Individualised pelvic floor muscle training in women with pelvic organ prolapse (POPPY): a multicentre randomised controlled trial

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Published in:
Lancet

DOI:
10.1016/S0140-6736(13)61977-7

Publication date:
2014

Document Version
Author accepted manuscript

Title page

Brief title: RCT of pelvic floor muscle training for prolapse

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Individualised pelvic floor muscle training in women with pelvic organ prolapse: a multicentre randomised controlled trial

Abstract

Background Pelvic organ prolapse is common and is strongly associated with childbirth and increasing age. Women with prolapse are often advised to do pelvic floor muscle exercises, but supporting evidence is limited. Our aim was to establish if one-to-one individualised pelvic floor muscle training (PFMT) is effective in reducing prolapse symptoms.

Methods A parallel-group multicentre randomised controlled trial (ISRCTN35911035) in female outpatients with newly-diagnosed, symptomatic stage I, II or III prolapse, comparing five PFMT appointments over 16 weeks (n=225) versus a lifestyle advice leaflet (n=222). Treatment allocation was by remote computer allocation using minimisation. Our primary endpoint was participants' self-report of prolapse symptoms at 12 months. Group assignment was masked from outcome assessors. We compared outcomes between trial groups in an intention-to-treat analysis. The cost of PFMT and savings on subsequent treatments were calculated to estimate cost-effectiveness.

Findings Compared to the control group, the intervention group reported fewer prolapse symptoms at 12 months (mean difference between groups in change score 1.52, 95% CI [0.46, 2.59], p=0.0053); reported their prolapse to be "better" more often (57.2% versus 44.7%, difference 12.6%, 95% CI [1.1%, 24.1%], p=0.0336); and had an increased but non-significant odds of having less severe stage of prolapse at their 6-month clinical examination, (OR 1.47, 95% CI [0.97, 2.27], p=0.07). The control group had a greater uptake of other prolapse treatment (49.6% versus 24.1%, difference 25.5%, 95% CI [14.5%, 36.0%], p<0.0001). Findings were robust to missing data. The net cost of the intervention was £131.61 per woman and the cost per one-point reduction in the symptom score was £86.59, 95% CI [£50.81, £286.11].

Interpretation One-to-one PFMT for prolapse is effective in improving prolapse symptoms. Longer-term benefits should be investigated, as should the effects in specific subgroups.

Funding Chief Scientist Office, Scottish Government Health Directorates; New Zealand Lottery Board; National Health and Medical Research Council Australia (Grant number 508925).

Word count 308

Introduction

Pelvic organ prolapse is a common female condition, with 40% of women over the age of 50 years having some degree of prolapse on examination.[1] Approximately 11% of all women undergo surgery for urinary incontinence or prolapse during their lifetime, and 7% for prolapse alone.[2] In England around 29,000 prolapse repairs were performed in 2010/2011[3] at a cost of around £60m, and surgery numbers are likely to increase substantially as the population ages.[4] Increasing age and parity, and family history of prolapse have been reported as the main risk factors for prolapse, although factors such as obesity, heavy lifting and constipation may also play a role.[5] One study reported a total population-attributable risk for prolapse of 46% associated with having prolapse symptoms during pregnancy, a mother with prolapse, and undertaking heavy physical work.[6] Prolapse is characterised by symptomatic descent of the vaginal walls, apex or vault from the normal anatomical position.[7] Women with prolapse may present with vaginal, bladder, bowel, back, abdominal and sexual symptoms. The condition can affect daily activities and quality of life. Current treatment options include surgery and conservative management, the latter being considered if the prolapse is less severe or the woman is a poor candidate for surgery. Conservative interventions include: physical interventions which aim to improve pelvic floor muscle function and support via pelvic floor muscle training (PFMT); mechanical interventions which aim to support the prolapse (e.g. use of vaginal pessaries); and lifestyle interventions which seek to avoid exacerbation of the prolapse by decreasing intra-abdominal pressure (e.g. weight loss, avoiding heavy lifting).

Many physiotherapists who specialise in women's health offer women with prolapse individualised PFMT.[8] The aim of PFMT is to improve pelvic floor muscle function (strength, endurance and coordination) and ultimately increase the structural support for the pelvic organs. There is evidence that PFMT is effective in the treatment of urinary incontinence[9] but the evidence for PFMT in the management of prolapse is less clear. The Cochrane systematic review updated in 2011[10] identified four trials (including two pilot trials) comparing PFMT with control, two of which were at significant risk of bias. Symptoms, although measured differently in different studies, were improved in the short-term in three trials, and pooled data on severity from two trials indicated an improvement post-treatment in prolapse stage due to PFMT. The review concluded that reliable evidence

relating to effectiveness and cost-effectiveness of PFMT for symptomatic prolapse in the medium and long term is needed.

We report findings of the Pelvic Organ Prolapse PhysiotherapY (POPPY) trial which compared an individualised PFMT programme compatible with UK NHS practice (five one-to-one appointments over 16 weeks), with a control group allocated to a prolapse lifestyle advice leaflet and no PFMT. Our hypothesis was that, in women with stage I to III prolapse of any type, one-to-one pelvic floor muscle training, as compared to a lifestyle advice leaflet, would reduce the symptoms of prolapse and the need for further prolapse treatment, and that it would be a cost-effective treatment for prolapse.

Methods

Participants

Between September 2007 and February 2010 we identified new attendees at outpatient gynaecology clinics presenting with symptomatic prolapse in 25 centres (23 UK; 1 Dunedin, New Zealand; 1 Sydney, Australia). Centres were a mix of university teaching hospitals and district general hospitals, all offering similar specialist pelvic floor physiotherapy services. Women were asked to take part if stage I, II or III prolapse of any type (anterior, posterior, apical, or a combination) was confirmed by their gynaecologist on vaginal examination using the Pelvic Organ Prolapse Quantification (POP-Q) measurement system,[11] and if prolapse was their main presenting complaint.

