CHAPTER 11
SUMMARY AND GENERAL DISCUSSION
The Pelvic Organ Prolapse in Primary Care: Effects of Pelvic Floor Muscle Training and Pessary Treatment Study (POPPS) addressed the urgent need for evidence on the effectiveness of conservative treatments for prolapse in primary care. The trial had a long follow-up, focused on patient-reported outcomes, and aimed to provide information for general practitioners to use when counselling women on prolapse treatment. In this chapter, the main results of the POPPS trials, the clinical implications, and suggestions for further research are summarized and discussed.

SUMMARY OF MAIN RESULTS

In Chapter 2, the POPPS trial design, the challenges encountered, and the chosen solutions were described in detail. The POPPS trials were two randomized controlled trials including women aged 55 years and older with a symptomatic prolapse who were recruited in primary care. In the first trial, women with a mild prolapse (where the leading edge was above the hymen) were randomly assigned to either watchful waiting (n = 142) or PFMT (n = 145). In the second trial, women with a symptomatic advanced prolapse (where the leading edge was at or beyond the hymen) were randomly assigned to either pessary treatment (n = 82) or PFMT (n = 80). For both trials, the primary outcome was the change in pelvic floor symptoms, as measured by the PFDI-20 questionnaire. Secondary outcomes were also measured, including condition-specific and general quality of life, costs, sexual functioning, prolapse stage, pelvic floor muscle function, and perceived change of symptoms. Follow-up was by questionnaire and physical examination at 3, 12, and 24 months after the intervention started.

In Chapter 3, the short-term effectiveness (after 3 months) of PFMT was compared with that of watchful waiting in women with mild prolapse (POPPS Trial 1). Women receiving PFMT showed greater symptom improvement compared with women followed up by the watchful waiting strategy. Although the difference in the PFDI-20 score between the two groups was significant (9.1 points [95% CI 2.8 to 15.4]), it was below the presumed level of clinical relevance (15 points). Nevertheless, 57% of women in the PFMT group reported an overall improvement in symptoms, which contrasted starkly with the 13% who reported improvement in the watchful waiting group. None of the other secondary outcomes showed significant differences between the groups.

In Chapter 4, the results of the two-year follow-up of POPPS Trial 1 were described. Similar to the short-term results, PFMT led to a greater improvement of pelvic floor symptoms. During the two years, participants in the PFMT group improved by an average of 12.2 points (95% CI 7.2 to 17.2) more on the PFDI-20 than participants in the watchful waiting group, but the difference between groups was still too small.
to be clinically relevant. However, training was associated with an additional €239 in costs per patient, but with lower costs for absorbent pads (€40 for training versus €77 for watchful waiting) and greater overall subjective improvement in symptoms compared with watchful waiting (43% of women reported improvement after PFMT compared with 14% after watchful waiting). A subgroup analysis demonstrated that PFMT was more effective in women experiencing higher distress from their pelvic floor symptoms (i.e., had a higher PFDI-20 score) at baseline. None of the other secondary outcomes showed significant differences between the groups.

In Chapter 5, the results of POPPS Trial 2 were described, comparing pessary treatment to PFMT in women with advanced prolapse. During the two-year period, there was no significant difference between these treatments in the reduction of pelvic floor symptoms, with a difference of -3.7 points (95% CI -12.8 to 5.3) in the PFDI-20 score in favour of the pessary group. Women with typical prolapse symptoms, as measured on the POPDI-6 subscale of the PFDI-20, seemed to benefit more from pessary treatment than from PFMT, with a difference in the POPDI-6 score of -3.2 points (95% CI -6.3 to -0.0) in favour of the pessary group. Also, pessary treatment was preferable to PFMT in the cost-effectiveness analysis, where the direct medical costs per person over two years were shown to be €290 for pessary treatment and €410 for PFMT. But, pessary treatment was associated with mild side effects (60% of women reported one or more side effects), while PFMT was not associated with any, and pessary fitting was unsuccessful in 42% of the participants. None of the other secondary outcomes showed significant differences between the groups.

In Chapter 6, for the total population of older women with pelvic floor symptoms, it was shown that increasing age (OR 1.1 per year [95% CI 1.1 to 1.2]) and lower educational level (OR 2.3 [95% CI 1.5 to 3.5]) were predictors of sexual inactivity, whereas pelvic floor symptoms and prolapse were not. In sexually active women, higher reported distress measured by the PFDI-20 questionnaire (OR -0.051 per point [95% CI -0.07 to -0.04]) and a history of pelvic floor surgery (OR -1.5 [95% CI -2.8 to -0.3]) were associated with poorer sexual functioning. The severity of prolapse, by contrast, was not associated with sexual functioning.

