

Short title: Statement on pelvic pain and endometriosis BP

Introduction

The World Health Organisation has described persistent pelvic pain (PPP)^[1] as "a neglected reproductive health morbidity".¹ PPP is recognised to have wide-reaching impacts on the quality of life, education and work potential of millions of women/wahine, girls and those assigned female at birth (henceforth referred to as "women") in Australasia.

PPP has been defined as "chronic or persistent pain perceived^[1] in structures related to the pelvis of either men or women". International studies have reported the prevalence of dysmenorrhea (period pain) to range from 2% to 97%, cyclic pelvic pain 45% to 97%, and dyspareunia (pain with sex) from 1% to 45% of women.¹

Longitudinal Australasian research has identified that more than 50% of women reported pelvic pain in the previous 12 months². While 93% of Australasian adolescents report pain as a typical symptom during their menstrual cycle, very few go on to receive a diagnosis of menstrual disorder despite 33% seeking medical help for their symptoms.^{3,4} Period and pelvic pain leads to significant school absence and interference with life activities,³ and thus, though definitely common, cannot be seen and accepted by our society as normal.

The ongoing burden of suffering persists despite billions of dollars of healthcare costs per year worldwide, implying that current management approaches are inadequate.

The Faculty of Pain Medicine (faculty) endorsed the 2011 Pelvic Pain Report⁵ which is entitled "The \$6 billion woman" as this was the estimated direct cost per annum of medical and surgical treatments for endometriosis in Australia. In 2019 the estimate of the cost of illness from PPP was reported to be approximately \$20,000 per woman per year, mainly due to productivity loss.⁶

There are more than 20 guidelines on managing PPP or pain attributed to endometriosis with 270 recommendations, mostly for pharmaceutical and surgical interventions. Although most allude to sociopsychobiomedical aspects of care, recommendations were sparse for psychological, physiotherapy and other conservative interventions.⁷

This position statement endorses a widening of approach in line with current evidence on managing PPP as a chronic pain condition rather than managing it as the presence or absence of pathology such as endometriosis.

Historically, many women have had their suffering dismissed. PPP symptoms have been described as anything from demonic possession and witchcraft to hysteria and nymphomania.⁸ In the 20th century, doctors were urging women to get pregnant to improve their symptoms.⁸ The experience of women with PPP has changed little since then.^{11,14} Additional stigmatisation can occur even within patient support groups where those with pelvic pain and no diagnosis of endometriosis may feel excluded from public advocacy and private support.¹¹

The clinical approach to managing PPP was informed by misconceived notions that pelvic pain was an 'expected' component of womanhood. Healthcare providers still may have this belief

system.^{5,6,10} This has entrenched a sense of helplessness in many sufferers and has allowed an ongoing lack of a response from healthcare systems to PPP that is commensurate with the size and scope of the problem.

Because of the social importance of having a diagnosis attention is often directed towards identifying and treating endometriosis lesions. Such a focus on presumed end-organ pathology is in contrast with current best-practice pain management approaches and the World Health Organisation's definition of health.⁹

Standard care brings resolution of PPP to only 20% of women.¹⁵ Surgical treatment of endometriosis lesions or to divide adhesions is often seen as a mainstay of treatment. The benefits of such surgery appear short-term at best, and it is common for women with PPP to undergo multiple operations.^{16,17} There is however growing evidence that non-surgical management can be effective.¹⁸ The multidisciplinary multimodal sociopsychobiomedical model of care for people living with pain has been shown to reduce healthcare use and cost. This approach if applied systematically to women with PPP is likely to translate to a reduction of the burden of disease both for women and the communities they live in.¹⁹⁻²¹

The relationship between endometriosis and PPP

It is often stated that endometriosis is one of the most common causes of PPP²², however there is increasing evidence to question this assertion.

Endometriosis is a histological diagnosis - classically defined as the presence of endometrial glands and stroma in ectopic locations outside the uterine cavity.²³ The pathophysiology and natural history of these lesions are incompletely understood²³.

