions the women performed PFMT in different body positions and ”Knack training”[107] [90].

The PFMT home training program was individually adjusted according to the results of the PFM assessment. The home training program should be performed five days a week with the use of a training dairy [108]. The dairy was a simple two-week training dairy and the women noted in the dairy if the PFMT had caused any bother. Participants handed in their training dairies at every session, exchanging it for a new one (at the end of the session). The training program included three sets of PFM contractions with a short break between sets of max 1- 2 minutes. Progression was enforced through verbal instructions by adjusting number of contractions, length of each contraction and body positions during home training [109]. The aim was to reach 3 x 10 contractions lasting 10 seconds each and with a maximum of 10 seconds rest between each contraction. The participants were encouraged to perform “the knack” during every-day life when lifting, pushing, coughing etc[91].

The lifestyle advice program

The LG and the TLG was offered and identical lifestyle advice program. Specialized pelvic floor physiotherapists were instructed in teaching the sessions independently of the primary investigator.

The lifestyle advice program included six pre-developed power-point presentations lasting 45-60 minutes each. Each session had a different subject related to POP.

The women were instructed in the anatomy of the pelvic floor and the most common symptoms related to POP were described, including possible promoting factors. This was followed by specific lifestyle advice to alleviate symptoms[56] [68] [36, 67] (table 2).

POP has been found to have a negative impact on body image and sexual life[110-112]. Since these aspects can be difficult to talk about, a group session was specifically designed to encourage the women to speak openly about this. The power-point presentation for this session included relevant statements on these aspects found in the scientific literature [111].

The research nurse gave each of the included women a schedule for their visits and a folder describing the content of the six group sessions before commencement of the group sessions. The women were encouraged to try out any of the presented advice from the sessions that they found relevant and to share their experiences with rest of the group.

The women were given bladder and bowel diaries, and leaflets on laxatives. Handouts from the presentations were offered.

The group sessions for the LG and the TLG were held on separate days and the two groups never met. In order to make it possible for a diversity of women to participate we offered both afternoon and evening classes.

Table 2: Content of the six lectures in the structured lifestyle advice program

Week 2 - 12	Content	Specific suggestions
Introduction	Explanation of pelvic floor anatomy and possible causes for POP. Description of anterior, posterior and apical/uterine POP	• Exercises to relieve pressure on the pelvic floor • Reduce heavy lifting
Bladder	Explanation of bladder anatomy Function/dysfunctions Urinary incontinence and voiding dysfunctions	• Normalize fluid intake and micturition • How to get a proper micturition technique. Double/triple voiding
Bowel	Explanation of normal bowel function including digestion Anal and fecal incontinence Constipation and obstructed defecation	• How to use laxatives including use of enemas • How to get a proper defecation technique
Diet	Explanation of official guidelines on healthy diet	• How to improve diet by increasing fibers and reducing fat • How to lose weight
Quality of life	Impact on quality of life including sexual life	• To talk about POP • How to change habits
Exercising	Description of low impact sports and reassurance of the positive effect of exercising	• Presentation of different types of low weight/impact sports

Subjective evaluation of POP

The primary outcome was the Patient Global Index of Improvement scale (PGI-I) at six months follow-up. The PGI-I was also used as a secondary outcome at three- and 12-month follow-up [113 ,114]. Secondary outcomes were the Pelvic Floor Distress Inventory - short form 20 (PFDI-20) and the Pelvic Floor Impact Questionnaire - short form 7 (PFIQ-7) to reveal symptoms and affection of quality of life related to pelvic floor disorders, respectively[1 74]. Impact on sexuality was evaluated with The Pelvic organ prolapse/urinary Incontinence Sexual Questionnaire 12 (PISQ-12) [115]. The score has 12 items revealing impact on sexuality

caused by POP, urinary incontinence and partner related problems. A total score can be calculated if there are no more than two missing response. Only single item scores were reported because of low item response rate. In the TLG the women were to note their PFMT home training in a training dairy and they were asked to describe if the PFMT gave any bother in a Numeric Rank Scale (NRS) ranging from 0 to 10. A higher number indicated more bother.

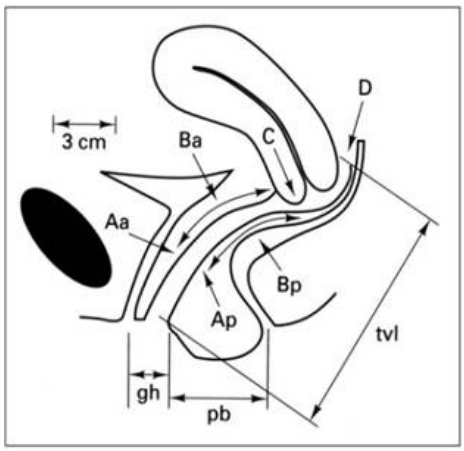
The participants filled in the symptom- and HRQoL-scores with a minimal assistance at baseline and at the three-month follow-up visit. Six-month and 12-month follow-questionnaires were sent to the women. At the six- and 12-month follow-up the women were asked to report and specify if they had received further treatment after the three-month follow-up. The questionnaires were handed or sent to the women by the research nurse who also collected all questionnaires. The primary investigator only had access to the questionnaire scores after the research nurse had entered them into a database.

Objective evaluation of POP

The Pelvic Organ Prolapse Quantification system (POP-Q) was used to evaluate objective POP at baseline and at the three-month follow-up. A POP-Q score of ≥ II was furthermore an inclusion criteria for our study. The primary outcome assessor was trained to do the POP-Q by a senior consultant urogynecologist [116]. The research nurse took notes on a standardized sheet during the examination. The sheet was removed after the examination and primary investigator was blinded to the results of the baseline examination at the three-month follow-up.

The research nurse entered all results from the examination in the database. The examination was performed in the lithotomy position with the use of speculums and a measuring stick (centimeter). To standardize the examination as much as possible the women were asked to strain maximally with an open mouth for at least 6 seconds to obtain maximum descent for all points, where straining was needed [117].

Figure 6: The nine landmark points examined in the POP-Q assessment (Bump 1996[118])



POP of the anterior, the middle and the posterior compartments is measured with the hymen as a reference point; POP in the anterior wall is measured with two points (Aa and Ba), POP in the posterior wall is measured with two points (Ap and Bp) and POP in the middle compartment with the C (Cervix) and the D points (posterior fornix). Genital hiatus Gh) is measured from the urethra to the hymen. Perineal body (pb) is the length of the perineal body form the hymen to anus. Total vaginal length (tvl) is the only point not measured during maximal straining. POP above the hymen is indicated with a negative number. POP beyond the hymen is described with a positive number[4].

Methodological considerations - Study 2

Materials

Only women with symptomatic POP stage ≥ II were included in the study because pelvic floor symptoms are more likely to be caused by POP if the objective POP is close to the hymen [67, 119, 120]. Only 6-11% of women with POP stage 0-I will describe the cardinal symptom of POP: a bulge. However, describing a bulge has been found to have a positive predictive value of 81% and a negative predictive value of 76% for POP stage II [64]. Furthermore the hymen is classified as point of success after surgery with the subjective sensation of not having a bulge[121]. POP stage I has moreover been defined as good organ support[70]. Finally, we wanted to include only women who would hypothetically be eligible for pessary or surgical treatment. Women with a POP stage I, are not likely to receive either.

Some studies have found that certain POP symptoms correlate with POP in a specific compartment such as bladder symptoms with anterior POP and bowel symptoms with posterior POP [122, 123] while others cannot find this association [68, 124]. We therefore chose to include both women with anterior and/or posterior POP.

Study design

To be able to perform a randomized controlled trial we had to invent a design that could separate the effect of PFMT from the effect of lifestyle advice. We did not find studies that had used a relevant design that we could adopt for our study; One study examining the effect of a 8-week individual PFMT program for post natal women with SUI offered massage to the control group [108]. Another study for patients with fecal incontinence gave patient education and life style advice during a four-week period. If the patients had relief of symptoms they were excluded from the study and were not offered PFMT[125].