We excluded women if they had had previous prolapse treatment including surgery, if they were pregnant or less than six months post-natal, or if they were unable to comply with the intervention (i.e. if they were not able to attend the clinic for appointments with the physiotherapist). Women who, on examination, were deemed to need treatment for vaginal atrophy were eligible after completing a course of local oestrogens.

The trial methods were based on our pilot trial findings.[12] Women gave signed informed consent to being randomised and to long-term follow-up. Our trial was carried out in accordance with the Declaration of Helsinki. It was approved by: Scotland A Research Ethics Committee, Edinburgh, Scotland; Lower South

Regional Ethics Committee, Ministry of Health, Dunedin; Human Research Ethics Committees of The University of Melbourne, Victoria, Australia and St George Hospital, Kogarah, New South Wales, Australia. It was overseen by an independent Trial Steering Committee (TSC) and a separate, independent Data Monitoring Committee (DMC).

Procedures

Women allocated to the intervention were invited to attend five one-to-one PFMT appointments over 16 weeks (at weeks 0, 2, 6, 11 and 16) with a women's health physiotherapist. The intervention duration of 16 weeks was chosen on the basis of both muscle physiology (15 weeks specific muscle training is required to gain muscle hypertrophy[13]) and UK clinical guidelines for the management of urinary incontinence recommend PFMT for "at least 3 months".[14] Appointment frequency was based on current practice within the UK NHS; first appointments close together to allow reinforcement of correct exercise technique and understanding of all advice given, later appointments becoming further apart to encourage independent home exercise.

At the first appointment an explanation of types of prolapse, pelvic floor muscle anatomy and function were given using diagrams and a model pelvis. Internal pelvic floor muscle assessment to correct exercise technique and assess muscles (using the PERFECT Scheme)[15] was completed. An individualised home exercise programme was prescribed based on examination findings. Women were encouraged to progress exercises, aiming for ten times ten second maximal holds and up to fifty fast contractions, three times per day and to record all exercises in a diary. Women were also taught how to pre-contract the pelvic floor muscles against increases in intra-abdominal pressure ("the knack") and encouraged to use this technique daily. The home exercise programme was modified at each appointment as indicated by examination findings and diary recordings. The use of electromyography biofeedback, pressure biofeedback and electrical stimulation were not permitted. Trial physiotherapists attended training prior to their involvement in intervention delivery within the trial. No additional training was given to physiotherapists during intervention delivery.

Participants received a lifestyle advice leaflet that gave advice about weight loss, constipation, avoidance of heavy lifting, coughing and high impact exercise: control women received this by post, whilst intervention group women received it at their first appointment. The leaflet contained no information about pelvic floor muscle exercises or techniques. Women attended a review appointment with their gynaecologist at six months post-trial entry, at which time they could be referred for further prolapse treatment if desired.

We used postal questionnaires to collect data at the time of trial entry (baseline), and at 6 and 12 months after trial entry. Our primary clinical endpoint was prolapse symptoms at 12 months as measured by the Pelvic Organ Prolapse Symptom Score (POP-SS),[16] a validated, patient-completed instrument with seven items, relating to frequency of prolapse symptoms over the previous four weeks, each scored from 0 (never) to 4 (all of the time) (total score 0 to 28). Secondary outcomes included: women's perceived change in prolapse since the start of the study (same, better, worse); quality of life measured as interference of prolapse symptoms with everyday life (scored 0 'not at all' to 10 'a great deal'); number of days with prolapse symptoms in the previous four weeks; uptake of further prolapse treatment (surgery, ring pessary, referral to physiotherapy, referral to dietician, oestrogen cream/tablets or HRT); impact of incontinence (International Consultation on Incontinence Questionnaire Urinary Incontinence Short Form - ICIQ UI SF – scored 0 to 21, higher values indicating greater severity)[17]; bowel symptoms (early short form version of ICIQ bowel symptom questionnaire provided by the developers); sexual symptoms (Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire, PISQ-12)[18]; general health (SF-12)[19]; use of health services in primary and secondary care; and frequency of the practice of pelvic floor muscle exercises in last 4 weeks (a few times only, once a week, a few times a week, once a day, a few times a day, and contractions per day: <5, 5–10, 11–20, 21–30, 31–60, >60). Intervention adherence was measured in terms of attendance at appointments and the amount of exercise women recorded in their daily exercise diary. In addition, the physiotherapists delivering the intervention collected data at each appointment about women's adherence to the prescribed exercise.

Assessment of prolapse type and stage by the gynaecologist in clinic was carried out in all women before group allocation and at the 6-month review appointment using the POP-Q system.[11] Formal POP-Q training

was given at each trial centre initiation visit. This included: a verbal explanation of POP-Q system; observation of the American Urogynecological Society POP-Q training DVD; information on standardising conditions for POP-Q examination (e.g. examination position, bladder emptying, equipment use); use of the recording form and a question and answer session. Each centre was provided with a copy of the DVD and the publication describing the POP-Q.[11] Centres were encouraged to carry out further in-house training, and additional centre visits were offered if necessary.

Group allocation and masking

Women were allocated to groups using the remote-computer determined randomisation application at the Centre for Healthcare Randomised Trials, Health Services Research Unit, University of Aberdeen, UK. Treatment allocation used minimisation to balance group sizes on key prognostic factors at baseline. These were centre, stage of prolapse (I, II or III), and the woman's motivation for prolapse surgery (not considering surgery/considering surgery). The latter is potentially an important factor influencing how adherent women will be to PFMT. The university-based trial coordinator accessed the web-based application and then informed the woman, and the physiotherapist as necessary, of the allocated group. The intervention could not be masked from women or treating physiotherapists. Outcome assessment was by participant-completed questionnaires, thus avoiding assessor bias: data entry was carried out blinded to group allocation. The gynaecologist undertaking the POP-Q assessment at 6 months was blinded to women's trial group until after the examination.