Several studies have attempted to identify the anatomic thresholds at which prolapse becomes symptomatic or clinically relevant. These showed that prolapse of the anterior and posterior vaginal wall became symptomatic when protruding at or just beyond the hymen, while prolapse of the apical compartment became symptomatic at or beyond 5 cm above the hymen. To date, these cut-off points have shown reasonably good sensitivities and specificities in specialist urogynaecology clinics. In Chapter 7, using the baseline data of both POPPS trials, we evaluated the discriminative value of these cut-off points in a population typically seen in general practice, and that
therefore lacked the selection bias of populations seen at specialist clinics. Although this resulted in reasonable specificities, both cut-off points produced disappointing sensitivities. It was therefore concluded that, rather than focusing on typical prolapse symptoms and anatomical change, the evaluation of women with prolapse in primary care should involve a careful assessment of the symptoms and signs of pelvic floor dysfunction.

In Chapter 8, the predictors of unsuccessful pessary fitting were explored. Pessary fitting, which typically involved an open ring, was successful in 58% of cases, indicating that pessary treatment might be suitable for many, but not for all, women with advanced prolapse in primary care. The results of this exploratory study indicate that the condition of the pelvic floor plays a role in the success of pessary fitting, as evidenced by the association with underactive pelvic floor muscles (OR 2.6 [95% CI 0.8 to 8.4]), and BMI (OR 1.1 per kg/m² [95% CI 1.0 to 1.3]). In addition, the association with age (OR 0.9 per year [95% CI 0.9 to 1.0]) might reflect a higher acceptance of pessary treatment in older women.

In Chapter 9, the factors that predict treatment success in women undergoing PFMT for prolapse were investigated. This showed that presence of one or more indicators of obstetric trauma (including high birth weight, episiotomy, perineal laceration during vaginal delivery, forceps delivery, or vacuum extraction) and a prolapse above the hymen independently predicted treatment success, giving ORs of 4.3 (95% CI 1.6 to 11.9) and 2.0 (95% CI 1.0 to 3.8), respectively. By contrast, the odds of successful treatment decreased with age (OR 0.94 per year [95% CI 0.9 to 1.0]). However, these predictors only explained 14.6% of the variance in the outcome measure, implying that based on these factors we could not accurately predict the outcome of PFMT in women with prolapse.

In Chapter 10, the results of the investigation into the minimal important change (MIC) was reported for the PFDI-20 questionnaire for women in the POPPS trial population with relatively mild prolapse symptoms who often qualify for conservative treatment. We found a MIC for improvement of 13.5 points (95% CI 6.2 to 20.9), which equated to a 23% reduction in the PFDI-20 score. In Chapter 10, the interpretation of the MIC and the uncertainties that need to be taken into account when applying MIC values to individual patients were also explained.

GENERAL DISCUSSION

Conservative prolapse treatment: Indications
In most cases, the natural course of prolapse is non-progressive, and it seldom leads to life-threatening problems. Moreover, there is often a discrepancy between the
severity of prolapse and the severity of symptoms. Many women are asymptomatic, implying that treatment is not always necessary. To provide good healthcare to women seeking advice from their general practitioner, it is relevant to know who will benefit from treatment. In secondary or tertiary care, the presence of vaginal bulging is often used to indicate symptomatic (or clinically relevant) prolapse. However, prolapse can also lead to, or co-exist with, several other pelvic floor symptoms. The POPPS trials showed that most women in primary care (74%) who had an advanced prolapse did not have symptoms of vaginal bulging, but instead experienced other pelvic floor symptoms. Therefore, it would appear inappropriate to use the presence of vaginal bulging as a substitute for symptomatic (or clinically relevant) prolapse in this setting. Treatment should instead be offered to women with a prolapse who present with bothersome symptoms that are attributable to the prolapse, as determined by a thorough history and a careful physical examination, including assessment of the degree of prolapse and pelvic floor muscle function.

**Conservative prolapse treatment: Existing evidence**

In the Netherlands, most women with symptomatic prolapse are treated conservatively in primary care, usually with either PFMT or a vaginal pessary.

*Pelvic Floor Muscle Training*

Before the POPPS trials, only two small randomized controlled trials had been performed concerning the effectiveness of PFMT on symptoms of mild prolapse.\(^5\,6\) Both trials were hospital based, but did show the beneficial effects of PFMT on prolapse symptoms. In a third trial, the effect of PFMT on the degree of prolapse at physical examination, but not on symptoms, was examined.\(^7\) The study showed that PFMT improved the degree of prolapse, but it had serious methodological flaws. During the time that the POPPS trials were being conducted, several other studies have also shown PFMT to be effective in the treatment of women with prolapse.\(^8\,14\) However, most of these studies were performed in secondary or tertiary care, which limits their generalizability to primary care.