We did not wish to offer an irrelevant treatment for comparison and our intervention groups should be as equal as possible regarding attention from the physiotherapist to reduce risk of performance bias[126]. To obtain this, standardization of the lifestyle advice was required. We chose to offer both study groups, six lectures comprising an identical lifestyle advice program and added group PFMT and PFMT home training to one group. The two groups were: "*the Lifestyle advice Group"* **(LG)** receiving structured lifestyle advice only and "*the Combined pelvic floor muscle Training and Lifestyle advice Group* **(TLG)** receiving structured lifestyle advice in combination with PFMT.

We offered the interventions as group lectures for several reasons: 1) To ensure that the two groups received identical lifestyle advice through standardized lectures. 2) To ensure that both groups had the same number of lectures. 3) To ensure that interventions would be reproducible in another setting using pre-developed presentations and PFMT programs. 4) Finally, that the interventions would be financially manageable even in a setting with limited resources.

Assessment of pelvic floor muscle function

It has been found that women with pelvic floor disorders are more prone to be unable to contract their PFM correctly[87, 89].. A recent study showed that sixty (24%) of 250 women referred to an uro-gynecology clinic could not perform a correct PFM contraction at their first

attempts. Nineteen (23%) of the 83 women who said they did PFMT regularly were unable to perform a correct PFM contraction[127]. All women in the TLG were offered an individual assessment of their PFM function and instruction in PFMT to assure that they could perform the PFMT program correctly. Women unable to contract their PFM correctly were offered additional individual sessions and learned to contract correctly[128].

A reliability study based on the ICS standardization terminology on PFM assessment, found substantial intra-observer reliability (Weighted Kappa >0.60) for voluntary PFM contraction and relaxation, for involuntary contraction and for muscle strength and endurance. However, the study found that inter-observer reliability was disappointing and it was concluded that visual and digital assessment of PFM function was for clinical use only[106]. In the present study the results from the PFM examination were therefore only used to guide the women and no individual follow-up on PFM function was performed.

The pelvic floor muscle training program

A recent review concluded that PFMT was more efficient than no PFMT for the treatment of urinary incontinence. However it was not possible to establish which PFMT program was most efficient program. It was suggested to follow general training principles using progressive overload and specificity when prescribing PFMT [109]. The same principles are most likely applicable in relation to PFMT for POP. To an untrained person this requires a program using 60-65% of one Repetition Maximum (RM) (one RM = 100% effort) 3-5 times a week for 12 weeks [129]. Furthermore, three sets of contractions seem to be more efficient than doing one set of contractions[130]. The studies on PFMT for POP have described different strategies but they have all used three sets of 8-12 PFM contractions daily followed by three to 50 fast contractions. Some have described the use of maximal strength training (>65% of 1RM)[25,22] while others have not described level of effort[30, 31]. The studies have described instruction in the use of "knack training" as part of the PFMT program [90].

In our study the women were told that every contraction should be held firmly and with as much effort as possible to increase muscle strength, but with normal breathing to avoid excessive co-contraction of the abdominal muscles[131]. Excessive co-contraction of the abdominal muscles during a PFM contraction has been found to increase the IAP unnecessarily causing a downward movement of the organs instead of the desired lift of the organs [131].

Because women with POP have been found to miss involuntary PFM contractions during increased IAP [88] the "Knack training" was emphasized during the group sessions [107] [90]. To progress the skill learning a short catalogue with different knack exercises was developed to inspire the physiotherapists during the sessions.

We chose to offer PFMT as group training supplemented with home training. No other studies have examined individual PFMT versus group PFMT for women with POP but studies comparing group PFMT versus individual PFMT for women with SUI have found equal effect [132, 133] [134]. We therefore expected that group PFMT also would be applicable for women with POP.

The lifestyle advice program

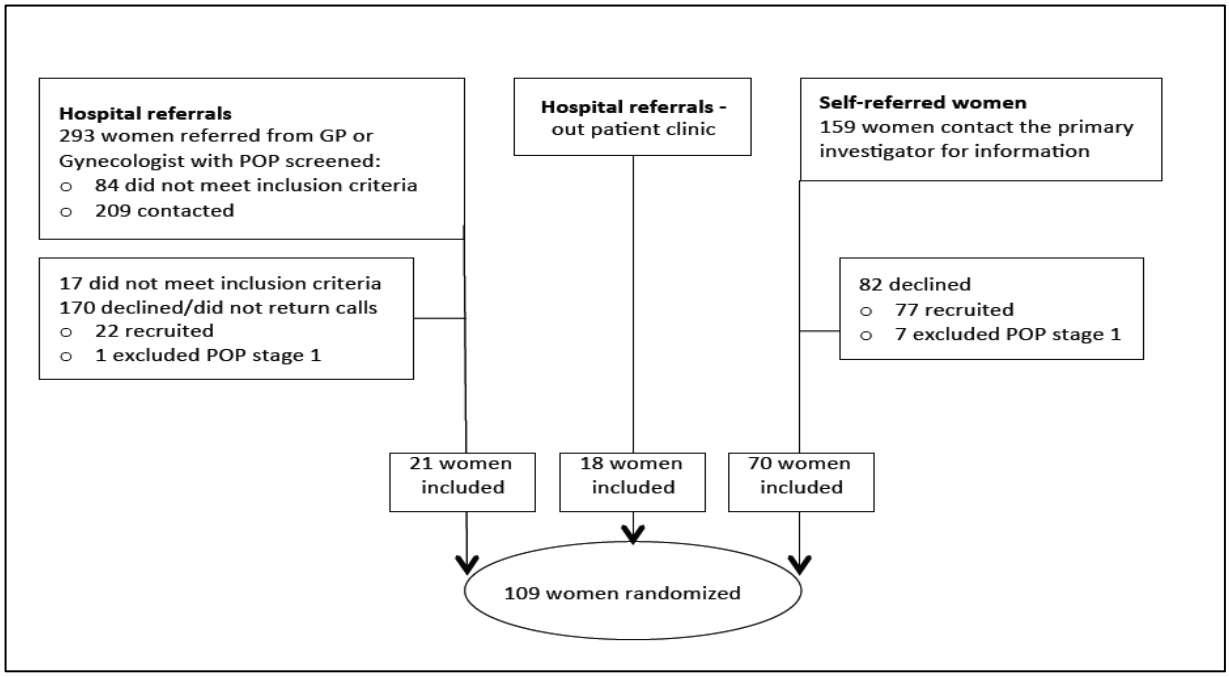
The aim of the lifestyle advice program was to increase awareness among the women about how to reduce known promoting factors for POP[35] [34]. We emphasized presenting the advice in different ways to make as many participants as possible benefit from them. It has been proposed that people have different learning strategies and a number of models exist. One model, the VARK model (Visual, Aural, Reading/writing, Kinestetic) by Neil D. Fleming is widely used [135].

A variety of illustrations of the pelvic floor were used and the women were continuously offered the opportunity to ask for more explanations. It was aimed to use an understandable vocabulary, since many women do not understand the medical wordings related to pelvic floor disorders[104]. The lifestyle advice program was discussed with specialist nurses and physiotherapists to assure content validity. A pretest was performed on patients with POP for relevance and understandability.

Recruitment of participants

Initially the participants were recruited from the hospital referral list only[136]. However, the recruitment from the hospital referral list was very slow [137] A recent a study found that women recruited from the public had similar symptoms as women referred by a clinician and we decided to attempt to recruit through the public[137]. Advertising was conducted on Facebook ™, posters at public places such as libraries, shopping centers and hospitals and in local new papers (Figure 7).

Figure 7: Flow-chart describing the recruitment process (adapted from[128])



Transperineal ultrasound

With the use of ultrasound [138] it has become possible to visualize the PFM with a short non-invasive and reliable[139]. In the RCT the primary investigator did transperineal ultrasound at baseline on all included women as it was hypothesized that thinning or avulsions of the PFM and the following enlargement of the genital hiatus would decrease the effect of PFMT[140]. Because the primary investigator was blinded to group allocation all included women were examined. Transperineal ultrasound was performed during rest as 3D images and during straining as 4D films. The results from this examination were to be used as a possible explanatory factor for treatment effect after either intervention. Unfortunately it was not possible for the primary investigator to achieve adequate skills to analyze the images within the timeframe of the study. The results are therefore not reported in this thesis.