Sample size

We estimated a difference between groups in mean POP-SS of 2.5 as our effect size, based on the pilot trial.[12] With 253 women per group the trial had 80% power at the 5% significance level to detect a different of 2.5 points in the primary outcome measure, assuming a common standard deviation (SD) of 8 points.[20] This calculation allowed for 10% loss to follow-up overall, and 15% of the control group receiving all of the benefit of PFMT by undertaking exercises under their own initiative.

Statistical analysis

We tabulated descriptive statistics, reporting baseline demographics and clinical characteristics with means and SDs, or median and inter-quartile range (IQR) as appropriate. We used intention-to-treat analyses to compare the primary outcome at 12 months by fitting a linear mixed effects model to change from baseline in POP-SS at 6 and 12 months, with a random intercept for subject within centre and a random slope for time within subject, and adjusted for baseline POP-SS score and the minimisation variables. Such models implicitly adjust the model estimates where there are missing data, assumed them to be missing at random, according to observed values.[21] Women who had observations at baseline and at least one follow-up time-point were included in the model. The difference between the intervention and control groups in estimated mean change from baseline was presented for 6 and 12 months with 95% confidence intervals and p-values. We also assessed the assumption of missing at random and corresponding impact of missing responses on the primary outcome using multiple imputation.[22] Model assumptions were checked using residual plots and found to hold.

POP-Q stage was compared between groups in an ordinal regression model with 6 month POP-Q stage as the dependent variable, and baseline POP-Q stage and minimisation variables as covariates. The pooled odds ratio from the ordinal model was calculated with a 95% confidence interval and p-value. Stage II prolapse was subdivided depending on whether the prolapse was above the hymen, or at the hymen or below. Change in POP-Q stage between baseline and six months was also presented. Other secondary outcomes were compared between groups using the Mann-Whitney (M-W) test for continuous and ordinal variables and the chi-squared or Fisher's exact test for categorical variables.

Through planned subgroup analyses we explored the effect on the primary outcome of prolapse stage and type, age and motivation for surgery, using stricter levels of statistical significance (two-sided $p<0{\cdot}01$).

Analyses were conducted according to a pre-specified Statistical Analysis Plan using the R programming package[23] and the mi package in R[24] for post-hoc multiple imputation analysis. The analyst was independent of the research team and was blinded to group allocation until after the main analysis had been undertaken.

Economic analysis

Our economic assessment was a within-trial analysis at 12 months after recruitment taking an NHS cost perspective. Direct health-service costs were used to generate the total cost for each participant. Based on the number of trial physiotherapy appointments attended, we estimated the amount of physiotherapy time which was involved in the delivery of the intervention and the associated costs of clinic space. All women were asked in follow-up questionnaires about their use of health services (general practitioner, practice nurse consultations) and any further prolapse treatment they had received. Costs were attributed to these items using UK data from: Personal Social Services Research Unit, Unit Costs of Health and Social Care; Scottish Health Service Costs; British National Formulary; and C&G Medicare Limited.[25–28] The costs were balanced against changes in the primary clinical outcome. We assumed that where we observed a difference between the trial groups in rates of subsequent treatments such as surgery at the end of the trial follow-up period, these represented savings. Sensitivity analyses were performed to assess the possible impacts of varying the intervention effect size and the uptake of subsequent prolapse treatment.

This trial is registered with Current Controlled Trials, number ISRCTN35911035.

Role of the funding source

The funders of the study had no role in trial design, data collection, data analysis, data interpretation, or writing of the report. GM, JN, SB, AE, SH and AW had access to trial data. All authors agreed to submit for publication.

Results

We approached 2093 women attending outpatient gynaecology clinics of whom 603 were eligible and 447 (74%) consented to take part in the trial (Figure 1). Follow-up rates for questionnaires were 85% (381/447)

at 6 months and 66% (295/447) at 12 months; 77% (365/477) attended for 6-month review. Non-responders at 12 months were significantly younger and had a higher BMI than responders. There was no evidence of differential dropout between the trial groups. The mean age of participants was 56.8 years (SD 11.5); the median number of births per woman was 2 (range 0 to 7); 412/445 (92.6%) of women had had at least one vaginal birth, 28/447 (6.3%) had had at least one caesarean section, 118/445 (26.5%) had had at least one forceps delivery, and 9/447 (2.0%) had had a vacuum extraction. Women were on average in the overweight category (mean BMI 27, SD 5.1). The most common presentation was combined anterior, posterior and upper compartment prolapse (202/445 (45.4%)), followed by combined anterior and posterior (108/445 (24.3%)). Most women (338/447 (75.6%)) had stage II prolapse (95/447 (21.3%) above the hymen, 243/447 (54.4%) at or below the hymen). Median duration of prolapse symptoms was 12 months (IQR 6 to 24). As expected for a trial of this size, the trial groups were well-balanced on clinical and demographic factors at baseline (Table 1).

Intervention adherence

Of the women allocated to the intervention group, 80% (178/222) attended 4 or 5 out of the possible 5 physiotherapy appointments over the 16 week intervention period (Table 2). Adherence to the prescribed number of sets of exercise or greater between appointments was achieved by just under three quarters of women. Women in the intervention group were more likely than those in the control group, although not significantly so, to report performance of pelvic floor exercises in the last four weeks at 12-month follow-up (115/147 (78%) versus 95/138 (69%); risk difference 9.4%, 95% CI [-0.8%, 19.6%], p=0.07; risk ratio 1.13, 95% CI [0.96, 1.34], p=0.15).

