The Persistent Pelvic Pain (PPP) Study: Factors that influence outcomes in women referred to a public hospital with chronic pelvic pain – a study protocol

Running title: Trial protocol for a pragmatic pelvic pain study

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ABSTRACT:

Background:Persistent pelvic pain affects between 10-20% of women with a significant impact on their physical and mental health, sexual relationships, families and society. Estimates of the cost to women and the community is over $9billion/annum. Although endometriosis is considered a leading cause of pelvic pain, no symptoms reliably allow the identification of those with and without endometriosis. Furthermore, the significance of mild endometriosis is now debated. The optimal clinical approach for pelvic pain and endometriosis remains unclear, with increasing evidence of other contributing factors such as central sensitisation. Studies to date have significant limitations due to their sample size, relatively short follow-up, and inclusion of only women with laparoscopically identified endometriosis.

Aims:To undertake a real-world study of women referred with pain to gynaecology outpatients of a womens' hospital and explore factors influencing 3-year outcomes.

Materials and methods:500 women will be randomised to one of two gynaecology units. The units will provide routine clinical care but their approaches to management of women with pelvic pain and endometriosis differ: one with skilled endoscopic gynaecologists has greater emphasis on surgery, the other, gynaecologists have more medical expertise in managing pain and menstrual problems. Participants will complete 6-monthly questionnaires regarding pain and quality of life for 3years. This information will not be available to clinicians. Their medical care will be followed from their medical records. The cost of outpatient care and admissions will be calculated. Data will be analysed using STATA software with appropriate post hoc tests.

Australian and New Zealand Clinical Trials Registry(ANZCTR:ACTRN12616000150448)

INTRODUCTION:

Persistent Pelvic Pain (PPP) affects 10-20% of adult women[1-3] and can greatly impact on quality of life (QoL). It is the single most common indication for referrals to gynaecology clinics, accounting for 20% of appointments, and 40% of gynaecological diagnostic laparoscopies[4,5]. PPP is a major health problem with wide-reaching physical, social and economic consequences: 11% of women limit their home activity, 12% limit their sexual activity, 16% take medications, and 4% miss >1 day of work/month[6] and up to 40% report pelvic pain negatively impacting their concentration at work or studies, an entity known as presenteeism[7]. The estimated prevalence of PPP is comparable to chronic back pain rates[4,8]. PPP can lead to long-term suffering and disability, loss of employment, and relationship dysfunction, and thus is of critical concern for both gynaecologists and the community.

PPP also imposes considerable costs on the patient, their family, health care systems, and nationally, on productivity associated costs. The economic costs of PPP have only been

estimated for endometriosis, a condition thought to be a leading cause of PPP and reported to affect ~8-12% of Australian women of reproductive age[2]. The direct economic burden of endometriosis is estimated at $7.4billionAUD per annum[2], however loss of work productivity, loss of employment, disability and absenteeism is thought to cost $9.85billion per annum.

For the Australian health care system, each laparoscopy performed for the diagnosis or treatment of endometriosis is estimated to cost $6336.00AUD. Figure 1 shows the reported Medicare number of cases and costs in 2017-2018 for procedures performed in private hospitals in females 0-34years. These are procedures that are likely to be indicated for the investigation and management of pelvic pain. Individuals costs and private health insurance fees are more than this, with conservative estimates of gap payments of $17,438,227AUD[9].

In contrast to surgical interventions, medical treatments can also be an effective alternative method of long-term management[10]. There is also increasing evidence that central pain sensitization plays an important role in the persistence of pain[11]. Other factors may also potentially impact – from adverse childhood events[12] to the individuals response to pain as measured by the pain catastrophisation scale(PCS)[13]. Thus, of factors that may contribute to the long-term outcomes of women presenting with PPP, some reflect the clinical approach to tackle the clinical problem and some are related to the individual.

Studying the potential range of factors that might influence these outcomes is challenging in the setting of a randomised controlled trial(RCT), where enrolling women following pain scoring, QoL and catastrophisation assessments, and then randomising their management where clinician management approaches differ, would be challenging, if not completely unrealistic. Decisions to operate or not operate are usually determined by the combination of clinician and patient discussion in the clinical consultation. Thus, any trial that attempted to dictate randomised management in this setting would need to occur in a highly rarefied research setting, not a realistic clinical environment[14,15].