Materials and methodology – study 3

In study 3 all participants from study 2 who completed the 12-month follow-up were included. Analyses were based on 12-month scores of the PGI-I, the PFDI-20, the PFIQ-7 and

the PISQ-12[74, 114, 115] (see materials and methodology - Study 2) The primary investigator remained blinded to all data.

Long-term treatment effects, number of women who had sought further treatment and kind of treatment were examined.

Possible associations between having sought further treatment before the 12-month follow-up and baseline data and three-month follow-up scores were evaluated: From the baseline data influence of age, BMI, parity, POP stage, position of POP, working status, referral status, and baseline symptoms- and HRQoL scores, on having sought further treatment were used in the analyses. From the three-month follow-up data results from symptoms- and HRQoL scores and results from the POP-Q assessments were used.

Methodological consideration – study 3

Long-term follow-up is an important measure of treatment effect. Knowledge about the long-term effect of PFMT in relation to POP is limited. Only one study so far has reported 12-month follow-up data[31]. No prior studies describing causes for seeking further treatment after PFMT were identified. We therefore explored not only long-term treatment effects of either intervention but also if specific factors were associated with seeking further treatment before the 12-month follow-up.

Statistical considerations

In the three studies included in this thesis we used descriptive statistics to describe baseline data of our populations and we used the Chi-square/Fischers´exact test for categorical variables. Both parametric and non-parametric statistics were used for paired an unpaired analyses.

In study 1 [1] data were tested for normality of distribution with the Kolmogorow-Smirnov test and if data were not normally distributed non-parametric statistics was primarily used but both mean (standard deviation (SD)) and median values (range) were reported. The Cronbach´s Alpha was carried out to analyze internal item consistency and inter-item total correlation of the PFDI-20 and the PFIQ-7 subscale and total scales. Test-retest stability of the PFDI-20 and the PFIQ-7 was examined with the Intra Class Correlation coefficient (ICC). The non-parametric Spearman´s rank order correlation test was used to evaluate; the correlation between the PFDI-20 and the PFIQ-7 scores; between objective baseline POP and

questionnaire scores, and between improvement of symptoms and quality of life and response to the global score (PGI-I). Receiver Operating Characteristic (ROC) curves was made to evaluate sensitivity and specificity of the PFDI-20 and the PFIQ-7 in relation to the PGI-I. We furthermore, calculated effect-size and standardized response mean to evaluate responsiveness of the questionnaires [74].

In study 2 and 3 [128, 141] the PFDI-20 and the PFIQ-7 total and subscale scores were analyzed with both parametric and non-parametric statistics. When both methods showed similar results only results from the parametric analyses were reported because calculated scores from the two questionnaires are normally reported as mean values (Standard Deviation). Non-parametric tests were used for the analysis of baseline data and of single item scores. A sample size calculation was performed based on the PGI-I and the PFDI-20 with 80% power at a 5% level to find a 15% difference of the PFDI-20 [74]. Based on this 45 women were required in each arm and to account for possible dropout of 20% we included 108 women (included 109). In study 2 and 3 univariable and multivariable logistic regression analyses were performed. Variables from the univariable analyses were included in the multivariable analyses if they had a p-value of 0.2 or less. Level of significance of all statistical analyses was set at a p-value of 0.05 for all statistical tests used and all p-values were reported two-sided. The analyses were performed with the SPSS, version 19.0-22.0 (SPSS Inc. Chicago, IL, USA) [142].

Results

Study 1

One hundred and thirty-two women with POP participated in the study. Seventeen women were interviewed, mean age 68.5 years (median 70.5, range 36–84). Questionnaire responses from 115 women, mean age 63.5 years (median 65, range 30–92) were entered into a database.

After two revisions the questionnaires seemed well accepted. Response rate in the pretesting was 70%.

The PFDI-20 was found to reveal relevant POP symptoms and no floor or ceiling effect was found, while the PFIQ-7 showed ceiling effect (best score =no symptoms at baseline).

Scores of the two questionnaires correlated weakly and only single items correlated with signs of POP. The questionnaires showed good test-retest reliability but the response rate in the test-retest was only 60%.

Sensitivity to change after POP surgery was sufficient for both the PFDI-20 and the PFIQ-7, while it was not possible to accurately define the Minimal Clinical Important Difference (MCID). Only improvement of POP subscales correlated with improvement in a global scale.

Study 2

Baseline

A total of 109 women with symptomatic POP were included. Sixty-two women (57%) had POP stage II and 47 women (43%) had stage III and. Fifty-three women were allocated to the LG, 56 women to the TLG.

Table 3: Type of POP and POP stage at baseline (adapted from x)

	LG (n=53)	TLG (n=56)	Total	P value
POP-Q stage II/III, No. (%)	29/24 (55/45)	33/23 (59 /41)	62/47 (57 /43)	0.66
Anterior POP	47 (89)	49 (88)	96 (88)	0.40
Posterior POP	34 (64)	36 (64)	70 (64)	0.10
Combined POP	32 (61)	32 (57)	64 (59)	0.73
Anterior POP ≥ 0 cm	38 (71)	40 (71)	78 (72)	0.80
Posterior POP ≥ 0 cm	28 (53)	30 (54)	58 (53)	0.79

The two groups were comparable in all baseline data[128]: Median age was 60 years (range 33-79) (P=0.77), median BMI 25 (range 19-37) (P=0.46), median parity 2 (range 1-9)(P=0.07). Number of referred versus self-referred women; number of women who had received previous surgery and number of women working was similar in the two groups (table 4).

Table 4: Baseline characteristics in the two groups (Adapted from[128])

Variable	**LG**	**TLG**	**Total**	**P Value**
Surgery, No. (%)[a]	7 (13)	9 (16)	16 (15)	0.67
Referred/self-referred, No. (%)[a]	20/33 (38 / 62)	19/37 (34 / 66)	39/70 (36 /64)	0.68
Working, No. (%)[a]	33 (62)	31(55)	64 (59)	0.60

[a]*Chi-Square tests*

Symptom- and HRQoL scores including sexuality scores (data not shown) were similar in the LG and the TLG (table 5).

Table 5: Baseline symptom and HRQoL scores in the two groups (Adapted from[128])

Number analyzed in each group	LG (n=53)	TLG (n=56)	P value
Symptom and bother[a]			
POPDI-6	30.3 (19.6)	36.9 (24.4)	0.13
CRADI-8	24.2 (18.5)	24.6 (21.3)	0.93
UDI-6	32.3 (22.6)	29.6 (23.2)	0.53
PFDI-20	86.9 (46.3)	91.0 (59.4)	0.69
Quality of life (HRQoL)[a]			
UIQ-7	18.3 (20.6)	12.7 (18.3)	0.13
CRAIQ-7	8.15(16.0)	9.9 (18.6)	0.61
POPIQ-7	12.2(19.8)	14.54 (19.3)	0.53
PFIQ-7	37.7(45.2)	37.07 (46.9)	0.94

[a] *Unpaired T-tests with scores reported as mean scores (SD)*

Three-month follow-up

Eighty-nine women (82%) of the 109 included women completed three-month follow-up Dropout was 11% in the LG and 25% in the TLG and. Dropouts were younger (P=0.004), had more affection of bowel-related HRQoL (P=0.053) and more bother related to urinary incontinence during sexual intercourse (P=0.027).

Significantly more women in the TLG reported improvement in the PGI-I compared to the LG (p=0.003). Both groups showed significant improvement of the total PFDI-20 score but only the TLG had significant improvement of the POP subscale (P=0.001). The LG only had significant improvement of the PFIQ-7 caused by improvement in the bladder subscale (UIQ-7, P= 0.014)[128].

The LG showed a mean improvement in the total PFDI-20 score of 12.4 points (SD 30.3) corresponding to a 14% overall improvement of symptoms. The TLG had a mean improvement of the PFDI-20 total score of 15.6 points (SD 29.5) corresponding to a 17% improvement. The between group difference was 3.2 (95% CL -7.9 - 14.3, P= 0.57)[128].

Objective POP and the sexuality score did not improve significantly in either group

Between-group differences of symptoms or HRQoL scores were insignificant at the three-month follow-up (table 6).