PPP is pain symptoms perceived to originate from pelvic organs/structures typically lasting more than 3 months. These are often associated with symptoms suggestive of lower urinary tract, sexual, bowel, musculoskeletal, or gynaecologic dysfunction and can have negative cognitive, behavioural, sexual, emotional, social and vocational consequences.²⁴

Endometriosis lesions are neither necessary nor sufficient for pain to be experienced. While endometriosis lesions are found at laparoscopy in around half of those with PPP,²⁵⁻³⁰ they are also found in up to 45% of pain-free women.^{25,31,32}

Furthermore, pain intensity, disability and quality of life has not been shown to reliably correlate with lesion volume, distribution, histological type or surgical staging.³³⁻³⁶

Despite extensive research efforts there are no symptoms or symptom clusters that have been proven as predictive for the presence of endometriosis lesions. Women suffering from PPP are recognised to experience a complex array of symptoms, suffering and comorbid pain syndromes but these are the same whether lesions are present or not.^{30,37-40}

Australasian research has confirmed that women with PPP report a profoundly negative impact on quality of life, education and employment. The degree of impact from symptoms was predicted by pain intensity but not by whether the pain was accompanied by endometriosis lesions or not.^{39,40}

In women with PPP in whom endometriosis is found, it is not clear whether these lesions are coexistent or causative. While current classification systems include "endometriosis associated pain" it has been proposed that this phenotype should be removed from the classification because the finding of endometriosis lesions may be incidental.²⁴

Central nervous system changes similar to those found in people with other persisting pain states have been identified in women living with pelvic pain. These changes are observed in those with and without endometriosis lesions, but not found in women with endometriosis who have no pain.⁴¹⁻⁴⁴ The use of a surgical staging system implies parallels with malignancy; and management of pelvic pain historically has followed oncological principles of identifying lesions and surgical and/or medication cytoreduction. However, unlike malignancy, the lesion status/stage is not prognostic, nor is the natural history necessarily progressive in the untreated.^{45,46}

Evidence against progression is that the stage of endometriosis diagnosed does not differ by age in adult women,^{47,48} and cohort studies and the placebo arms of controlled trials have demonstrated that without active treatment, lesions remained stable or spontaneously regressed in over 70% of women.^{45,46,49} Further, moderate to severe endometriosis found in young women with obstructive Müllerian anomalies can completely resolve spontaneously following correction of the anomaly.⁵⁰

Increasing efforts are focused on identifying and reducing delay to diagnosis of endometriosis with assumption that doing so will improve outcomes.⁴⁰ However, endometriosis does not fulfil the WHO/ Wilson & Junger criteria for screening. In addition to the lack of an understood and progressive natural history with recognised latent stage; there are no predictors of which asymptomatic lesions will progress to a symptomatic state, and no treatments proven to prevent such progression to nervous system upregulation and development of persistent pain.⁵¹

The current literature on pain attributed to endometriosis has a number of shortcomings. There is often lack of uniformity in definition – variably using clinically, radiologically or surgically diagnosed or self-reported diagnoses; and in reporting “return of endometriosis” between return of surgically visible lesions, return of pain or of both. The use of “pain free controls” further limits the validity of the evidence, as these are typically women of unknown lesion status - many of whom are likely to have asymptomatic endometriosis lesions. This invalidates any conclusions drawn as it is impossible to establish if findings result from pain symptoms or the presence of lesions. This focus also limits the generalisability of the research to women with PPP of unknown or negative endometriosis lesion status.

Surgical treatment of lesions

While laparoscopic surgery is often described as ‘gold standard’ treatment for pain attributed to endometriosis, the current evidence base leaves uncertainty as to its efficacy and safety.⁵² High rates of recurrence of symptoms (which does not always correlate with return of lesions) and resultant repeat surgery have been reported at greater than 50% after 5-7 years and over 70% in the 19-29 years age group further calling efficacy of this approach into question.^{53,54}

The 2021 Royal Australian and New Zealand College of Obstetricians and Gynaecologists Guideline for Endometriosis²² recognises this, concluding that surgical management options have supporting evidence that is “very low” to “low”, recognising that “further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate”. Conversely this guideline lists the evidence for efficacy of hormonal management as “moderate”, this being the highest level of evidence identified for any treatment option in the document.