Studies to date have not allowed comparison of medical and surgical management modalities for women presenting with PPP. RCTs have been undertaken exploring laparoscopic interventions for pelvic pain, but have specifically excluded women with pain but negative laparoscopy findings[16,17]. These studies have demonstrated a benefit[16,17] in surgical excision of endometriosis, although not consistently[18]. Additionally, these studies have small numbers

with short timelines of follow-up: study characteristics were n=63 and 6months follow-up; n=39, 12months follow-up; and n=16, 12months follow-up for the Sutton[16], Abbott[17], and Jarrell[18] studies respectively. The duration of follow-up in studies is relevant, as the need for repeat surgery for pelvic pain has been reported to be 50% by 2years, with many women undergoing repeated laparoscopies without long-term resolution of their pain[19].

A further issue with the literature to date relates to the highly controlled environment of these studies. Outcomes from research studies, and 'gold standard' RCTs, are often not reproducible in 'real world' settings[20] due to the specialised environment of these studies. Clinicians are blinded, but participants are recruited, aware of the study protocol and randomization, have an interest in participating in studies, are supported by research nurses, and often have closer and more personalized follow-up.

The distinction between those women with dysmenorrhoea and/or pelvic pain who have endometriosis found at laparoscopy and those with a negative laparoscopy remains challenging with repeated studies failing to identify clearly defined symptoms that will allow this distinction[21-24]. Furthermore, the identification of mild superficial endometriosis has been questioned, as it is unclear if surgical removal has any long-term impact[25].

Due to the wide-reaching burden of PPP it is important that the factors influencing pelvic pain are properly understood and that optimal cost-effective care is offered to women. The combination of this burden and the gaps in current evidence, lead to the conclusion that a pragmatic "real world" study should be undertaken to enable an exploration of factors that might influence the longitudinal outcomes for women simply presenting with dysmenorrhea and pelvic pain, including an analysis of the impact of clinical practice. A comparison between two clinical practices[26], both considered "usual care", one more medically based, and the other more surgically oriented, with both occurring within the same hospital, offers the opportunity to fulfill the nine domains of PRECIS-2 criteria for this pragmatic clinical trial design[27]. Recruiting all women referred with pain fulfills the required eligibility and recruitment criteria, with the recruitment efforts directed to these women at the time of their referral to the public gynaecology outpatient clinic (the setting). The outpatient setting (organization) already provides a range of different services (or treatment approaches), with units providing either a more medical or surgical approach to care dependent on the clinicians, although all gynaecologists have the flexibility to deliver the relevant appropriate health care interventions

in discussion with individual patients. Standard hospital processes are in place to encourage patient attendance, but specific follow-up processes within the study will be instituted in an endeavor to maximise long-term follow-up. Outcome endpoints include QoL and pain scores with analysis of all data in the primary analysis, with careful comparison of study participants with those women not recruited, and participants who remain involved compared to those who may be lost to follow-up.

Justification and aims of the study

The study team are keen to understand whether there are specific features of the woman, including the pain type and severity, duration of these symptoms, or her response to her pain (eg catastophisation), that might influence or predict her outcome and thus potentially allow selection of the most appropriate therapeutic approach for specific patient characteristics. Additionally, by undertaking the study as a pragmatic clinical study, the study team are keen to follow the course of the recruited cohort of women over the subsequent 3 years with the aim of understanding what forms of management lead to better outcomes. In performing this pragmatic study in the routine clinical setting, the outcomes will hopefully provide relevant results to everyday gynaecological practice.

The results of this trial will guide care of women with PPP in Australia and New Zealand and will likely have major relevance to the worldwide community.

Primary Aim:

We aim to gain a greater understanding of the factors involved in outcomes for women with PPP.

Secondary Aims:

We aim to examine whether surgical or medical approaches to PPP management result in better outcomes. At present there is no clear evidence to determine the factors that predict which women will gain most benefit from the different clinical pain management approaches (medical versus surgical). Although a surgical approach has long been considered a critical component in care, more recent evidence relating to pain pathways and central sensitisation suggests that surgery will not improve symptoms for many women and may indeed worsen their pain.

We will also evaluate short and medium-term outcomes of patients with PPP who have been referred to our tertiary institution, comparing their baseline quality of life and pain response scores, to the care offered.

We will also evaluate the hospital related costs for patients–both outpatient clinics attendances and hospital admissions.

Key Research Questions:

1. What are the baseline QoL, pain scores, and PCS in women who present with PPP and how do they change during follow-up?
2. Are there patient factors or management approaches (surgical or medical) that are predictive for long term outcomes in women with PPP?
3. What factors influence decisions to undertake surgery for PPP?
4. Who is likely to benefit from the various management modalities?
5. What are the needs at a public health provision level for the management of women with PPP?
6. What is the cost to the hospital for providing outpatient and inpatient care and is this influenced by the approach taken?