Table 6: Three-month follow-up symptom and HRQoL scores in the two groups (Adapted from [128])

Number analyzed in each group	LG (n=53)	TLG (n=56)	P value
Symptom and bother[a]			
POPDI-6	29.3 (17.0)	30.4 (22.6)	0.77
CRADI-8	19.0 (16.7)	20.6 (18.0)	0.63
UDI-6	26.6 (20.7)	24.9 (22.1)	0.68
PFDI-20	74.9 (39.5)	75.9 (54.9)	0.91
Quality of life (HRQoL)[a]			
UIQ-7	13.09 (17.1)	10.7 (17.0)	0.48
CRAIQ-7	5.58 (14.8)	10.4 (19.1)	0.15
POPIQ-7	9.34 (17.4)	12.7 (19.7)	0.39
PFIQ-7	28.02(37.6)	34.0 (49.1)	0.48

[a]*Unpaired T-tests with scores reported as mean scores (SD)*

There were no significant associations between any baseline data and self-reported improvement in the PGI-I in the univariable and the multivariable logistic regression analyses (factors analyzed: age, BMI, parity, work, surgery, POP-Q stage, POP position, symptoms- and HRQoL total and subscale scores).

Thirty-one of the 42 women (74%) in the TLG who completed three-month follow-up handed in their training dairies. Eleven women reported a median low bother of 2 out of ten (0-5) in the NRS scores in 11% of their reported home training sessions, while reporting a bother of 0 in 89% of their home training sessions.

Six-month follow-up

Eighty-five women (78%) responded to the six-month follow-up.

At the six-month follow-up significantly more women in the TLG reported improvement in the PGI-I (P=0.02)[128]. Between the LG and the TLG no significant differences were found in any of the symptom- and HRQoL scores.

In the LG 68% had sought further treatment, compared to 28% in the TLG (P= <0.001). (table 7). Referred women or women who previously had received POP surgery, did not seek further treatment significantly more often than self-referred women or women who had not previously received surgery[128].

Table 7: Number of women who had sought further treatment at the six-month follow-up (adapted from [128])

Number analyzed in each group[a]	LG (44)[b]	TLG (40)	P Value
Other treatment	30 (68%)	11 (28%)	<0.001
PFMT	24	3	<0.001
Pessary	2	4	0.30
Surgery	3	2	0.79
Other treatment (not described)	4[c]	2	0.77

[a]*Chi-Square test and with Fisher´s Exact Test .* [b]*One woman did not answer these questions* [c] *In the LG three women reported receiving an unspecified conservative treatment in addition to a specified treatment.*

Women in both groups who had sought further treatment had significantly more POP in the anterior compartment (P= 0.03) but not significantly higher total POP-Q scores (P=0.62) nor more POP of the posterior compartment. Women seeking further treatment experienced more impact on bladder related HRQoL (UIQ-7, P= 0.05) at baseline and at three-month follow-up (UIQ-7, P= 0.04) (unpaired non-parametric tests).

Study 3

Eighty-three women (76%) responded to the 12-month follow-up, 43 in the LG and 40 women in the TLG. A total of 34 women had not sought further treatment, 30% (13/43) women in the LG and 52% (21/40) women in TLG, respectively (P=0.05). Compared to baseline the LG had significantly improved bladder symptoms (UDI-6, P= 0.01), while those in the TLG had significantly improved POP symptoms (POPDI-6, P=0.02) and bowel-related HRQoL (CRAIQ-7, P=0.04)[141].

Single item analysis showed that the LG had significant improvement of two items in the total PFDI-20 scale regarding stress urinary incontinence and "small amount leakage". In the TLG one item about the "bulge" of the total PFDI-20 scale was significantly improved. No single item of the CRAIQ-7 was significantly improved and significance was only found in the total CRAIQ-7 score. The symptoms- or HRQoL scores did not differ significantly between the LG and the TLG (data not shown)

None of the items in the sexuality score were significantly improved between baseline and the 12-month follow-up (data not shown)

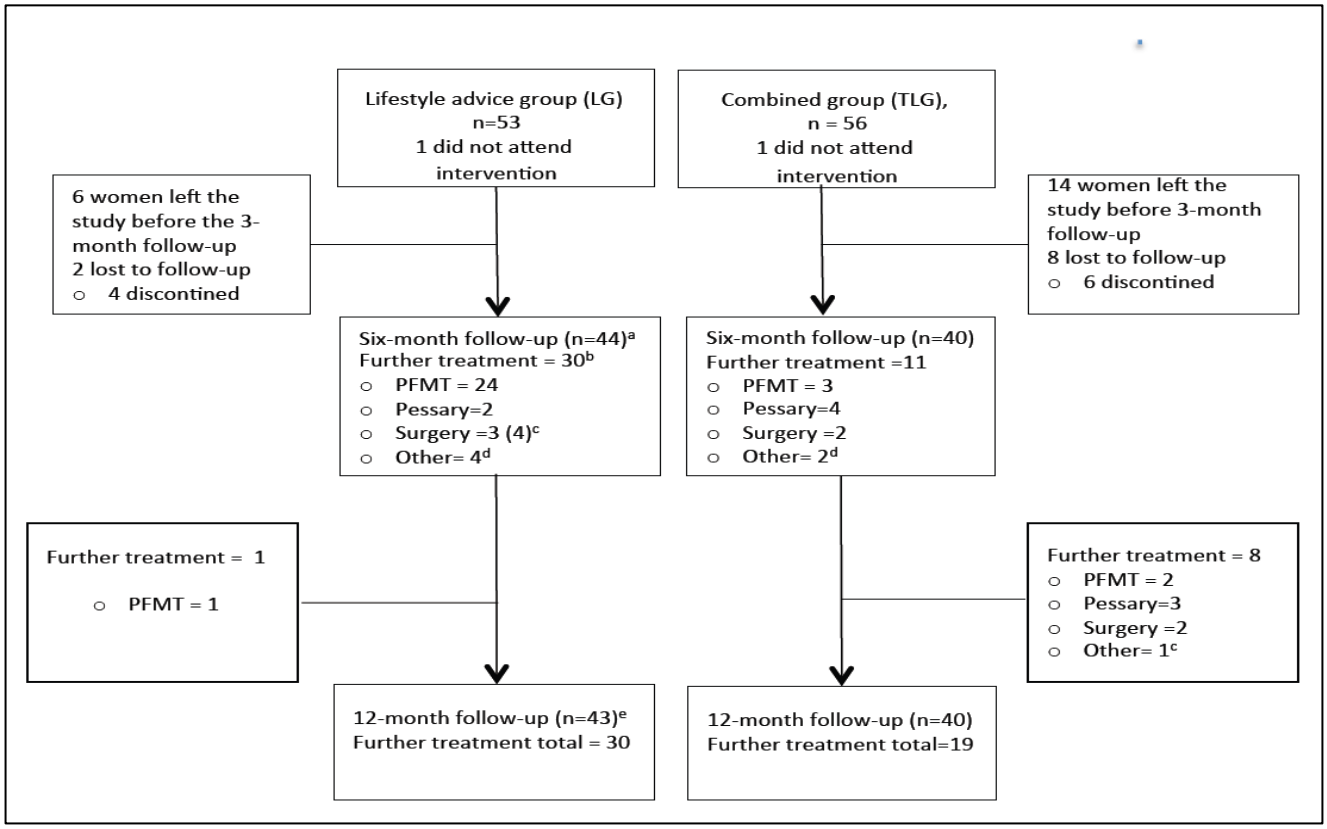
Forty-nine women (59%) of the 83 respondents had sought further treatment. Thirty (70%) in the LG compared to nineteen (48%) in the TLG, respectively. Eight women, four from each group had received surgery, while 41 had received conservative treatment. Twenty-five of 30 in the LG had sought PFMT compared to five of 19 in the TLG (Figure 8)

Between women who had or had not sought further treatment no significant differences were found in any of the PFDI-20 total or subscale scores in the three-month follow-up scores (unpaired tests). In the TLG only, the women who had sought further treatment showed significantly more impact on POP related HRQoL (P= 0.03)

More anterior POP (at or beyond the hymen) and more impact on bladder and POP related HRQoL was associated with seeking further treatment before the 12-month follow-up based on univariable logistic analyses of baseline data (before allocation) In the multivariable

analysis working status became significant, while the effect of POP related HRQoL disappeared.

