CHAPTER 2

PELVIC FLOOR MUSCLE TRAINING VERSUS WATCHFUL WAITING OR PESSARY TREATMENT FOR PELVIC ORGAN PROLAPSE (POPPS): DESIGN AND PARTICIPANT BASELINE CHARACTERISTICS OF TWO PARALLEL PRAGMATIC RANDOMIZED CONTROLLED TRIALS IN PRIMARY CARE

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ABSTRACT

PFMT and pessaries are commonly used in the conservative treatment of prolapse. Because there is a lack of evidence regarding the optimal choice between these two interventions, we designed the "Pelvic Organ Prolapse in Primary Care: Effects of Pelvic Floor Muscle Training and Pessary Treatment Study" (POPPS). POPPS consists of two parallel open label randomized controlled trials performed in primary care, in women aged ≥55 years, recruited through a postal questionnaire. In POPPS Trial 1, women with mild prolapse receive either PFMT or watchful waiting. In POPPS Trial 2, women with advanced prolapse receive either PFMT or pessary treatment. Patient recruitment started in 2009 and was finished in December 2012. Primary outcome of both POPPS trials is improvement in prolapse-related symptoms. Secondary outcomes are quality of life, sexual function, POP-Q stage, pelvic floor muscle function, post-void residual volume, patients' perception of improvement, and costs. All outcomes are measured 3, 12, and 24 months after the start of treatment. Cost-effectiveness will be calculated based on societal costs, using the PFDI-20 and the EQ-5D as outcomes. In this paper the POPPS design, the encountered challenges and our solutions, and participant baseline characteristics are presented. For both trials the target numbers of patients in each treatment group are achieved, giving this study sufficient power to lead to promising results.

INTRODUCTION

Prolapse is 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 after hysterectomy).[1] The incidence and prevalence of prolapse increase with age.[2] In a cross-sectional study on an open Dutch population of women aged 45–85 years, 75% had some degree of prolapse.[3] Prolapse can cause a variety of symptoms including vaginal bulging, pelvic pressure or heaviness, pelvic pain, and urinary or fecal incontinence or obstruction. These symptoms can have considerable influence on daily activities, sexuality[4] and quality of life.[5] Treatments for prolapse include watchful waiting, PFMT, vaginal pessaries, and surgical correction of the prolapsed tissue. In older women co-morbidity and frailty can make surgery impossible or undesirable, whereas in younger women an active child wish or reluctance to undergo surgery may impair surgical treatment. The risk of complications during or after surgery and the long term risk of prolapse relapse are other disadvantages of surgical correction. Thus, for the majority of women with prolapse conservative treatment may be the best option; however, limited evidence is available to support conservative treatment options. PFMT may reduce prolapse symptoms and improve prolapse severity in women with mild to moderate prolapse on the short term. However, long-term benefits and the effects of PFMT on more severe prolapse are unknown.[6] Observational studies have shown that pessary treatment reduces symptoms and may prevent progression of prolapse, but little evidence is available from randomized controlled trials and no controlled trials have directly compared pessary treatment and PFMT.[7] Therefore, we designed the "Pelvic Organ Prolapse in Primary Care: Effects of Pelvic Floor Muscle Training and Pessary Treatment Study" (POPPS). This comprises two parallel open label randomized controlled trials. In POPPS Trial 1 we investigate short and long-term effects of PFMT compared to watchful waiting in women with mild prolapse. In POPPS Trial 2 we investigate the short and long-term effects of PFMT and pessary treatment in women with advanced prolapse. Both trials will also include a cost-effectiveness analysis. The aim of this paper is to describe the POPPS design and the challenges we encountered, and to present the participants baseline characteristics.