*Evidence on Pessary treatment*

Before the POPPS trials, there had been no randomized controlled trials on the effect of pessary treatment. However, observational studies had shown pessaries to be effective in improving pelvic floor symptoms related to prolapse.\(^15\,21\) While the POPPS trials were being conducted, some new observational studies have also confirmed these findings.\(^22\,24\) A recent randomized controlled trial has also shown that using a
vaginal pessary in addition to pelvic floor exercises resulted in significantly improved symptoms and quality of life compared with pelvic floor exercises alone.\textsuperscript{25}

**Conservative prolapse treatment: The POPPS trials**

*Interpretation of the POPPS results*

In POPPS Trial 1, which was for women with mild prolapse, PFMT resulted in a greater improvement of the PFDI-20 score compared with watchful waiting, and the between-group difference (12.2 points) was statistically significant. However, for a treatment effect to be considered clinically relevant, a statistically significant improvement in the questionnaire score should exceed the MIC (i.e., what patients perceive as a meaningful change). Using data from the POPPS trials, we calculated the MIC for the PFDI-20 to be 13.5 points in women qualifying for conservative treatment. Although this was lower than the 15 points we estimated in the planning phase of the trials, the observed difference between PFMT and watchful waiting was still too small to be clinically relevant.

The MIC can also be used for responder analysis in which one determines, for all participants, whether the change score was larger (responders) or smaller (non-responders) than the MIC; subsequently, the proportions of responders in each trial arm can be compared and the number needed to treat, which is useful for assessing the clinical relevance of a treatment effect, can be calculated.\textsuperscript{26,27} In POPPS Trial 1, we found that 54\% (64/118) of women in the PFMT group improved by at least the MIC, compared with 37\% (46/126) in the watchful waiting group. For one additional patient receiving PFMT to achieve the MIC, the number needed to treat was 5.6 (95\% CI 3.3 to 18.4).

In POPPS Trial 2, we found no significant difference between pessary treatment and PFMT in women with advanced prolapse. In addition, the improvement of pelvic floor symptoms by both treatments was rather low in our trials compared to the results of other studies. The cost-effectiveness analysis was also revealing, with PFMT shown to be more expensive, but no more effective, than pessary treatment. Before the trial, we hypothesized that pessary treatment would result in a greater improvement of pelvic floor symptoms than PFMT in women with advanced prolapse. Because we recruited participants by screening, it is possible that its sensitivity caused discrepancies between our hypothesis and the results of POPPS Trial 2 by including women with only mildly distressing pelvic floor symptoms. As a consequence, the effects of both PFMT and pessary treatment may have been underestimated. By performing a study in a population of women who actively seek care could obviate this problem. That said, it remains possible that the conservative treatments for prolapse might not be as effective as expected.
Subgroups of women might benefit from conservative prolapse treatment

Pelvic floor muscle training
Although neither POPPS trial showed clinically relevant differences between treatments at the group level, PFMT did seem to be effective in a subgroup of women. The responder analysis in POPPS Trial 1 did show, as commented, that approximately six patients needed to be treated by PFMT for one patient to benefit. We did not perform a responder analysis on the results of POPPS Trial 2 because such analyses are only useful for the further evaluation of statistically significant differences. However, given that 34% of women with advanced prolapse reported an overall subjective improvement of symptoms after PFMT, there may be a subgroup of women with advanced prolapse who received benefit from PFMT.

The identification of factors that predict successful treatment would be helpful when selecting subgroups of patients that might benefit from PFMT, and when providing counselling to patients on the likely outcome of treatment. In both trials, women randomized to PFMT showed substantially greater improvement of urinary symptoms than of prolapse and anorectal symptoms, suggesting that this training was of particular value for women with associated urinary symptoms. Also, a subgroup analysis of POPPS Trial 1 showed that women with more distress from pelvic floor symptoms before the study (i.e., a higher baseline PFDI-20 score) showed greater improvement of pelvic floor symptoms after PFMT. We therefore included the PFDI-20 baseline score as a predictor of successful PFMT; but, after taking other factors into account, the PFDI-20 baseline score was not associated with the success of PFMT. It is important to note that this study on predictors was performed in women from both POPPS trials, whereas the subgroup analysis was only for women from POPPS Trial 1. Based on the results of our study, we are not able to predict accurately those patients in whom PFMT will be successful.