Adverse effects

Eight adverse events (6 vaginal symptoms, 1 back pain, 1 abdominal pain) and one unexpected serious adverse event (skiing injury), defined as affecting normal everyday activities, were reported by participants; all were from women in the intervention group. None of these were judged to be related to the intervention or to trial participation.

Prolapse outcomes

Women in the intervention group reported more improvement in prolapse symptoms (a significantly greater reduction in POP-SS) compared to the control group both at 6 months (difference between groups in change from baseline 2.84, 95% CI [2.05, 3.63], p<0.0001) and at 12 months (1.52, 95% CI [0.46, 2.59], p=0.0053) (Table 3). Combining the results of refitting the model to five imputations of the missing POP-SS scores gave very similar estimates of the differences between the groups (6 months: 2.79, 95% CI [1.91, 3.67], 12 months: 1.66, 95% CI [0.74, 2.58]).

The most commonly reported symptom at baseline was "a feeling of something coming down" (around 90% in both groups, Table 1); this persisted at 6 and 12 months (Table 3). All POP-SS symptoms were significantly less common in the intervention group at 6 months, and for "discomfort worse when standing" and "lower abdominal heaviness" this was true at 12 months also (Table 3). Women in the intervention group were also less likely to report having prolapse symptoms in the last 4 weeks both at 6 and 12 months (Table 3).

When asked "how do you feel your prolapse is now compared to the start of the study?", intervention women were significantly more likely than controls to report their prolapse was "better", both at 6 months (98/187 (52%) versus 32/189 (17%), M-W p<0.0001) and 12 months (83/145 (57%) versus 63/141 (45%), M-W p=0.0125) (Table 3).

After adjusting for baseline POP-Q stage, centre and whether the woman was motivated to have surgery, the odds of a less severe prolapse stage at six months was greater in the intervention group although this was not significant (OR 1.47, 95% CI [0.97, 2.27], p=0.07). A greater proportion of women in the intervention group had an improvement in their prolapse stage by 6 months (45/168 (26.8%) versus 33/171 (19.3%), Table 5) but this was not significant (risk difference 7.5%, 95% CI [-1.4%, 16.4%], p=0.10; risk ratio 1.39 [95% CI 0.94 to 2.06], p=0.10).

Effect of prolapse on quality of life and other clinical outcomes

Women were asked to report how much prolapse interfered with dimensions of their quality of life and about other symptoms (Table 4). At 6 months the intervention group scores were significantly lower (better) in all aspects of daily life, and sexual, bladder and bowel function (except for faecal incontinence), but this was not evident at 12 months (Table 4).

Further prolapse treatment

We asked women what further prolapse treatment they had received. By 12 months, significantly more control women (71/143 (49.6%)) reported they had received further treatment compared to the intervention women (35/145 (24.1%)) (risk difference 25.5%, 95% CI [14.5%, 36.0%], p<0.0001; risk ratio 2.1, 95% CI [1.5, 2.9], p<0.0001). There was a similar uptake of surgery, pessary and other non-trial treatments in the trial groups by 12 months, but significantly more control women had received a physiotherapy referral for PFMT (Table 5).

Subgroups

The treatment effect at 12 months was consistent for all subgroups pre-specified in the analysis plan. That is, there were no significant interactions between trial group and any of the subgroup terms in the model: prolapse stage (I to III) (p=0.38), prolapse type (most descended part anterior/posterior/upper) (p=0.61), age (under 50/50 years or over) (p=0.29); and motivation for surgery (keen/wants to avoid) (p=0.89).

Costs and benefits

The cost of the physiotherapy intervention was £170.24 based on an hourly cost of a Band 6 physiotherapist of £30.67.[25] Trial physiotherapists reported initial appointments took 80 minutes (60 minutes face-to-face plus 20 minutes of administration); follow-up appointments (maximum of 4) took 40 minutes. For overheads such as the cost of the examination room, a figure of £16 per appointment was used.[26] On average women attended for 4.2 sessions out of the possible 5 therefore we applied an 84% uptake.rate.

Based on the questionnaire responses regarding further treatment received, and published cost estimates of the various treatment courses (surgery £1,044;[26] pessary £229.45;[27,28] referral for physiotherapy £170.24, oestrogen/HRT £195.51[27]), the difference between the groups in mean cost of subsequent treatment was £38.63 (95% CI [-£41.95, £126.41], p=0.34). The mean cost per woman in the control group was £306.86 (95% CI [£250.74, £368.29]), and intervention group £268.23 (95% CI [£210.35, £333.59]). Overall the net cost of the intervention per woman was £170.24 - £38.63 = £131.61.

This cost is set against a significant difference between groups in the primary clinical outcome measure. The net cost per one-point improvement in POP-SS was £131.61/1.52, or £86.59. When we consider the 95% confidence interval around the difference in change in POP-SS from baseline (0.46 to 2.59), the cost per point improvement on POP-SS ranges from £51.81 to £286.11. When we consider the 95% confidence interval around the net costs (£170.24-£126.41 to £170.24+£41.95) the cost per point improvement on POP-SS ranges from £28.84 to £139.60.

Discussion

We found a greater reduction in prolapse symptoms in the PFMT group at 12 months when compared to the control group. The difference was both statistically significant, and of a magnitude that would be important to women, as it exceeded the minimally important change for the POP-SS.[29] This finding was supported by a higher uptake of supplementary treatments (principally PFMT) in the control group after 6 months indicating residual need; a lower prevalence of each individual prolapse symptom, as well as in bladder, bowel and sexual symptoms, and better quality of life in the intervention group after 6 months of PFMT. Women in the intervention group were also more likely to say their prolapse was “better” at both 6 and 12 months. While more women in the intervention group demonstrated improvement in prolapse stage, this was not significantly different between the groups. Subgroup analyses indicated that these findings of effectiveness held regardless of the woman’s prolapse stage or type, her age or her attitude towards having surgery.