DESIGN AND METHODS

Study population and patient recruitment

Participants were recruited from 20 general practices in the northern part of the Netherlands. In the Netherlands, general practitioners keep a file of each patient registered in their practice. For the present study, each participating general practitioner

TABLE 1 SCREENING QUESTIONNAIRE

Do you have a sensation of/have you ever seen a bulge in your vagina?
Do you have a sensation of pelvic heaviness or pressure?
Do you ever leak urine?
Do you have to press to the vaginal wall to start or complete voiding?
Do you have to press to the vaginal wall to start or complete defecation?

selected all women aged ≥55 years who did not meet the exclusion criteria. Exclusion criteria were current prolapse treatment (pessary, PFMT or surgery) or prolapse treatment in the past year, current treatment for a gynecological or urological disorder, current gynecological or urological malignancy, severe/terminal illness, inability to visit the general practitioners office, cognitive impairment and inability to understand/complete a Dutch questionnaire. Then, a postal questionnaire to screen for possible prolapse symptoms was sent to all eligible women. This questionnaire is an adjusted version of the five-item questionnaire to predict prolapse developed by Tegerstedt et al., which has a sensitivity and specificity of 66.5 and 94.2%, respectively.[8] For the present study we made some adjustments in attempt to achieve higher sensitivity: i.e. we asked about all types of urinary incontinence without specification, and added two questions about feeling pelvic pressure/heaviness and about the need for digital assistance to start or complete defecation (Table 1). Symptomatic women (positive response to one or more screening questions) were asked to participate in the study and, if they consented, they were invited for a baseline assessment. Patient recruitment started at the end of 2009 and was finished in December 2012. Figure 1 summarizes the study design and recruitment for both POPPS trials. The study is registered in the Dutch Trial Register (www.trialregister.nl, identifier NTR2047) and was approved by the Medical Ethics Committee of the University Medical Center Groningen (METc2009.215).

Baseline evaluation

Participants filled in a questionnaire at home before the baseline assessment. This questionnaire comprised the Pelvic Floor Distress Inventory-20 (PFDI-20)[9] to measure bladder-, bowel- and pelvic floor symptoms, the Pelvic Floor Impact Questionnaire-7 (PFIQ-7)[9] to measure condition specific quality of life, the Pelvic Organ Prolapse/Incontinence Sexual Function Questionnaire-12 (PISQ-12)[10] to measure sexual function, the Medical Outcomes Study Short Form Health Survey-12 (MOS-SF-12)[11] to measure general quality of life, and the EuroQol-5D questionnaire [12,13]