Pessary treatment
Women treated with a pessary showed greater improvements in typical prolapse symptoms, as measured by the POPDI-6 subscale of the PFDI-20 questionnaire, compared with women treated by PFMT. Also, the improvements seen in the pessary group were sustained until the end of the study, whereas they were not sustained in the PFMT group. Pelvic floor muscle weakness, which is often due to damage caused by vaginal childbirth, is thought to play a major role in the development of prolapse. However, a considerable portion of women with advanced prolapse does not have evidence of pelvic floor muscle defects on magnetic resonance imaging. An explanation for this finding might be that other factors, for example weakness of the endopelvic fascia (the connective tissue attaching the pelvic organs to the pelvis),
are involved in the development of advanced prolapse.\textsuperscript{28,29} This might explain why pessary treatment, as a passive form of treatment that directly supports the pelvic organs to redress the prolapse, was more effective than PFMT in women with typical prolapse symptoms as PFMT only influences muscle strength and not the strength of the endopelvic fascia.

Pessary fitting proved to be successful in 58\% of women randomized to pessary treatment. Although this is comparable to the results of previous studies, in which the success rates vary between 41\% and 86\%,\textsuperscript{17,30-40} this also indicates that pessary fitting failed in a considerable portion of women. Consequently, it can be concluded that pessaries are not suitable for all women. Knowledge about the factors predictive of successful pessary fitting would be valuable for the counselling of patients. To date, the reported characteristics associated with unsuccessful pessary fitting vary between studies, so we cannot accurately predict who will be suitable for pessary treatment.

**Clinical implications for general practice**

The POPPS trials, together with several other randomized controlled trials, have demonstrated that PFMT is effective for improving pelvic floor symptoms in women with mild prolapse. However, the clinical relevance of these findings is still not completely clear. The natural course of prolapse is generally non-progressive, and whether treatment is more effective at an earlier stage or after the onset or worsening of symptoms of prolapse is unknown.\textsuperscript{4} Therefore, watchful waiting until symptoms deteriorate might be an appropriate management strategy for women with mild prolapse and minor or no bothersome symptoms. In this setting, PFMT would be best reserved for when a mild prolapse (leading edge above the hymen) is present with bothersome symptoms, especially when urinary symptoms co-exist. Although PFMT seems to be effective in a subgroup of women, we are still unable to predict in whom it will be successful.

Observational studies have shown pessary treatment to be effective for improving symptoms in women with prolapse. Based on the results of these studies and the POPPS trials, our advice would be to start with pessary treatment in women with an advanced prolapse and typical symptoms (e.g. vaginal bulging). General practitioners should, however, explain to their patients that pessary fitting fails in a considerable portion of women, and that it is associated with more side effects compared with PFMT. For women with an advanced prolapse and urinary or anorectal symptoms, we cannot give a preference for either treatment because we found no difference in effectiveness. Our advice would therefore be to inform women about the pros and cons of both treatments, and to allow them to make an informed choice. Based on our experience that active screening for prolapse might lead to the inclusion
of women with mildly distressing pelvic floor symptoms, we would not recommend routine screening for prolapse in primary care. However, a proactive attitude by physicians should be encouraged with regards pelvic floor symptoms and prolapse, because many women experience difficulties discussing their symptoms with physicians. A simple, easily introduced practice, would be for physicians to ask about pelvic floor symptoms when they encounter a prolapse by coincidence (e.g., when performing a cervical smear).

Suggestions for further research

Study population
In the design phase of the POPPS trials, screening for women with symptomatic prolapse was on the assumption that those with bothersome prolapse-related symptoms who wanted treatment would not necessarily consult a physician. We assumed that women we recruited by screening would be comparable to women seeking help for prolapse. However, it is possible that screening might have led to the inclusion of women with mild symptoms who may not have had an active wish for treatment. A subgroup analysis of the data from POPPS Trial 1 showed that women who experienced more distress from their pelvic floor symptoms at baseline had greater improvement compared with women who had less severe baseline symptoms. Future research should, therefore, focus on the effectiveness of both PFMT and pessary treatment in a primary care population of women with bothersome symptoms and an active wish for treatment.

Predictors of treatment success
There are very few studies on the predictors of treatment success in women with prolapse. Our study about the predictive factors of unsuccessful pessary fitting was the first performed in primary care. We were also the first to investigate the predictors of successful PFMT in women with prolapse. Although both studies yielded interesting results, larger prospective studies are needed in primary care populations to confirm the identified predictors of treatment success and failure, and to find other possible predictors, before this information can be used in patient counselling.
REFERENCES


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