METHODS AND STUDY DESIGN:

We will conduct a prospective cohort study at a single tertiary gynaecology referral centre.

Participants:

Our institution receives approximately 30 new outpatient referrals for PPP monthly. Of the five different gynaecology units, two have a specific interest in pelvic pain. All referrals for pelvic pain (dysmenorrhoea, dyspareunia, chronic pelvic pain), when received, are currently triaged on an ad hoc basis to these two clinics. One unit has clinicians with additional expertise in advanced laparoscopy. The second unit has gynaecologists with more extensive expertise in hormonal manipulation, although still able to undertake laparoscopic procedures. Both units initially utilise nonsteroidal medications, hormonal approaches, tranexamic acid, neuromodulators and GnRHa in a step-wise approach, although the extent of usage varies widely between clinicians as well as between units, and will be influenced by discussions and wishes of patients. For the purposes of this study, patients with appropriate referrals will be randomised 1:1 to these two clinics by the lead gynaecological nurse or research assistant,

using the Microsoft Excel(Microsoft Office, California, 2015) random number generator. We aim to have approximately equal numbers in each of the clinics, allowing for failure to attend for care and declined participation.

Inclusion Criteria:

Patients referred to our gynaecology outpatient department with pelvic pain will be approached to consent to study participation. Specific inclusion criteria include:

- Referral mentions "pelvic pain" (dysmenorrhoea, dyspareunia, bladder and/or bowel pain, and/or persistent pelvic/lower abdominal pain for more than 6 months)
- Age: 18–50years
- Consenting to 3-years follow-up

Exclusion Criteria:

Patients will be excluded where their referral contains information regarding:

- infertility or pregnancy planning
- Surgical complications of endometriosis: Obstructive uropathy, symptomatic bowel stenosis
- Previously documented extensive severe endometriosis
- Previous hysterectomy
- Ultrasound abnormality:
  - Ovarian cyst >4cm diameter
  - Other suspicious adnexal mass

Study Design

Patient participation packs will be mailed to all newly referred patients identified with pelvic pain. This will include study information, consent form, an initial questionnaire and a reply-paid envelope. Contact details will be provided should potential participants wish to contact the research team. The option of completing the initial and follow-up survey/questionnaire online or on paper will be offered. Patients may also be approached in the waiting room, whilst awaiting appointments, and invited to participate if they have not previously responded to the mailed invitation.

On arrival for their first appointment, the research assistant will ensure that initial paperwork and questionnaires were received, and offer the opportunity for questions. If the patient agrees to participate and has not completed the questionnaires they will be encouraged to do so whilst waiting. Consent to access patient data from medical records will also be sought. A "PPP Study" label will be applied to their hospital record, allowing easy identification of study participants. Patients will be asked for their preferred options for receiving future questionnaires (mail or email), and for follow-up contact details.

Information posters and brochures will be placed in the waiting room in the outpatient clinic.

Potential study participants will be allocated an identification code, to ensure confidentiality of results when they are posted. A list of all potential participants will be kept to ensure there is no difference in age and postcodes (a surrogate marker for socioeconomic status) of study participants and non-participants.

All clinical decisions regarding management will be independent of study questionnaires. Clinicians, who with the patient, decide that surgery for the PPP is warranted, will be asked to complete a brief survey regarding the factors influencing this decision in the initial 100 study patients.

Follow-up questionnaires at 6-monthly intervals will be sent either electronically utilising Survey Monkey©(San Mateo, California, United States) or in paper format, depending on patient preference. Patients will be contacted with an electronic or mail reminder if follow-up is not received within 1 month. A phone call will be made if follow-up paperwork is not received within 2-months. A text message reminder service will also be used to remind subjects to complete questionnaires. The study will conclude at a minimum of 36 months. Where 6-monthly questionnaires have not been completed, the next 6-month questionnaire will be sent out at the appropriate date. Patients will be excluded from subsequent 6-monthly surveys only if they inform the research team of their wish to be removed from the study. Prior information collected from these women will be included in the data set including information retrieved from their medical record unless they request that all their information be removed from the PPP study data base.

Patient questionnaires will take 15-30minutes. Data collection spreadsheets will be updated fortnightly and completed surveys stored securely onsite at the tertiary institution.

In preparation to undertake this larger cohort study, a successful pilot study was conducted to assess feasibility, as well as expected participation and drop-out rates.