Since there was a high degree of uptake of some form of PFMT in the control group before the primary outcome assessment at 12 months, and no evidence of differential use of other non-PFMT interventions, it seems plausible that the intention-to-treat treatment effect estimate is an underestimate of the benefit associated with PFMT at 12 months. We are confident therefore that the significant treatment effects reported represent real effects that are of importance to women and clinicians.

By 12 months a greater proportion of control women than intervention women had received further prolapse treatment (49% versus 23%), predominantly PFMT between 6 and 12 months: a quarter of the control group women sought a referral to physiotherapy, giving them access to PFMT, indicating residual need for treatment. However, similar proportions of women in both groups had undergone prolapse repair surgery by 12 months (11% intervention and 10% control), or received a pessary.

The observation that at 12 months the control group were as likely to be exercising as the intervention group may be explained partly by the uptake of physiotherapy in the control group. It is encouraging that almost 80% of intervention women were still exercising at 12 months, as long-term adherence is an important consideration for the effectiveness of this intervention.

The net cost of the intervention was £131.61 per woman. The main determinant of the cost is of providing the intervention. The main area of uncertainty is the longer-term impact of PFMT on the need for subsequent treatments such as pessaries, physiotherapy and surgery: our results are based on the trial follow-up period and we cannot exclude the possibility that treatments have been delayed rather than avoided. The sensitivity analyses show the plausible ranges around our results, however there are reasons for believing that the higher costs are unlikely, notably that the expenditure on the intervention is a one-off so all the costs have been incurred and it is plausible that the benefits in terms of reduced symptoms and treatments avoided will continue to accrue over time.

Assuming that intervention women gained 10% on their quality of life for a year as a result of the intervention, the cost per quality adjusted life year (QALY) gained is around £16,000. This level of cost per QALY is commonly accepted as worthwhile by organisations such as the National Institute for Health and Clinical Excellence in the UK.

The main strengths of the trial were its size, rigour and pragmatic design, with the intervention being relevant to UK NHS practice, and potentially to other similar health systems worldwide, and the outcomes being woman-centred. Participants' compliance with trial processes and the intervention were generally high. Unlike other trials in this area, our main focus was the prolapse symptoms which led the women to seek treatment, and which we used to measure treatment success.

In terms of limitations, we achieved 88% of our target sample size of 506, and experienced a lower questionnaire response rate at 12 months (66%) than expected, despite postal and telephone reminders. However, as the observed SD of the POP-SS was smaller than originally assumed, we nevertheless had sufficient power to identify important differences. There was no evidence of differential dropout as the response rate was similar in both trial groups, and results were also found to be robust to missing data. Not all women had a prolapse assessment at 6 months; therefore there was also attrition in the POP-Q responses (75% intervention, 77% control). This may have contributed to the non-significant POP-Q finding. There was significant crossover of control women to the intervention due to their uptake of PFMT after 6 months, and this makes interpretation of the findings more challenging. A further limitation is the short follow-up period of 12 months: due to natural fluctuation in prolapse symptoms and the effect of different treatment modalities, clinical and cost differences between the groups might be expected to change with time. Women included in this trial were treatment-naïve, presenting for treatment for the first time. However, PFMT may also be effective in enhancing surgical or pessary treatment, or for use after surgical failure, or shortly after childbirth and these situations need further research. In the economic analysis we did not estimate QALYs gained since we found in our pilot work that the SF-12 was insensitive to meaningful changes in prolapse symptoms in this population. Decision-makers therefore must interpret the results based on a careful reading of the symptoms

women suffered and the extent to which these were relieved. The lack of other economic studies in this field makes it difficult to compare results, and we look forward to future studies that provide comparisons for these results.

There are six other randomised studies published to date comparing PFMT with a control.[12,30–34] Three of these are pilot trials making it problematic to draw conclusions from their findings due to their developmental nature and small sample sizes.[12,30,31] Three other full-sized trials have been published.[32–34] The Piya-Anant trial[32] had methodological limitations and high risk of bias and cannot reliably contribute to the evidence-base. No information was provided on the processes of random sequence generation or allocation concealment; there was no reporting of attrition, selective reporting of only a subgroup of the women randomised, and uncertainty as to whether the analysis was an intention to treat analysis.

Of the remaining two trials, the Brækken single-centre trial[33] of PFMT versus control randomised 109 women with stage I to III prolapse, of which a subgroup of only 69 women were symptomatic and hence comparable to our population. The very intensive PFMT regimen consisted of weekly appointments for 3 months, followed by bi-weekly appointments for 3 months: a model of treatment that it would not be possible to deliver in the UK and many other countries. Kashyap[34] recently reported on a single-centre trial in women with stage I to III prolapse which compared taught PFMT plus a self instruction manual (n=70) with the self instruction manual alone as control (n=70). A single person delivered the PFMT intervention to all women. The content of the manual was not described and therefore it is unclear what written instruction the control group received. More importantly, four women transferred from the control group to the PFMT plus manual group and it is not clear in which group these women were analysed: until this is clarified the results have limited utility.

Symptom benefit from PFMT was reported by both Braekken[33] and Kashyap[34]. Braekken analysed women with symptoms at baseline, and found that those who had received PFMT compared to controls were more likely to have reduced frequency of symptoms (74% versus 31%) and reduced bother (67% versus 42%). Kashyap reported a significantly greater mean reduction in POP-SS score post-intervention for the PFMT plus manual

group compared to the control group (2.99 versus 1.25). Neither trial sought evidence about longer term outcomes or effect on the uptake of other treatments.