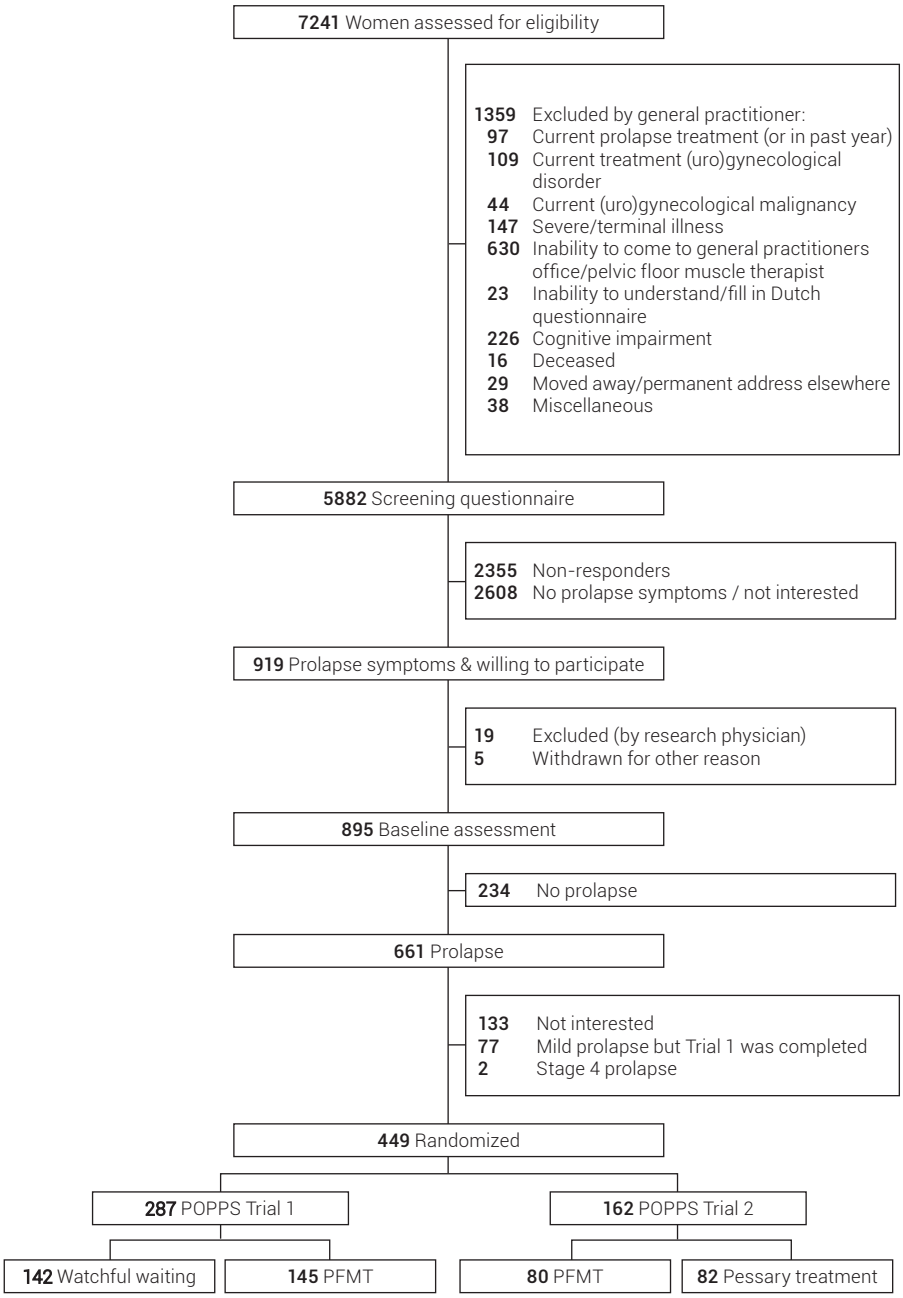

FIGURE 1 POPPS RECRUITMENT AND PARTICIPANT FLOW

to measure utility. During the baseline assessment written informed consent was obtained, information on demographics and medical and obstetric history was collected, and a physical examination and urinalysis for urinary tract infection was performed by a research physician. This physical examination included postvoid residual volume measurement with an abdominal ultrasound (BladderScan®), POP-Q measurement,[14] and evaluation of pelvic floor muscle function.[15] When urinalysis was positive for a urinary tract infection, participants received antibiotic treatment and were asked to fill in a new baseline questionnaire after resolution of the infection. Based on the baseline POP-Q examination women were categorized as follows: Women with mild prolapse were eligible for POPPS Trial 1, and women with advanced prolapse were eligible for POPPS Trial 2. Mild prolapse was defined as prolapse with the leading edge staying above the hymen (POP-Q stage 1 and mild stage 2). Advanced prolapse was defined as prolapse with the leading edge at the hymen or beyond (POP-Q advanced stage 2 and stage 3). Women with stage 4 prolapse were not included, but were referred to their general practitioner to evaluate treatment options because PFMT was not considered suitable for this category of patients.

Randomization

Within each trial, women were randomly assigned to one of the two treatment arms in a 1:1 ratio. Block randomization by means of an external computer system with an interactive voice response system (accessible by telephone) was used. The research physician enrolling the patients was blinded to the block size and allocation sequence.

Interventions

Watchful waiting

Women with mild prolapse in POPPS Trial 1 randomized to watchful waiting do not receive active treatment but are followed during a two-year period. They may visit their general practitioner because of prolapse symptoms; this is recorded at follow-up which starts after randomization.