All surgery is associated with risk of complications. The overall risk of serious complications from diagnostic laparoscopy is approximately 2 in 1000 women, with risk of death 3–8 in 100 000 women.⁵⁵ Surgical risks increase with complexity of procedure with 5-10% of women undergoing treatment of deep infiltrating endometriosis suffering a major complication, the most frequent being bladder denervation and rectovaginal fistula formation.^{56,57}

Further underappreciated risks of surgical intervention include new or increased pain which has been reported post laparoscopy in up to 30% of women.^{58,59} Laparoscopic adhesiolysis is commonly

performed for PPP however it has been demonstrated to worsen pain outcomes.⁶⁰ Hysterectomy may improve pain for some women with PPP however one in seven women report having results worse than expected, a quarter have a slower recovery than expected and 5% have new onset of pain.⁶¹

Surgery which carries a higher cost and risk has not been shown to be more effective than non-surgical treatments with lower cost and risk profile.⁶²⁻⁶⁵ Hippocratic principles as well as economic considerations should support prioritising non-maleficence in pursuing lower risk and cost interventions until higher risk or cost alternatives are proven superior.

PPP shares many important similarities with other types of persistent pain states

The current approach to persistent musculoskeletal pain is informed by the observations that anatomical findings that were previously considered to be sources of nociception are commonly identified in individuals without pain; and equally, individuals suffering pain often have no observable anatomical abnormalities.⁶⁶ As discussed above, this parallels with pelvic pain and endometriosis lesions.

Women with PPP commonly also experience other persisting pain syndromes, including migraine, fibromyalgia, IBS and chronic fatigue syndrome.^{37,40,67} Notably four of the ten recognised “chronic overlapping pain conditions” are forms of PPP.⁶⁸ Evidence is emerging to suggest a common genetic vulnerability to these conditions.⁶⁹

Similar to other persistent pain states, there are changes identified in the nervous system in those with PPP. Central nervous system sensitisation is recognised as a contributor to pain in PPP with evidence of impaired pain inhibition, increased pain facilitation and changes in white and grey matter.^{41,44,70-72}

Evidence of central sensitisation has been identified in 75% of women with PPP;⁷³ both PPP that occurs daily and in cyclic pelvic pain,^{71,74,75} and to occur equally in those with and without endometriosis lesions.^{43,72,76} Markers of such nervous system upregulation have been found to be predictive of outcomes.^{58,77}

There is considerable overlap between risk factors for PPP and other persistent pain states. Psychometric markers of distressing pain cognitions such as catastrophising and fear avoidant coping are frequently present in women with PPP.^{30,79-87} The role of adverse childhood events as potential priming factors for PPP is common to other persistent pain states.⁷⁸

In common with other persisting pain conditions, interventions which result in improvement in these constructs are associated with greater improvements in pain intensity, quality of life and symptoms of depression.^{15,88}

The aims of therapy or pain self-management programs generalise well to women with PPP. Examples of helpful cognitions include recognising that ‘pain system hypersensitivity’ results in ‘overprotective pain’ in the absence of damage and that increasing physical activity and actively managing stress is as effective as any medical treatment for this condition. Gaining this understanding can empower women to change their behaviours in ways which may change their pain.^{89,90}

There are however notable differences

Pelvic pain can afflict anyone with a pelvis however the incidence is three times higher in women than men.^{24,91} While in early childhood the occurrence of persisting pain is similar in boys and girls, from adolescence girls experience more persistent pain. This increased prevalence of pain in girls is more often headache and abdominal pain and it is notable that the timing coincides with the usual age of onset of menstruation.^{92,93}

Persistent pain services need to cater to a wide range of diagnoses, levels of function and demographic diversity.^{94,95,96} Women with pelvic pain may not feel completely comfortable attending a generic persistent pain service, and hence more specialised services are likely to have a higher uptake.

Many people living with pain attribute the onset of their pain to a single inciting event or injury which does not recur. In contrast the repeated inflammatory insult produced by menstrual events occurring generally monthly, present a substantial risk factor for nervous system sensitisation. Particularly in the setting of increased neuroplasticity seen in the adolescent age group⁷⁴.