Braekken[33] also reported that PFMT improved POP-Q stage: 19% had an improved stage in the intervention group versus 8% in the control group (11% risk difference). Our finding for POP-Q was marginally non-significant but of a similar size (risk difference 7.5%, 95% CI [-1.4%, 16.4%]). The most likely reason for the non-significant finding in our trial is that the study was not powered to show a difference for this outcome. Data on change in the POP-Q or prolapse stage in the Kashyap trial were not adequately reported to allow comparison.[34]

We chose our primary outcome measure to be symptom change: this is usually the driver for seeking treatment for prolapse, and hence the most important outcome for women. It is increasingly recognised that there is little correlation between 'stage' of prolapse and the prolapse symptoms ascribed to it.[35,36] Therefore it is not surprising that, as we found, an improvement in symptoms does not necessarily correspond to an improvement in stage.

We found that 45% of women in the control group reported that their prolapse was better at 12 months. This is in part due to the fact that around half (49%) of these women had received further treatment for prolapse by this time-point. Although significantly more women in the intervention group compared to the control group reported their prolapse was better (57% versus 45%), the remaining 43% reported no change or worse prolapse. Thus we conclude that a substantial group of women did not benefit. One potential reason is that a more intensive intervention might be required for some women. Another is that some types or stages of prolapse do not respond to PFMT as well as others and hence better selection of women for PFMT might be required. Although our subgroup analyses (for prolapse stage and type, age and motivation for surgery) did not support these hypotheses, the analyses were exploratory and under-powered to draw firm conclusions.

It is recognised that prolapse can regress with time, and this could partially explain the improvement we observed. Three studies of the epidemiology of prolapse have concluded that prolapse can both progress and regress.[37–39] The studies by Handa[37] and Bradley[38] looked at change in severity of prolapse, but in populations older than our own. The study by Miedel[39] is most relevant for comparison as it examined both symptoms and stage of prolapse over time in women with a mean age of 56. They found that 44% of stage I prolapses had regressed (improved) to stage 0, 24% of stage II showed regression, and 64% (95% CI [56%, 72%]) of women had a reduction in symptoms by 5 years. However the study population was mainly non-consulting women identified by a positive questionnaire response to "a feeling of a vaginal bulge", rather than women who were actively seeking treatment for prolapse. As the authors pointed out, results cannot automatically be generalised to patients who present to health care. Thus we do not know to what extent women in our trial naturally improved. However, we would expect that any natural regression or progression would occur equally in both groups by virtue of the group allocation, and hence the observed significant differences between the groups must be due to the intervention.

Our trial constitutes the largest, rigorous, pragmatic multicentre trial of PFMT for prolapse, with the longest follow-up, and as such provides the necessary evidence to support changes in clinical practice. However the resource implications of implementing these findings need to be considered. The physiotherapists delivering the trial intervention were specialists in women's health; their numbers are limited and workload is large, currently consisting mainly of the management of urinary incontinence. With the establishment of an evidence-base for PFMT in the management of prolapse, healthcare providers will need to invest in extra resources to ensure that a similar service can be provided for women with prolapse. In addition, outwith the clinical arena, the role of pelvic floor muscle exercises in alleviating prolapse symptoms is an important public health message, which needs to be shared widely with females of all ages.

In summary, we found individualised PFMT was effective, leading to greater reduction in prolapse symptoms in the PFMT group. The net cost of the intervention was £131.61 per woman, and under plausible conditions this would prove cost-effective.

We conclude that PFMT should be recommended for the conservative management of prolapse. Effectiveness of PFMT in the long-term, in women who have had previous prolapse surgery, in conjunction with pessary use and within populations of women with different types or combinations of prolapse should be investigated further.

Word count 5624

Research in context (box)

Systematic review

The Cochrane review on the topic of conservative management of prolapse was updated in 2011 by two of the authors, prior to the completion of the analysis of the current trial. Four trials compared PFMT with a control,[12,30,32,33] but two were at significant risk of bias;[30,32] of the remaining two, one was the pilot study preceding the current trial.[12] Prolapse symptoms were measured differently in the three trials where this was reported,[12,30,33] however all three found greater improvement in symptoms in the PFMT group. Limited data from the two trials with low risk of bias[12,33] suggested that PFMT increases the chance of an improvement in prolapse stage compared to no PFMT.

Interpretation

Our trial represents the largest, rigorous, pragmatic trial of PFMT versus control for prolapse, and as such provides important robust evidence to inform clinical practice. Its findings confirm the findings of other smaller or less rigorous studies that PFMT is beneficial in terms of reducing women's prolapse symptoms. The findings have implications for a range of healthcare professionals who care for women with prolapse (general practitioners, gynaecologists, physiotherapists, nurses, healthcare managers) and for women themselves.

Authors' contributions

- SH was the chief investigator of the study: she had complete involvement in and oversight of the study design, execution, and data collection, and was responsible for the writing of the final manuscript.
- DS contributed to the design of the trial overall and the physiotherapy intervention specifically, was responsible for training the physiotherapists delivering the trial intervention, centre initiation visits and for writing the associated sections of the manuscript.
- CG contributed to the design of the study, its delivery and the writing of the manuscript, and also to the development, choice and design of the outcomes measures.
- SD, the UK trial coordinator, was responsible for the day-to-day management of all aspects of the trial, centre initiation visits and the trial office, and also contributed to the final manuscript writing.