Figure 8: Describing the number and kind of treatment sought before the 12-month follow-up in the two groups (Adapted from[141]).



[a]One woman did not respond to these questions [b] One woman who had received PFMT did not complete 12-month follow-up, [c]One woman had surgery between the six and 12-month follow-up after describing "other treatment" [d]Other unspecified conservative treatment. [e]Two women from the LG left the study between the six- and 12-month follow-up.

Group allocation to the LG and more POP and bladder symptoms including impact on bladder and POP related HRQoL, was associated with seeking further treatment in the univariable analyses based on three-month follow-up scores. In the multivariable analysis the influence of group allocation, POP symptoms and impact on bladder and POP related HRQoL disappeared, and only more advanced anterior POP and more bladder symptoms remained significant, with more anterior POP being the strongest factor.

General discussion

Patient reported outcome measures

To be able to measure symptoms/bother and HRQoL and any effect of an intervention, it is important to have valid and reliable tools [101]. In the literature a variety of scores exist measuring symptoms and impact from pelvic floor disorders[68]. Some scores are specific for POP [68, 143], while others cover other aspect of pelvic floor disorders that are not necessarily correlated to POP [144]. The PFDI-20 and the PFIQ-7 are internationally recognized[73] and they have been translated and validated in a number of languages [74] In study 1 we chose to translate the questionnaires in their validated short-forms [74].

The process revealed that PFDI-20 had sufficient content validity, while the PFIQ-7 suffered from ceiling effect and missed relevant items on HRQoL.

We believe that we made the best choices with the PFDI-20 and the PFIQ-7 [74] but the PFDI-20 has some constitutional problems, which became clear to us during the translation procedure. In fifteen of the 20 items of the PFDI-20, the item had two questions in one item, saying: "Do you usually have.." instead of "Do you have..?" This lack of unidimensionality caused confusion both for the translating panel and for the patients [101]. During the patient interviews we explored the word "usually" and we realized that the participating women interpreted this word very differently. We had to compromise using a word with the meaning: "most of the time". We believe that this inherent problem is a weakness of the PFDI-20, which might also affect the cross-cultural validity of the scores.

We also have to account for some methodological problems in the study. The test-retest was performed in 50 women and it is recommended to have at least 100 participants completing the test-retest [145]. Secondly we only calculated the Intra Class Correlation coefficient (ICC). It has been found that ICC overestimates reliability while there are more exact methods to determine reliability. The 95% limits of agreement (LoA) between the test and the retest could have been established using the Bland–Altman method[146] or by calculating the Standard error of measurement (SEM)[145] . This would have increased the precision of the reported measurement error and thereby the smallest clinically relevant change[146]

It could also have strengthened the validity of the Danish versions of the PFDI-20 and the PFIQ-7 if it had been examined if improvement of symptoms and HRQoL correlated with

improvement of objective POP after surgery. Since this was not a routine procedure at the hospital, data were not available on all women and we did not perform this[147].
Finally, a reference group of Danish women without pelvic floor disorders, or a group of women with pure urinary incontinence or anal incontinence could have been included, which would have strengthened interpretability and a wider usability of the translated questionnaires[146].

The Design of the randomized controlled trial

The aim of a randomized controlled trial (RCT) is to reduce any systematic bias that could possibly affect the outcome of an intervention. A very important factor is to avoid that bias related to the design could cause an under- or an overestimation of the true effect of an intervention. In physiotherapy studies, including studies on PFMT, "performance bias" could introduce a serious risk of bias.
According to the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011], The Cochrane Collaboration, 2011[126] *: "Performance bias refers to systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest."* (Chapter 8.4. section 2, line 1, www.cochrane-handbook.org) [126]. Performance bias might have resulted in an overestimation of the effect of PFMT found in earlier studies comparing an active PFMT program with a lifestyle advice leaflet or a short instruction. The aim of our design was therefore to reduce the risk of bias related to attention. This, to minimize that any superior effect attributed to PFMT could be caused by the extra attention and information rather than by the PFMT itself.

We believe that our design was ideal to examine our hypotheses but it was not possible to blind the participants to their group allocation and this could have affected the outcome in the TLG. The women in the TLG might have felt that they received a better intervention than the LG, which may be supported by the unintended crossover with the majority of the LG seeking PFMT after completing their intervention. Interestingly, significantly more women in the TLG indicated improvement in the global scale at the three- and six month follow-up despite they had not achieved better symptom- or better HRQoL scores than women who did not indicate this improvement in both groups. A study comparing an individually tailored PFMT program with "watchful waiting" (no contact) also found that women who had received PFMT

compared to no treatment reported more improvement in a global scale despite that they had not obtained a clinically relevant improvement in their symptom- or HRQoL scores[28]. Bias is a likely explanation for our result and as in the study by Wiegersma et al. the women in the TLG probably felt "lucky" or even felt better because of higher expectations. However, it is possible that they did experience a superior effect in areas that we did not measure, such as a sensation of improved awareness of the pelvic floor[148].

While we believe that our subjective outcome measures were comprehensive and suitable for women with POP other factors could have influenced the superior self-reported improvement found in the TLG. Improved body-image or the ability to be more active without getting POP symptoms could hypothetically be the cause because of the possible improvement of the support for the organs after PFMT[111, 33, 149].

It is a limitation of our study that we did not explore this finding further. We could have used a mixed methods design, combining both quantitative and qualitative approaches to learn more about our participants[150, 151]. While our hypotheses mainly gave reason to conduct a quantitative study, adding qualitative methods could have helped us explain why the TLG felt more improved despite of not showing superior effect in most of the symptoms- and HRQoL scores.

The choice and timing of our primary outcome might furthermore represent a weakness of our study design. We chose the Patient Global Index of Improvement scale (PGI-I) at the six-month follow-up, three months after the women had completed the interventions. The PGI-I was furthermore used as secondary outcomes at the three- and 12-month follow-up. Possibly there was recall bias at the six-month (and at the 12-month) follow-up because the women were asked to remember how they felt before entering the study (or before they had sought further treatment)[152]. This could carry a risk of over- or underestimation of the true effect of the study [153]. By using the PGI-I scale at the six- and 12-month follow-up there was a risk of asking the women two questions in one; had she experienced positive effect of the intervention and was the effect better or worse compared to last follow-up. It might have improved validity of our results if we had described how the women felt "right now" utilizing a Visual Analog Scale (VAS) or a Numeric Rank Scale (NRS) and we suggest the use of these scores in future studies on PFMT instead [154].

Pelvic floor muscle training

Based on the literature PFMT could hypothetically restore some of the support for the pelvic organs and thereby improve symptoms [58, 90] [25, 33]. In our study, we could not confirm this superior effect of PFMT on POP related symptoms except for the positive response in the global scale and the significant improvement of POP symptoms at the three-month follow-up, which did not result in significantly reduced symptoms in the TLG compared to the LG[128]. Previous studies on PFMT for POP have found significantly reduced symptoms after individual PFMT compared to lifestyle advice, but a lifestyle advice leaflet alone have also shown to improve symptoms and bother [22, 25, 29-31]. In the study with the most intensive PFMT program, including women with POP stage I-III, "bulge symptoms" were decreased in 74% and bother was decreased in 67% of the women who had received weekly or bi-weekly PFMT for six months (18 individual sessions). In the control group, who had received a single instruction in lifestyle advice and of "the knack", 31% reported reduced bulge symptoms and 42% reported less bother. It was not described "how much" symptoms and bother was improved and of 109 participants only 69 (63%) reported symptoms at baseline. Considering the effort of a six-month program to achieve the improvement compared to a single instruction it is most likely that the included women were very resourceful and probably not representing average women with POP.