Pelvic floor muscle training

In POPPS Trial 1 and 2, PFMT is given by a registered pelvic physiotherapist according to the standards of the Dutch Pelvic Physiotherapists' Organization (NVFB). We did not use a standard protocol for the PFMT intervention but chose a more flexible, pragmatic approach in which the participating pelvic physiotherapists adjust their treatment to the need of each patient, as would be the case in normal practice. To minimize the effect of any possible differences in the experience, skill or foresight of every single pelvic physiotherapist, the pelvic physiotherapists involved in the study

had to be registered with the Dutch Pelvic Physiotherapists' Organization (NVFB). To gain this registration, physiotherapists have to complete an extra three-year training program about the prevention and treatment of pelvic floor disorders in men and women. To gain insight in the treatment techniques and treatment duration in our study population, pelvic physiotherapists register their treatment (instructions, pelvic floor muscle exercises, use of myofeedback or electric stimulation, lifestyle advice) and the number of visits for each patient. Follow-up begins after starting PFMT. At the first follow-up visit after 3 months, all women in the PFMT groups receive a leaflet with information and advice about pelvic floor use during daily activities, toilet habits and pelvic floor muscle exercises. In this way, women are stimulated to continue pelvic floor muscle exercises after their last visit to the pelvic physiotherapist.

Pessary treatment

There is no consensus as to what is considered successful pessary fitting.[16] Some consider pessary fitting to be successful if the pessary is retained during a Valsalva maneuver and feels comfortable to the patient at the initial visit.[17,18] Others regard pessary fitting to be successful if it is used without discomfort for 2–4 weeks after insertion.[19–22] We decided to evaluate pessary fitting after two weeks, because it takes some time to experience if it does not come out during daily activities and can be worn without discomfort. Participants who discontinue pessary use within the first two weeks are refitted with another pessary. No more than three fitting attempts are allowed. Pessaries were fitted by a trained research physician. First choice was an open ring pessary, followed by a ring pessary with support. If a ring pessary could not be fitted, a Shaatz or Gellhorn pessary was tried. A pessary was considered to have the right size when the research physician could place a finger between the pessary and the vaginal wall, prolapse was reduced above the hymen, it felt comfortable to the participant, and it was retained during a Valsalva maneuver and coughing in both supine and standing positions. Follow-up starts as soon as a successful pessary fit has been achieved. Additional control visits to clean the pessary, evaluate treatment and monitor side-effects are scheduled with one of the research physicians or with the participant's own general practitioner every three months. Topical estrogen is prescribed in case of symptomatic vaginal decubitus. All pessaries used are made of silicone (Milex, Chicago, IL, USA).

What if pessary fitting fails?

In some participants pessary fitting will not be successful.[23] One of the challenges in designing POPPS Trial 2 was how to deal with this group. We considered the following: (1) When pessary fitting is unsuccessful women cannot receive the treatment they

are allocated to after randomization; (2) When this group of women is evaluated as if being treated with a pessary, the effect of pessary treatment will be underestimated; (3) Excluding women with an unsuccessful pessary fit might introduce bias because there is no such selection in the PFMT group; and (4) Fitting a pessary in all women with advanced prolapse before randomization, and randomize only the women with a successful pessary fit was considered unethical because it would mean unnecessary pessary fitting for participants eventually randomized to the PFMT group. Furthermore, study results on PFMT would then only be generalizable to women in whom a successful pessary fit can be obtained. Taking all these arguments into consideration, we decided to follow-up all women in the pessary group, also those in whom a pessary fit could not be achieved. This will make it possible to do an intention to treat analysis as well as a per protocol analysis.

Follow-up

In both POPPS trials, follow-up will be at 3, 12, and 24 months after the start of treatment. At each follow-up participants will fill in a follow-up questionnaire similar to the baseline questionnaire but with the addition of two VAS scales evaluating improvement and/or worsening of symptoms, and two questions on Global Perception of Improvement answered on a 5-point scale.[24] Consultations and/or treatment for prolapse-related symptoms (other than trial related) and cost items, will be registered in each treatment group. Women receiving PFMT are asked if they have completed the treatment and, if applicable, the reason for discontinuation is registered. POP-Q measurement and evaluation of pelvic floor muscle function are performed at each visit. Post-void residual measurement is repeated at 12 and 24 months. Pessaries are removed 24–48 hours before each follow-up visit (by the participant, a research physician, or general practitioner).