Outcome Measures:

The questionnaires to be included in the study are 1) The Pain Catastrophizing Scale(PCS), 2) The World Health Organisation Quality of Life–Bref (WHOQoL–Bref) Questionnaire and 3) individual pelvic pain levels in the prior three months. Pain levels will be assessed using a subjective pain level rating of the women's 'average' pain levels experienced over the past three months. Pain levels will be reported using a 6-point Likert rating scale (0 – 5) where 0 indicates no pain was experienced and 5 indicates the worst pain imaginable was experienced. This rating scale will be used to assess pain with menses (dysmenorrhea), non-cyclical pain (pelvic pain), pain with micturition (dysuria), with defaecation (dyschezia), and with sexual intercourse (dyspareunia).

Informed Consent

Informed consent is required. While patient care/treatment will not be altered, we require consent to contact and follow participants potentially over a minimum of a 3-year period, and to use their health records (de-identified) for audit purposes.

An Information pack and consent form will be posted to potential participants. The consent form can be signed on the day of initial consultation, so that questions may be answered.

Ethics and Dissemination

The PPP Study was granted ethics committee approval by the Mercy Hospital for Women Human Research Ethics Committee(HREC): HREC R14-31. No financial or other competing interests have been identified or declared. PPP has been registered with the Australian and New Zealand Clinical Trials Registry(ANZCTR: ACTRN12616000150448).

We will provide participants with a summary of findings after 3 years. Interim findings will not be made available to participants, given the risk of bias.

If significant information is obtained during the course of the study, the results will be submitted for publication in a peer-reviewed journal.

Statistical analysis

The planned cohort sample size of 500 participants is considered feasible given clinic throughput. Baseline data collection will provide sufficient precision in the primary outcome measure of (pain score, QoL and PCS) to determine clinically important differences during follow-up and non-inferiority or equivalence between medical and surgical pathways; and non-inferiority or equivalence between the 2 gynaecology units. All data analysis will be performed using STATA 16.1 software. Normal distribution will be confirmed using Kolmogorov-Smirnov test. If the data is normally distributed, analysis of variance with repeated measures will be used to compare the pain scores, QoL scores and PCS at different time points. For non-parametric results will be compared using Wilcoxon matched-pairs signed-ranked tests. If significant, then post hoc tests will be used. A P value of <0.05 will be considered significant.

TRIAL STATUS:

At the time of manuscript submission recruitment for this study had concluded. 460 women had been recruited to the PPP Study, and 3-year follow-up was continuing.

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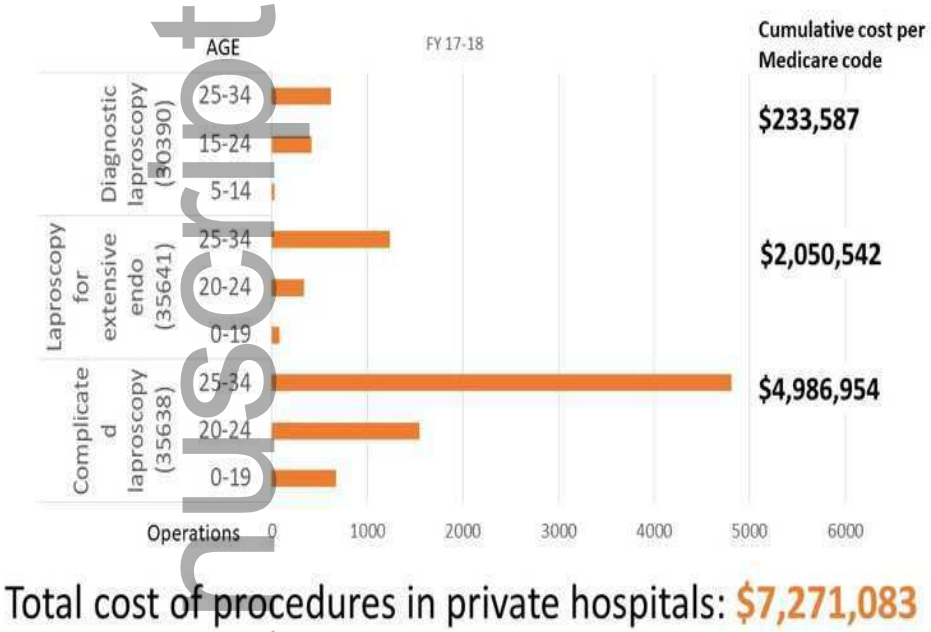
Figure 1: Medicare data for 2017- 2018 for laparoscopies in Australian private hospitals with estimates of cost

*Note: Medicare does not provide age specific data for these procedures in >35yo age groups and thus data for those women 35-50yrs has not been included.



Total cost of procedures in private hospitals: $7,271,083