- SB carried out the statistical analysis of the trial data and contributed to the write-up of the methods and results sections.
- HF was Project Manager for the trial in Australia, a member of the TSC, and contributed to the final manuscript.
- MPG was Principal Investigator for the trial in Australia, overseeing its overall management, and contributed to the final manuscript.
- JL assisted with day-to-day trial management, liaised with centre staff, undertook data reporting and contributed to the final manuscript.
- AMcD gave guidance on trial management throughout, and contributed to the final manuscript.
- GMcP designed the programming of the study database and group allocation system, was involved in the data reporting, including CONSORT, and contributed to the final manuscript.
- KM was local Principal Investigator in Sydney, responsible for local set up and delivery of the trial, and contributed to the final manuscript
- JN contributed to the study design, the development of the statistical analysis plan and its implementation.
- AW contributed to the design and analysis of the health economics component of the study and also to the writing of the health economics sections.
- DW contributed to the overall study development, oversight of the trial delivery in New Zealand, and guidance on the final manuscript writing.
- AE developed the programme that calculated prolapse stage from the individual POP-Q measurements, and contributed to the statistical analysis and reporting.

Full details of the POPPY collaborators are in the webappendix. Link to the full trial protocol is as follows: https://w3.abdn.ac.uk/hsru/poppy/Public/DownloadPage.aspx.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgments

The UK component of the trial was funded by the Chief Scientist Office (CSO) of the Scottish Government (project number CZH/4/377) and is summarised at http://www.cso.scot.nhs.uk/Publications/ExecSumms/JuneJuly11/HagenNeeds.pdf. NMAHP RU and HSRU are also funded by the CSO. However, the views expressed in this publication are those of the authors and not necessarily those of the CSO. Funding for the international components from the NH&MRC, Australia and the New Zealand Lottery Board is also acknowledged. The authors accept full responsibility for the research. The POPPY trial group thank all the women who willingly participated in the POPPY trial and completed their questionnaires and attended physiotherapy and gynaecology appointments. We also thank the staff at each of our centres for recruiting, motivating and treating our participants. Thanks to the POPPY trial office staff in the UK (Kim Stewart, Lucy Pyart), and to those who administered the trial in Dunedin (Gaye Ellis) and Sydney (Wendy Allen). The TSC and DMC members are thanked for giving their time in advising the trial team throughout the work.

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3

4

3 **Table 1. Baseline characteristics**

	Intervention (N=225)	Control (N=222)
Age (mean [SD]), n	56.20 [11.60], 225	57.50 [11.39], 222
BMI (mean [SD]), n	27.15 [4.99], 214	27.42 [4.57], 210
Parity (median [IQR]), n	2 [2-3], 223	2 [2-3], 217
Stage of prolapse[#] (freq [%]):		
Stage I	23/225 (10.2)	18/222 (8.1)
Stage II (above the hymen)	48/225 (21.3)	47/222 (21.2)
Stage II (at or below the hymen)	116/225 (51.6)	127/222 (57.2)
Stage III	38/225 (16.9)	29/222 (13.1)
Stage IV	0/225 (0.0)	1/222 (0.4)
Type of prolapse (freq [%]):		
Anterior	23/225 (10.2)	25/220 (11.4)
Posterior	13/225 (5.8)	11/220 (5.0)
Anterior + posterior	54/225 (24.0)	54/220 (24.5)
Anterior + upper	27/225 (12.0)	22/220 (10.0)
Posterior + upper	6/225 (2.7)	8/220 (3.6)
Anterior + posterior + upper	102/225 (45.3)	100/220 (45.5)
Duration of prolapse symptoms in months (median [IQR], n)	12 [6-24], 196	12 [6-24], 201
Baseline POP-SS score (mean [SD]), n	10.04 [6.0], 224	9.51 [5.64], 222
Symptom reported in last 4 weeks (n/N [%]):		
Something coming down	193/219 (88.1)	195/219 (89.0)
Discomfort worse when standing	140/221 (63.3)	147/220 (66.8)
Abdominal pain when standing	153/222 (68.9)	145/217 (66.8)
Lower back heaviness	131/222 (59.0)	125/216 (57.9)

Strain to empty bladder	138/221 (62.4)	109/218 (50.0)
Feel bladder not empty	159/221 (71.9)	152/218 (69.7)
Feel bowel not empty	154/221 (69.7)	140/222 (63.1)
Faecal urgency*	138/223 (61.9)	135/221 (61.1)
Faecal incontinence*	60/223 (26.9)	55/222 (24.8)
Urinary incontinence	145/225 (64.4)	156/221 (70.6)
Urinary incontinence score (ICIQ UI SF+) (median [IQR]), n	4 [0-7], 218	4 [0-7], 216

POP-Q stage reported here was calculated at the analysis stage using a specially developed programme using the 9 individual POP-Q measurements recorded by the gynaecologist. On occasion this differed from the stage assigned by the gynaecologist which determined women's trial eligibility.

+ ICIQ UI SF score: 0=no incontinence, no interference with everyday life; 21=maximum leakage and interference

* faecal urgency = sudden, irresistible need to have a bowel movement; faecal incontinence = any involuntary loss of faecal material

Table 2. Intervention group women's attendance at physiotherapy appointments

No. of appointments attended (%)	Frequency (%) N=222*
0	10/222 (4.5%)
1	9/222 (4%)
2	10/222 (4.5%)
3	15/222 (7%)
4	22/222 (10%)
5	156/222 (70%)

* missing data for 3 women from the intervention group

Table 3. Self-reported prolapse symptoms at 6 and 12 months

	6 months			12 months		
	Intervention	Control	Adjusted** difference in mean change from baseline, (95% CI) p-value	Intervention	Control	Adjusted** difference in mean change from baseline, 95% CI, p-value
POP-SS (mean (SD), n)*	6.56 (5.09), 188	9.17 (5.81), 189		5.74 (4.89) 145	7.04 (5.43), 139	
Reduction in POP-SS from baseline (mean (SD))	3.16 (4.78)	0.12 (3.86)	2.84 (2.05, 3.63) <0.0001	3.77 (5.62)	2.09 (5.39)	1.52 (0.46, 2.59), 0.0053
Prolapse symptoms reported in last 4 weeks			p-value			p-value
Feeling of something coming down	136/185 (73.5%)	162/187 (86.6%)	0.0001	98/139 (70.5%)	102/138 (73.9%)	0.09
Discomfort worse when standing	81/184 (44.0%)	122/185 (65.9%)	<0.0001	54/141 (38.3%)	78/137 (56.9%)	0.0016
Abdominal pain when standing	89/187 (47.6%)	114/184 (62.0%)	0.0001	56/143 (39.2%)	69/135 (51.1%)	0.0077
Lower back heaviness	88/187 (47.1%)	108/182 (59.3%)	0.0036	63/143 (44.1%)	68/137 (49.6%)	0.10
Strain to empty bladder	87/185 (47.0%)	106/185 (57.3%)	0.0325	67/143 (46.9%)	64/136 (47.1%)	0.95