Other studies with a less intensive but individualized PFMT program have also found positive, but less substantial effect of PFMT on symptoms compared to a lifestyle advice leaflet [29-31]. The largest study published so far included women with mild to moderate symptoms and POP stage I-III. They found that significantly fewer women receiving an individual PFMT program for 16-week reported symptoms within the preceding four weeks and the women reported significantly improved HRQoL compared to women who had received a lifestyle advice leaflet [31]. The difference in number with reduced symptoms between the study groups was 10-22% in favor of PFMT. Whether the difference was clinically relevant is debatable, but the intervention seemed more realistic and implementable.

We believe that the PFMT program used in our study was comprehensive enough to improve PFM function while still realistic for the women to accomplish[109]. The women were thoroughly instructed and given appropriate information to understand the purpose of the PFMT program. However, it is possible that more frequent individual instructions focusing on individualized adherence strategies and the use of digital reminders could have improved

both short- and long-term effect of the PFMT program[155]. A limitation to the study is that not all women handed in their training dairies and that we had no other possibility to measure adherence to the PFMT program. Our results give a realistic impression of what could be expected after a PFMT program for women with POP. The group design was in addition feasible in most settings within public health care service. Group supervision might also have been more motivating for some of the participants compared to individual sessions[156,155].

Although most published studies on PFMT have found significant improvement of POP symptoms after PFMT, the effect has been moderate and many women have not benefitted from PFMT. Possibly the impact of ageing on PFM function and especially the combination of ageing and injuries on the PFM caused by vaginal delivery and promoting factors are likely to reduce the potential effect of a PFMT program [59, 83].

Increased muscle strength and thereby improved cross-sectional area and stiffness of the PFM can be difficult to obtain if a woman has very weak and untrained muscles. The use of biofeedback or electrical stimulation in conjunction with PFMT could possibly have increased the effect of the PFMT program but the evidence is limited and other studies using either have not been able to show substantially superior effect[28, 31, 157].

Hypothetically alternative methods could be used to enhance the effect of a strength-training program. A low intensity training program with a simultaneous partial occlusion of the blood supply for the training muscle, so called "Kaatsu" training has been found to increase muscle strength faster than ordinary strength training but with much less effort. [158]. Moreover, it has been found to increase the number of stem cells in a muscle with up till 400%[159]. It seems difficult to make occlusion of the PFM during PFMT but a different way to use this strategy may be possible. A study found that low intensity training of the quadriceps femoris (Less than 12 RM= <50% af 1RM) with partial occlusion of the blood supply did not only increase muscle strength of the quadriceps femoris muscle. If the biceps humeri muscle was trained with low-load training and no occlusion in the same training session it also improved muscle strength of that muscle[160]. The specific reason for this this "cross-transfer effect" could not be fully explained but it was believed to be caused by a systemic effect caused by growth hormones. Perhaps Kaatsu training could be useful for women with POP who have weak but intact pelvic floor muscles.

We did not succeed in analyzing our ultrasound images for this thesis, but it is likely that some of the participants had avulsions of their PFM, which might have affected the outcome of the PFMT program. Repair of PFM avulsions has been attempted but with little success [161]. Perhaps in the future, the use of stem cells, especially muscle-derived stem cells could be a way to restore the missing muscle tissue in women with POP, which could thereby improve the effect of PFMT. Transplantation of fresh myofibers with their satellite cells in the urethra of pigs gave improved tonic activation after 30 days indicating innervation of the new myofibers, which could imply that it is possible to create new muscle fibers to replace missing muscle tissue[162].

The lifestyle advice program

From our study it seems that a comprehensive lifestyle advice program addressing known promoting factors for POP and aiming to reduce typical POP related symptoms through simple lifestyle advice, reduced most of the superior effect of a PFMT program compared to other studies [22, 25, 29-31]. Surprisingly, only the LG had significant improvement of their HRQoL at three-month follow-up, while the TLG did not have significant improvement in any HRQoL subscales[128]. The improvement in the LG was in the bladder- and bowel-related HRQoL and it is likely that women in the LG gained more benefit because the lifestyle advice matched their specific problems better than in the TLG.
It was emphasized to offer relevant advice and in different ways to make most women benefit from the advice[135]. Furthermore, the participants could continuously ask for explanations if they did not understand an advice. This would not have been possible if the women had been offered a lifestyle advice leaflet only.

We did not ask the women why they decided to participate in our study, but it is likely that the LG experienced a positive short-term effect because they received information and reassurance about their condition[13]. Probably almost all women in the LG sought PFMT because they hoped that PFMT could reduce their POP symptoms even more [163].
A limitation of our study is that we had to compare "a package" of lifestyle advice with or without PFMT to perform the study. Neither was the sample size large enough to stratify for either position of POP nor specific symptoms. Furthermore, the participants were not encouraged to follow the same advice and probably the women chose only to follow specific

advice relevant to their needs. Since the study was not designed to evaluate the particular effect of a specific advice it is not known if any lifestyle advice were more important than other lifestyle advice.

Effect on objective POP

We only included women with POP stage ≥ II, and more than 70% of our participants had a POP at or beyond the hymen. Women with POP stage 1 were excluded, because this stage rarely gives the cardinal symptom of POP: "the bulge"[64]. Opposed to earlier studies that included 10-22% with POP stage III we included 43% women with POP stage III [25, 30, 31].
None of the women participating in our study had achieved significant improvement of their objective POP at the three-month follow-up.
Except from one study showing a remarkable improvement of objective POP in women with POP stage II [29], other studies have only found reduction of objective POP in a few women after PFMT. The most intensive PFMT study found that 19% compared to 8% in the control group improved one stage but in women with POP stage III the change was similar whether they had received PFMT or not [25]. In the largest study, 7.5% more of the women who had received PFMT, improved one stage compared to the group receiving a lifestyle advice leaflet only. However, the total number of women with progression or regression of their objective POP was equal whether the women had received PFMT or not [31].
The primary investigator did all the POP-Q evaluations. The POP-Q is not part of normal postgraduate education to become a specialized pelvic floor physiotherapist. The primary investigator trained with a senior consultant uro-gynecologist before the study was initiated[116] It is therefore possible that the learning curve influenced the results of the POP-Q examinations. This could represent a systematic bias and it is possible that the three-month follow-up evaluations were less positive because the women were given more precise commands, were straining more correctly and the measurements were more precise[71].
It has been found that signs of POP can vary after strenuous physical activity without causing more symptoms[164] POP can also resolve without treatment over time [165 166]. Adding to this possible natural variation, a slight measurement error could account for some of the variation found in our study and in previous studies [167].
Based on our findings we believe that it is unlikely to expect a significant improvement of advanced objective POP after PFMT. Possibly a small number of very motivated women can

reduce their objective POP through a very intensive PFMT program but it requires a very resourceful patient and a very resourceful health care system[25].

The effect on sexual function

The women included in our study described low impact of their sexuality and almost 25% of our participants did not fill in the sexuality score because they were not sexually active (described as not having a partner). A hypothesis could be that the women declining participation had more impact of their HRQoL and sexual function than the women accepting participation[168], [169]. We do not know if the women in our study were restraining themselves from being sexually active because of their POP, and it is a limitation of our study that we did not ask them. However, we could not find significant improvement in the sexuality score at any follow-ups after either intervention. A study evaluating the effect of PFMT on sexual function found that women reported improvement of their sexual function during patient interviews but that this positive effect was not reflected in the used sexuality score[170]. It is possible that if a different score than the PISQ-12 had been used, we would have achieved a more diverse picture of how the women experienced their sexuality. The PISQ-12 is very "partner related" score and "The Female Sexual Function Index" (FSFI) could have provided a broader picture of sexual function and dysfunction because it is more orientated to the woman herself [171]. Finally, it is likely that we did not capture all relevant problems related to body image problems / partner related body image problems because we did not include scores on this [172].

The relevance of a conservative treatment program

The improvement of symptoms and HRQoL from either intervention barely reached our predefined minimally clinically important difference (MCID) of 15% improvement at the three-month follow-up. The long-term effect of both the LG and the TLG was furthermore marginal[141]. Although the overall effects were limited, some positive aspects appeared. The PFMT program caused low bother and no baseline data, including POP stage II or III could predict self-reported improvement in the short-term. Interestingly, more anterior POP and not symptoms nor impact on HRQoL was the strongest factors associated with having sought further treatment at the 12-month follow-up. This could indicate that both interventions were tolerable, that even women with advanced POP could experience some benefit from either

program, and that symptoms and impact on HRQoL alone cannot explain treatment-seeking behavior in women with POP[141].