Outcome measures

For both POPPS trials the primary outcome measure is the symptom score measured by the PFDI-20 questionnaire. Secondary outcomes are condition-specific and general quality of life, sexual function, POP-Q stage, pelvic floor muscle function, post-void residual volume, patients' perception of improvement, and costs.

Blinding

Blinding patients to the treatment is not possible; also, because treatment evaluation (e.g. side-effects of pessary treatment) is part of the follow-up assessment, blinding the research physicians to group allocation is also not feasible. The researchers performing the statistical analyses will be blinded to group allocation. The main outcome

measure is the PFDI-20 score, which cannot be influenced by the researcher. POP-Q measurement and evaluation of pelvic floor muscle function may be influenced by the fact that research physicians are not blinded to the received treatment. We tried to minimize this by blinding the research physician to the patients' answers on the self-administered questionnaires and to the outcomes of the previous physical examinations.

Sample size

POPPS Trial 1

Few data were available on women with mild prolapse, therefore we had to estimate the PFDI-20 baseline score for our study population. In a cross-sectional study in women with and without pelvic floor dysfunction, women with a vaginal descent <0.5 cm beyond the hymen had a mean PFDI-20 score of 47.4 points (95% CI 41.3–53.4).[25] That study also included women without prolapse (39 of 244 women), therefore we expected the PFDI-20 baseline score in our study population to be higher, and estimated it to be 60 points. We considered a 25% reduction in PFDI-20 score to be clinically relevant; this equals 15 points. Given a standard deviation (SD) of 36,[26] a two-sided significance level of 5%, a power of 80%, and a 15% drop-out rate, 108 women would have to be randomized in each treatment arm. Assuming a response rate of 70% of which 30% would be seen for a baseline assessment, a prevalence of mild prolapse of about 53%[3] and 70% giving informed consent to join POPPS Trial 1, at least 2778 women had to be screened.

POPPS Trial 2

Based on published data, we expected the PFDI-20 baseline score in women with advanced prolapse to be around 80 points.[25] A clinically relevant difference between the two treatment groups was considered to be 25% (20 points). Given a SD of 36,[26] a two-sided significance level of 5%, and a power of 80%, successful pessary fitting in 70%[23] and a drop-out rate of 15% in both treatment arms, 74 women had to be randomized to pessary treatment and because of the randomization ratio of 1:1 and no loss of patients due to unsuccessful pessary fitting in the PFMT group, this will lead to 63 women finishing PFMT treatment (vs. 44 women finishing pessary treatment). Assuming a response rate of 70% of which 30% is seen for a baseline assessment, a prevalence of advanced prolapse of about 22%[3] and 70% giving informed consent to join POPPS Trial 2, at least 4635 women had to be screened.

Statistical analysis

The mean absolute difference as well as the mean difference in terms of percentage in PFDI-20, PFIQ-7, PISQ-12, and MOS-SF-12 scores, the change in POP-Q

measurements, pelvic floor muscle function and post void residual volume, and the difference in Global Perception of Improvement between treatment groups will be compared in an intention to treat analysis. Missing data will be imputed with multiple imputation techniques. Additionally, we will perform a per protocol analysis to examine treatment effects in participants who completed the treatment intervention. Moreover, to determine the effect of any possible selective loss to follow-up a sensitivity analysis will be performed. When reasons for drop-out appear to be related to treatment characteristics we will use bestand worst-case scenarios analysis, otherwise we will use a multiple imputation model. If necessary, adjustments will be made for differences in baseline characteristics. Longitudinal data analysis will be performed to examine long-term trends.