Feel bladder not empty	109/187 (58.3%)	129/184 (70.1%)	0.0009	80/144 (55.6%)	85/137 (62.0%)	0.56
Feel bowel not empty	111/187 (59.4%)	134/184 (72.8%)	0.0014	85/140 (60.7%)	91/137 (66.4%)	0.41
Days with prolapse symptoms in the last 4 weeks†	137/185 (74.1%)	162/186 (87.1%)	0.0001	95/143 (66.4%)	104/139 (74.8%)	0.0233
How prolapse is now compared to start of study start			**p-value**			**p-value**
Better	98/187 (52%)	32/189 (17%)	<0.0001	83/145 (57.2%)	63/141 (44.7%)	0.0125
The same	77/187 (41%)	114/189 (60%)		49/145 (33.8%)	52/141 (36.9%)	
Worse	12/187 (6%)	43/189 (23%)		13/145 (9.0%)	26/141 (18.4%)	

** POP-SS score, 0=no symptoms, 28 = all 7 symptoms all the time*

*** Adjusted for baseline POP-SS, POP-Q stage, centre and whether the woman was motivated to have surgery*

† 'number of days with symptoms' question had a 7 category response (0 "none of the time" to 6 "every day"). Mann-Whitney test used on the number of categories changed since baseline

Table 4. Self-reported impact of prolapse symptoms, and prevalence of urinary and bowel symptoms at 6 and 12 months[$]

	6 months			12 months		
	Intervention	Control	p-value	Intervention	Control	p-value
Prolapse symptoms: **interference[^] with:** median (IQR[#]), n						
Everyday life	1 (0-3), 188	3 (1-6), 189	0.001	1 (0-3), 145	1 (0-4), 138	0.095
Physical activity	2 (0-5), 187	3 (0-6), 189	0.010	1 (0-3), 128	1 (0-4), 124	0.251
Social activity	0 (0-3), 187	1 (0-4), 189	0.012	0 (0-1), 128	0 (0-2), 123	0.173
Personal hygiene	0 (0-2), 188	1 (0-5), 189	0.003	0 (0-2), 128	1 (0-3), 124	0.079
Prolapse symptoms: **interference with sex life:** n/N (%)						
Not at all	75/146 (51.4%)	53/145 (36.6%)	0.033	52/95 (54.7%)	47/95 (49.5%)	0.510
A little	35/146 (24.0%)	46/145 (31.7%)		25/95 (26.3%)	29/95 (30.5%)	
Somewhat	19/146 (13.0%)	30/145 (20.7%)		11/95 (11.6%)	10/95 (10.5%)	
A lot	17/146 (11.6%)	16/145 (11.0%)		7/95 (7.4%)	9/95 (9.5%)	
Bladder symptoms:						
Urine leakage n/N (%)	103/188 (54.8%)	129/189 (68.3%)	0.01	72/132 (54.5%)	77/128 (60.2%)	0.430
ICIQ SF UI score[+] median (IQR), n	3 (0-5), 183	4 (0-7), 181	<0.001	3 (0-5), 126	3 (0-6), 126	0.118

Bowel symptoms:* n/N (%)						
Faecal urgency	96/188 (51.1%)	114/189 (60.3%)	0.041	63/130 (48.5%)	71/126 (56.3%)	0.120
Faecal incontinence	42/188 (22.3%)	47/189 (39.7%)	0.479	23/130 (17.7%)	34/127 (26.8%)	0.072

[$] women were asked to answer questions in relation to the last four weeks

[^] Prolapse-related interference scores range from 0=*not at all* to 10=*a great deal*

[+] ICIQ UI SF score: 0=*no incontinence, no interference with everyday life*; 21=*maximum leakage and interference*

∗ faecal urgency = sudden, irresistible need to have a bowel movement; faecal incontinence = any involuntary loss of faecal material

[#] IQR = interquartile range

Table 5. Change in prolapse stage (using POP-Q system) at 6 months, and uptake of further prolapse treatment by 12 months

	Intervention	Control	p-value
Change in POP-Q stage from baseline to 6 months	*N=168*	*N=171*	
+2 stages	4/168 (2.4%)	9/171 (5.3%)	
+1 stages	26/168 (15.5%)	29/171 (17.0%)	
no change	93/168 (55.4%)	100/171 (58.5%)	
-1 stage	34/168 (20.2%)	25/171 (14.6%)	
-2 stages	11/168 (6.5%)	8/171 (4.7%)	
Further treatment received by 12 months*	N=145	N=143	
Any further treatment received	35/145 (24.1%)	71/143 (49.6%)	<0.0001
Surgery	16/145 (11.0%)	14/143 (9.8%)	0.84
Pessary	8/145 (5.5%)	16/143 (11.2%)	0.13
Physiotherapy referral	2/145 (1.4%)	38/143 (26.6%)	<0.0001

Oestrogen, drugs, other	14/145 (9.7%)	15/143 (10.5%)	0.85

* The values of N represent the number of women who reported whether or not they received any further treatment at 12 months and are the denominators for the percentages.

Figure 1. CONSORT flow diagram