Our study design was developed to minimize bias but confounding factors such as difficult recruitment may have influenced our results. Almost 90% of the women contacted from the hospital referral list declined participation and the majority of our participants were self-referred. It could be suspected that women accepting participation were more resourceful compared to the women who could not be recruited and that we recruited a selected group of women[136, 137]. Our results may therefore not be extrapolated to other populations of women with POP stage II-III and our findings should be interpreted with caution.

Only 10% of our participants had received surgical treatment before the 12-month follow-up. This number was comparable to the other 12-month follow-up study that only included half as many women with POP stage III[31]. While it could be interpreted as a positive result our participants may have been a selected group, who had no prior wish for surgical treatment. It has been found that women POP accept conservative treatment or "watchful waiting" if they have less bother and less impact on their HRQoL compared to women seeking surgery and probably our participants belonged to that group[173].

Our findings give rise to the inevitable question if all women with POP, especially advanced POP routinely should be offered PFMT and also if the effect of a conservative treatment is worth the trouble. Are we wasting both our time and the women's time with lifestyle advice and PFMT and is conservative treatment for a selected group of women only?

Compared to the improvement of symptoms and HRQoL found after surgery the effect of both our two interventions was low[74 143]. Some might question the clinical relevance, and although in favor of PFMT the difference was negligible[146 174].

On the other hand "a bulge" is the only symptom that corrective surgery can improve and the bulge can still be objectively present even after successful surgery [62]. Any conservative treatment can always be followed with more invasive treatment, while surgery can cause continued problems or new symptoms [11].

One study reported offering a preoperative PFMT program [21], while two studies offered PFMT postoperatively with no significant superior effect compared to no post-operative PFMT [26, 27]. It is therefore uncertain if PFMT could improve the long-term effect of surgery or reduce the risk of new symptoms to appear after surgery[11 21, 26, 27]

Perspectives

The results from our study does not give reason to change the grade A recommendations for PFMT for POP[32]. However, as with PFMT for urinary incontinence it is unlikely that either lifestyle advice alone or in combination with PFMT can reduce POP related symptoms substantially[175]. On the other hand as stated in a recent review article: *"when choosing these conservative treatment options, patients have nothing to lose but time if they are unsuccessful"* (Culligan 2012, page 860, line 37-40) [176]. The interventions with or without PFMT were cheap and could easily be implemented in most settings and group education has been found to be as efficient as individual patient education[177].

We have not identified studies evaluating how Danish women seek information about "pelvic floor problems", but a British study from 2008 found that three out of four women had sought information on the internet before attending an outpatient clinic for pelvic floor disorders[178] . Danish women most likely do the same. Three recent studies, all published in 2015 have evaluated the quality of Internet based information on POP, in English-language websites[179-181]. The quality was found to be poor in the vast majority of the websites. Limited information was found about conservative treatment options or about what women could expect if they did not receive any treatment for their POP. Furthermore, the information was influenced by industrial sponsored websites with a tendency to promote the effect of non-evidence based surgery methods.

Any surgical procedure implies a risk to the woman´s health and as stated in a Cochrane review on POP surgery: *"The impact of pelvic organ prolapse surgery on bowel, bladder and sexual function can be unpredictable and may make symptoms worse or result in new symptoms, such as leakage of urine or problems with intercourse"* (Cochrane, Maher 2013, page 3, line 2-4)[182].

Based on our findings women with POP should be told to have realistic expectations about the effect of lifestyle advice with or without PFMT but with the low risk of adverse events in mind we think that motivated women with POP should be offered lifestyle advice in combination with PFMT. Possibly information, reassurance about the condition and improvement of body awareness are the key elements in a conservative approach and future studies should address this issue in women with POP[163].

Future studies

The studies included in this thesis have revealed areas that should be studied further.
In study 1 we used classical test theory (CTT) to perform the psychometric analyses of the translated versions of the PFDI-20 and the PFIQ-7. We discovered that some of the assumptions for making scores of questionnaires were not fulfilled, such as normal distribution of data and item equivalence. Furthermore, we found that most of the items in the PFDI-20 lacked uni-dimensionality and that the PFIQ-7 missed relevant items. We believe that a thorough analysis using Item Response Theory (IRT) models could improve validity of the PFDI-20 and the PFIQ-7[101] .
We also realized that we miss validated body image scores for women with POP in Danish[172].
A relevant future study would be to correlate PFDI-20 and PFIQ-7 scores with body image problems in Danish women with POP[110].

In study 2 and 3 we discovered that our studies gave rise to several more questions related to conservative treatment for POP. The questions could suggest that future studies should include both quantitative and qualitative methods addressing the following questions.

- What makes women seek conservative treatment in spite of advanced POP? Can other factors than symptoms- and HRQoL scores explain treatment-seeking behavior, such as health belief and personal resources?[183] [184]
- Could other scores than the symptom and HRQoL scores used in the present study be relevant when measuring treatment effect in Danish women with POP, such as activity, scores, body-image scores and other sexuality scores[149, 171, 172].
- Could the use of patient selected goals and composite endpoints give a better picture of treatment effect after a conservative intervention than symptom and HRQoL scores alone? [185]
- What would be the optimal PFMT program? Could alternative methods like "Kaatsu" training improve the effect of PFMT in relation to POP? [159, 160]
- What specific lifestyle advice for women with POP are the most important advice; is it reduction of straining, improvement of bladder habits, weight loss or conscious reduction of heavy lifting? Or is it something else?[56]

Danish summary

Denne ph.d-afhandling er baseret på 3 studier som er gennemført på Herlev Hospital. Afhandlingen omhandler 3 originale artikler.

Op imod hver tiende kvinde har symptomer på grund af genital prolaps (pelvic organ prolapse= POP). Tidligere modtog disse kvinder typisk et støttepessar eller en operation. Det er vist bækkenbundstræning reducerer POP symptomer bedre end livsstilsrådgivning i form af en pjece eller en kort instruktion. Ingen studier har undersøgt om bækkenbundstræning har bedre effekt, hvis det sammenlignes med et struktureret livstilsrådgivningsprogram uden bækkenbundstræning.

Formålet med afhandlingen var:

1. At oversætte og validere sygdomsspecifikke spørgeskemaer til kvinder med POP mhp. anvendelse af disse i studie 2 og 3
2. At undersøge effekten af et livstilsrådgivningsprogram med eller uden bækkenbundstræning til kvinder med symptomatisk POP ved en 3 og en 6 måneders opfølgning
3. At undersøge langtidseffekten af et livstilsrådgivningsprogram med eller uden bækkenbundstræning til kvinder med symptomatisk POP ved en 12 måneders opfølgning

Ad 1. I studiet oversatte og validerede vi symptomscoren: the Pelvic Floor Distress Inventory-20 (PFDI-20)og livskvalitetsscoren the Pelvic Floor Impact Questionnaire-7 (PFIQ-7) fra amerikansk til dansk. Spørgeskemaerne blev oversat af et panel og derefter afprøvet på danske kvinder med POP. Desuden blev de statistisk analyseret mhp. at vurdere deres gyldighed, reproducerbarhed og følsomhed for ændringer. Vi fandt at PFDI-20 var gyldigt og indeholdte relevante spørgsmål, mens PFIQ-7 havde loft-effekt (bedste score ved baseline), og manglede spørgsmål om livskvalitet. Begge spørgeskemaer var følsomme for ændringer, mens en mindste kliniske relevant forskel kunne ikke fastslås.