Economic evaluation

Economic evaluation will be from the societal perspective, meaning that all costs will be taken into account regardless of who pays for them. Patient costs include out-of-pocket costs like incontinence pads and travel costs. Health-care costs will be calculated by multiplying the volumes of health-care with standard unit prices derived from the Dutch Manual for cost research[27,28] or, if standard unit prices are not available, from market prices. Since we do not expect our study population to lose productivity due to prolapse we will only report direct costs within and outside the health care system. Cost-effectiveness will be assessed by relating the incremental societal costs of the two approaches studied within the two POPPS trials to the incremental outcomes in terms of prolapse related symptom burden, measured with the PFDI-20. Secondary analysis will include quality adjusted life years (QALY). Utility will be measured using the EuroQol-5 Dimensions (EQ-5D), valued by the Dutch EQ-5D tariff.[12,13] After the weights are obtained, areas-under-the-curves (AUC) will be provided to calculate gained QALYs for each individual patient.[29]

BASELINE CHARACTERISTICS OF THE STUDY POPULATION

Table 2 shows the baseline characteristics of participants in both POPPS trials. Women participating in trial 1 (mild prolapse) have a mean age of 64.2 years (SD 6.6), their mean BMI is 26.8 (SD 4.7), mean parity is 2.4 (SD 1.2) and 98% is postmenopausal. Previous hysterectomy is reported by 19% and 7% has had previous pelvic floor surgery. In trial 2 (advanced prolapse) participants have a mean age of 65.2 years (SD 6.9), their mean BMI is 26.3 (SD 4.0), mean parity is 2.5 (SD 1.0) and 99% is postmenopausal. Previous hysterectomy is reported by 16% and 9% has had previous pelvic floor surgery. In both trials, urinary incontinence is the most frequently

TABLE 2 BASELINE CHARACTERISTICS OF PARTICIPANTS

	POPPS Trial 1		POPPS Trial 2	
	Watchful waiting n = 142	PFMT n = 145	Pessary treatment n = 81	PFMT n = 79
Age (years), mean ± SD	64.0 ± 6.5	64.5 ± 6.8	64.9 ± 7.4	65.6 ± 6.4
BMI (kg/m^2), mean ± SD	26.6 ± 4.8	27.0 ± 4.7	26.0 ± 3.8	26.7 ± 4.2
Parity, mean ± SD	2.4 ± 1.1	2.4 ± 1.2	2.4 ± 0.9	2.6 ± 1.1
Educational level, n (%)				
Primary only	8 (6)	13 (9)	3 (4)	6 (8)
Lower	51 (36)	51 (35)	31 (38)	26 (33)
Intermediate	37 (26)	38 (26)	21 (26)	24 (30)
Higher	46 (32)	43 (30)	26 (32)	23 (29)
Menopausal status, n (%)				
Premenopausal	2 (1)	3 (2)	1 (1)	0 (0)
Postmenopausal	140 (99)	142 (98)	80 (99)	70 (100)
Surgical history, n (%)				
Hysterectomy	24 (17)	30 (21)	15 (19)	10 (13)
Pelvic floor surgery	6 (4)	13 (9)	8 (10)	7 (9)
Screening symptoms, n (%)				
Vaginal bulging	22 (16)	32 (22)	40 (49)	32 (41)
Pelvic heaviness/pressure	49 (35)	45 (33)	35 (44)	29 (37)
Urinary incontinence	124 (87)	131 (90)	62 (77)	63 (80)
Vaginal splinting to start or complete voiding	7 (5)	9 (6)	3 (4)	3 (4)
Vaginal splinting to start or complete defecation	32 (23)	30 (21)	15 (19)	15 (19)
PFDI-20 score, mean ± SD	59.0 ± 32.2	65.4 ± 40.0	60.2 ± 33.8	64.5 ± 35.6

mentioned screening symptom, reported by 89% of the participants in trial 1, and 78% of the participants in trial 2. Vaginal bulging is more common in participants of trial 2, reported by 45% (vs. 19% in trial 1). This also holds for pelvic heaviness, which is reported by 40% of participants in trial 2 versus 33% in trial 1.

STUDY'S EXPECTATIONS

These trials will provide valuable information for general practitioners, gynecologists, and others involved in the treatment of women with prolapse. For both trials the target

numbers of patients in each treatment group are achieved, giving us sufficient power to answer the research questions. The results of this study will enable patients and physicians to make an evidence-based choice between watchful waiting, PFMT or pessary treatment.

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