Endometrial shedding is accompanied by inflammatory substances including prostaglandins and cytokines, activation of leucocytes and release of matrix metalloproteinases.⁹⁷ Many of these substances are known nociceptor stimulators⁹⁸ and the repeated episodes of this inflammatory process are thought to contribute to the development of PPP.⁹⁹

Exacerbation of a range of systemic conditions occurs with menstruation – including asthma, fibromyalgia, chronic fatigue, migraines, inflammatory arthritis, irritable bowel syndrome, eczema, and anaphylaxis. Thus, menstrual management and avoidance of these cyclic inflammatory events is a key component of management of persisting pain in those who menstruate.

A significant and often cited concern in the management of pelvic pain is the dismissal of patient reported suffering. The argument that dysmenorrhea affects up to 90% of adolescent girls and is considered “normal”. This can lead to severe pain experiences being minimized^{10,100,101}. Similarly, dyspareunia is often dismissed with the sufferer believing that pain with intercourse is normal for women.¹⁰²

The psychological response to PPP and menstrual pain contains unique aspects of social and psychological constructs related to womanhood, fertility and femininity. These concerns may have an impact on the care that is provided.^{101,104,105} This may, in part, explain the higher levels of pain catastrophising experienced about PPP than found in other pain type samples.^{80,106} Modern pain management recognises the importance of addressing such psychosocial domains for those with persisting pain though there should be caution regarding attribution of causality.^{107,108}

A healthcare focus on early detection of endometriosis lesions contrasts strongly with other areas of persistent pain, where pathoanatomical diagnosis is less emphasised. Ongoing moves toward early lesion detection as a priority over symptom management further shifts the model of care away from that of other persistent pain types.

PPP results in loss of functioning across many roles in life

PPP, with or without co-existing endometriosis lesions, poses a substantial burden on those affected, their family/whanau and on health systems. The cost of illness burden has been estimated to be ~\$20,000 per woman per year with the majority of cost resulting from loss of productivity.⁴⁰ In a New Zealand cohort, more than half of those living with PPP reported that their period pain prevented work or daily activities often or always in the last 3 months; over 70% reported that pelvic pain had negatively affected personal relationships, and over 60% that their PPP resulted in lost time from education. Notably these findings were the same in those with PPP whether endometriosis lesions were present or not.³⁹

Documented beneficial response to comprehensive, whole-person, sociopsychobiomedical management.

As with other persisting pain conditions, a whole person sociopsychobiomedical approach to PPP typically includes the use of medications alongside a multidisciplinary team (MDT) supported pain self-management program.

Symptom directed medical therapy, including NSAIDs and menstrual suppression, is effective for the majority of women with dysmenorrhea^{109,110}. Hormonal suppression with oral contraceptives or GnRH agonists is as effective for reducing pelvic pain in those with and without endometriosis lesions^{111,112}

MDT pain programs for people living with persisting pain have been demonstrated to improve pain and quality of life, reduce healthcare usage and disability; and increase physical function, psychological well-being, quality of sleep and return to work^{113–115}. These programs have also been demonstrated to be cost effective – especially when compared to surgical approaches^{116,117}

Women with PPP attending mixed-pain group programs do less well than the rest of the cohort despite similar pain related disability¹¹⁸. However, the delivery of MDT pain programs within a dedicated PPP pain management program has been shown to overcome this.^{19,20,88,119–122}

The faculty asserts that PPP should be considered as a type of persistent pain state with unique characteristics. The overarching approach should adopt principles in line with best practice management of other persistent pain states, that of multidimensional whole person care.

The importance of moving away from an end organ pathology focused care

Over a decade ago the International Association for the Study of Pain (IASP) promoted a paradigm shift in the approach to back pain. The prevailing End-Organ Dysfunction Model “that patients feel back pain because of a nociceptive focus in the spine” was replaced with Altered Nervous System Processing Models which “share a rejection of the straightforward link between pathology in the end organ and the experience of pain”.⁹ The same drivers resulting in this change in approach can be identified in the current approach to PPP.