Ad 2: 109 kvinder med moderat symptomatisk POP blev ved lodtrækning allokeret til én af to grupper : En livsstilsrådgivningsgruppe (LG) og en gruppe som modtog både livsstilsrådgivning og bækkenbundstræning (TLG). Begge grupper modtog et identisk livsstilsrådgivningsprogram tilbudt som gruppeundervisning 6 gange indenfor 12 uger, men på separate dage, så grupperne aldrig mødte hinanden. Den ene af grupperne modtog desuden bækkenbundstræning i forbindelse med deres livsstilsrådgivningsundervisning efter en individuel undersøgelse af deres knibefunktion.
89 (82%) kvinder gennemførte 3 måneders opfølgningen og 85 (78%) 6 måneders opfølgningen. Ved både 3 og 6 måneders opfølgningen angav signifikant flere kvinder i TLG forbedring på en overordnet forbedringsskala (global score). Ved 3 måneders opfølgningen opnåede begge gruppe signifikant forbedring af deres totale symptoscore, men kun TLG opnåede signifikant forbedring af den underskala som vedrørte POP symptomer, mens LG alene opnåede signifikant forbedring af deres livskvalitet. Ingen af grupperne opnåede signifikant forbedring af deres objektive POP eller af deres seksualitetsscore. Effekten i begge grupper var knap nok klinisk relevant og der var ingen forskel grupperne imellem.
Ingen baseline data dvs. alder, paritet, henvisningsstatus (henvist/selvhenvist), kropsvægt, jobstatus, grad symptomer, påvirkning af livskvalitet eller størrelse af genital prolaps kunne anvendes til at forudsige hvilke kvinder der ville have angive bedring af symptomer på global scoren ved 3 måneders opfølgningen.
Ved seks måneders opfølgningen var der ingen signifikant forskel på symptomer eller livskvalitet mellem grupperne, men 68% af LG overfor 28% i TLG havde søgt yderligere behandling.

Ad 3: 83 kvinder (76%) gennemførte 12-måneders opfølgningen. 30% (13/43) i LG overfor 52% af (21/40) i TLG havde ikke søgt yderligere behandling. Langtidseffekten i begge grupper var minimal og der var ingen signifikant forskel på symptomer eller livskvalitet i de to grupper.
I alt 49 ud af de 83 kvinder havde søgt yderligere behandling før 12 måneders opfølgningen: 70% (30 /43) i LG, overfor 48% (19/ 40) i TLG. Otte kvinder, fire i hver gruppe, havde søgt kirurgisk behandling, mens de resterende 41 havde søgt konservativ behandling. I LG havde 25 kvinder søgt bækkenbundstræning overfor 5 i TLG. Baseline data og 3 måneders opfølgnings scorer blev anvendt til at undersøge om der var faktorer, som kunne forudsige

hvilke kvinder der ville have søgt yderligere behandling inden 12 måneders opfølgningen. En større grad af POP i forreste skedevæg var den stærkeste faktor i forhold til at have søgt yderligere behandling, uanset hvilken intervention kvinderne havde modtaget.

Det konkluderes at:

- at PFDI-20 er et anvendeligt spørgeskema til kvinder med POP, mens PFIQ-7 mangler relevante spørgsmål om livskvalitet og har lofteffekt.
- at bækkenbundstræning sammen med livsstilsrådgivning på kort sigt giver en lille yderligere bedring af oplevet effekt på en global score, men at det ikke giver færre symptomer eller bedre livskvalitet end et livsstilsrådgivningsprogram alene
- at bækkenbundstræning er forbundet med få gener
- at selvoplevet forbedring efter bækkenbundstræning ikke kan forudsiges ud fra baseline data inklusiv størrelse af objektiv genital prolaps
- at bækkenbundstræning sammen med livsstilsrådgivning ikke har bedre langtidseffekt på prolapssymptomer eller livskvalitet end et struktureret livsstilsrådgivning alene, men dog at færre kvinder som har modtaget PFMT vil have søgt yderligere behandling, ved en 12 måneders opfølgning
- at en større nedsynkning af forreste skedevæg er den stærkeste faktor associeret med at søge yderligere behandling efter deltagelse i et livsstilsrådgivningsprogram med eller uden bækkenbundstræning

English summary

This PhD thesis is based on three original studies. The studies were conducted at Herlev University Hospital, Copenhagen, Denmark

One in ten women experiences symptomatic pelvic organ prolapse (POP). A decade ago, these women would most likely be offered pessary treatment or surgical treatment. It has now been shown that pelvic floor muscle training (PFMT) reduces POP symptoms better than a lifestyle advice leaflet or a single lifestyle advice instruction. No studies have examined if PFMT is more effective than a structured lifestyle advice program offered without PFMT.

The purpose of the thesis was therefore to

1. To translate and validate condition specific patient related outcome measures for women with POP to get subjective outcome measures for a randomized controlled trial.
2. To compare the effects of a structured lifestyle advice program with or without PFMT for women with moderate to advanced symptomatic POP in a three- and in a six-month follow-up
3. To evaluate long-term effects of a structured lifestyle advice program with or without PFMT for women with moderate to advanced symptomatic POP in a 12-month follow-up

Ad 1: In the study we translated: the Pelvic Floor Distress Inventory-20(PFDI-20) and the quality of life score: The Pelvic Floor Impact Questionnaire-7 (PFIQ-7) form English and validated them in Danish women with POP. The two questionnaires were translated by a panel and were pre-tested in women with POP. Statistical analyses were performed to evaluate validity, reliability, sensitivity to change and responsiveness. We found that the PFDI-20 was valid and contained relevant questions related to POP, while the PFIQ-7 had ceiling effect and missed items on quality of life in women with POP. Both the PFDI-20 and the PFIQ-7 were sensitive to change, and the POP subscales were responsive to change.
Ad 2: A 109 women with moderate to advanced symptomatic POP were randomized to a Lifestyle advice Group (LG) or to a combined Training and Lifestyle advice Group (TLG). Both

groups received an identical structured lifestyle advice program offered as six group sessions with in 12 weeks, offered at separate days to avoid that the two groups met. One group, in addition to the lifestyle advice program, received an individual assessment of their pelvic floor muscle function and did group PFMT during the lifestyle advice sessions.
Eighty-nine women (82%) completed three-months follow-up and 85 (78%) completed the six months follow-up. At both follow-ups significantly more women in the TLG reported improvement in a global improvement scale compared to the LG. At the three-months follow-up both groups had achieved significant improvement of their total symptom score (PFDI-20), while only the TLG had significant improvement of the subscale revealing POP symptoms. Only the LG obtained significant improvement of their quality of life (PFIQ-7). None of the two groups had significant improvement of objective POP or of their sexual function. The overall improvement of the PFDI-20 was barely clinically relevant and there were no significant differences between the groups. No baseline data including age, parity, body mass index, being referred/self-referred, job status, former surgery, degree of symptoms and impact on quality of life or size of objective POP, could act as a predictor of self-reported improvement at the three-months follow-up.
At the six-months follow-up no significant differences in symptoms or impact on quality of life were found between the two groups, but in the LG, 68% had sought further treatment compared to 28% in the TLG.
Ad 3: Eighty-three women (76%) completed 12-months follow-up. 30% (13/43) in the LG and 52% (21/40) in the TLG had not sought further treatment. Long-term effect was marginal in both groups and there were no significant differences in symptoms and quality of life between the groups.
All together 49 of the 83 women had sought further treatment, 70% (30/43) in the LG and 48% (19/40) in the TLG. Eight women, four form each group had received surgical treatment, while the remaining 41 women had sought conservative treatment. In the LG, 25 women had sought PFMT, in the TLG five women. Baseline scores and three-months follow-up scores were used to analyze possible predictors associated with having sought further treatment before the 12-months follow-up. In both groups, not being working and more advanced anterior POP at the three-months follow-up were the strongest factors associated with having sought further treatment.

Based on the three studies it is concluded that:

- The PFDI-20 is a valid and useful questionnaire for women with POP, while the PFIQ-7 shows ceiling effect and misses items related to quality of life in women with POP
- When adding PFMT to a structured lifestyle advice program more women will report improvement in a global improvement scale and of POP symptoms, but PFMT does not result in better symptoms and quality of life scores than a structured lifestyle advice program alone
- PFMT causes low bother
- Self reported improvement after PFMT cannot be predicted from baseline data including size of objective POP
- Long-term effects of adding PFMT to a structured lifestyle advice program is marginal but slightly fewer women who have received PFMT will have sought further treatment at a 12-months follow-up
- That more advanced anterior POP is the strongest factor associated with having sought further treatment at a 12-months follow-up independent of whether the women have been offered PFMT or not

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