Research into the factors that contribute to long term outcomes of people with back pain have demonstrated a lack of correlation between imaging findings and outcomes. However, the language around these imaging findings can have a profound and negative impact on outcome.^{123–125} In the setting of PPP where endometriosis has been raised as a possibility, the management strategies and outcomes of the woman with PPP can be negatively impacted by this label. The unique nature of endometriosis diagnosis and management is particularly prone to nocebo effect.¹²⁶ Social media commonly describes endometriosis as an incurable, lifelong, crippling condition leading to infertility and hysterectomy.¹²⁷

What must not be drawn into question is an individual's report of pain. For both back pain and pelvic pain, the presence of pain and suffering without a positive physical or test finding does not imply that the pain is not real and experienced by the individual. Increasingly the concept of nociplastic pain, the shared phenotypes of chronic overlapping pain conditions and a greater understanding of the evolution of these conditions move us closer to understanding and educating patients and healthcare providers of the shortfall of an end organ management approach.

Reliance on surgery as a consequence of focus on end organ pathology

A consequence of the current focus on searching for end organ pathology, and in particular, endometriosis, means that access to laparoscopy has been considered imperative. Despite the lack of evidence to support the correlation between endometriosis lesions and pain,³⁴ many still see lesion-directed surgery as the gold standard thus creating a rate determining step for women to access timely care for their PPP. Delaying provision of appropriate multimodal whole person pain management¹²⁸ exposing women to repeated episodes of disabling period pain. These repeated episodes of inflammatory exposure contribute to the development of PPP (vide supra).

The emphasis on end organ pathology also risks overlooking other contributors to pain and suffering – including abdominal wall and pelvic muscle pain, psychosocial risk factors, chronic overlapping pain conditions, inflammatory bowel disorders, malignancies, central nervous system involvement and lifestyle factors such as diet and sleep quality.

Present funding models prioritise procedures and surgery over a broader sociopsychobiomedical approach. Access to thorough whole person history, examination and formulation is currently inequitable and undervalued by stakeholders and funders. Whilst small steps have been made to educate women, clinicians and funders, these steps have fallen far short of what is necessary.

A more inclusive approach

Education on modern understanding and management of persisting pain is sorely lacking in undergraduate and postgraduate medicine¹³¹ in contrast to the expertise in whole-person sociopsychobiomedical approach championed by the faculty and its fellows. If endometriosis continues to be considered the predominant cause of PPP, the management of women suffering pelvic pain will remain with an end organ focus.

Broadening access to optimal care requires upskilling of all clinicians who encounter PPP. Centres of excellence in research and treatment of PPP will be required for generation of new evidence to guide improved treatment in the future. Mechanisms for rapid translation of new evidence into practice need to be developed so that the model of care places effective treatment in the hands of frontline clinicians at the earliest opportunity. The needs of women with PPP and current best evidence should inform development of these new services and help to guide the research agenda.

Over 90% of adolescents with dysmenorrhea can be well managed with non-steroidal anti-inflammatory drugs and oral contraceptives.¹⁸ This conservative approach results in a low rate of laparoscopy and no cases of moderate or severe endometriosis, or adverse impact on fertility after a 10-year follow up.¹²⁹ Such an approach can be instigated in primary care and would not adversely affect the small number who may need further imaging and investigation. It will however result in timely support towards improved quality of life for all.

Current evidence-based understanding of the relationship between endometriosis lesions and PPP has moved beyond a simple assumption of causality. It is time to recognise that a sociopsychobiomedical approach to pelvic pain is most appropriate, whether endometriosis lesions are present or not.

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Footnotes

^[1] While identified as chronic pelvic pain in many clinical, research and policy settings, we have elected to use the term pelvic persistent pain (PPP) as this is the term preferred by consumers (Raffaelli *et al.*, 2021), and avoids the common misconception of ‘chronic’ as ‘severe’ and incurable.

^[2] Perceived indicates that the patient and clinician, to the best of their ability from the history, examination and investigations (where appropriate) have localised the pain as being discerned in a specified anatomical pelvic area.

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