When pain is not the whole story: presenting symptoms of women with endometriosis

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Background:
Endometriosis affects one in nine Australian women of reproductive age, and is often associated with pain and infertility. Many women may however be asymptomatic, or present with alternative symptoms.

Aim:
To identify reasons for initial specialist referral, among patients with endometriosis.

Material and Methods:
Patients were identified as having endometriosis intraoperatively based on ICD coding. Operation reports were reviewed and graded for severity of disease. This cohort was then retrospectively audited to identify reasons for initial referral to the General Gynaecology, Endosurgery, Gynae-oncology, Reproductive Medicine outpatient departments (OPD) at the Mercy Hospital for Women in Melbourne between 1st February 2015 and 31st December 2016.

Results:
300 patients were identified as having endometriosis at laparoscopy, including 90 women with Stage IV disease. Patients were a mean [SD] age of 33.1[7.6] years. While pain remained a common reason for referral (61.7% of referrals), 36.7% of women with Grade IV disease did not have pain included in their reason for referral. Severe disease was associated with increased age (regression coefficient 0.05;95%CI:0.03-0.07, p<0.01), but not with pain symptoms. Women referred with ovarian cysts or masses were more likely to be diagnosed with severe disease (regression coefficient 0.69;95%CI:0.37-1.01, p<0.01).

Conclusion:
Although pelvic pain is not a good predictor for a diagnosis of endometriosis, it remains a common symptom among women with the disease. However, more than one in three patients with Grade IV endometriosis presented without mention of pain symptoms, encouraging clinicians to adopt a broader approach to the presenting symptoms of endometriosis.

Introduction

Endometriosis is a chronic inflammatory disease characterised by deposits of endometrial tissue outside the uterus.[1] One in nine women in Australia are diagnosed with endometriosis by the age of 44,[2] typically presenting with a combination of chronic pelvic pain (CPP), dysmenorrhoea, dyspareunia and/or infertility, although some women may be asymptomatic.[3]

The disease is associated with impaired quality of life and significant economic burden due to productivity loss.[4] The World Endometriosis Society guidelines suggest that surgical excision of endometriotic deposits is an evidence-based first-line management option for pain related to the disease,[5] although there is increasing evidence that there may be no benefit in women with superficial peritoneal lesions.[6] Women with endometriosis often undergo multiple surgeries,[7] with postoperative disease recurrence and formation of symptomatic iatrogenic adhesions further complicating this poorly understood condition.[8]

CPP, by contrast, affects an estimated one in five Australian women,[9] and while many of these women are suspected to have endometriosis at some point, most of them do not.[10] Women with CPP are more likely to be offered surgery if they experience factors increasing the likelihood of pathology such as severe and prolonged pain.[11] However, the finding of endometriosis does not correlate with any specific pain symptoms,[10] or any cluster of symptoms,[12] and the extent of endometriosis does not correlate with severity of symptoms.[13] Furthermore with diverse symptomatology, there are often significant delays between first presentation and eventual diagnosis of endometriosis.[14] The associated pain comorbidities seen in women with endometriosis, CPP and other chronic pain conditions suggests that central sensitisation to pain is the key underlying factor in the pain presentations of women with endometriosis,[15] calling into question whether clinicians should be looking for endometriotic lesions or rather focussed on addressing the woman's symptoms.[16]

This paper then seeks firstly, to understand how women with endometriosis initially present to the outpatient department, and secondly, whether women with severe disease present differently to those with less severe disease.

Materials and Methods

Participants and Procedure

The Mercy Hospital for Women is a public tertiary women's hospital in Melbourne, Australia. Patients at this hospital who underwent a laparoscopy where endometriosis was identified and documented in their operative notes were identified through medical record coding, utilising the International Classification of Diseases (ICD) codes N80.0 through to N80.9 [Appendix 1].[17]

Operation notes for these patients were reviewed by HG and SM (the former a trainee gynaecologist, and latter a gynaecologist who has undergone training in advanced laparoscopic techniques), and staged according to the revised American Society for Reproductive Medicine (r-ASRM) classification system for endometriosis.[18] Participants were excluded if there was not enough information in the operative report to accurately assess severity of disease (n=1).

Patient records were subsequently audited to identify the indication for the initial referral for an appointment in the General Gynaecology, Endosurgery, Urogynaecology, Gynae-oncology, or Reproductive Medicine outpatient departments (OPD) between 1st February 2015 and 31st December 2016. Data were entered by HG with a random 3% of the sample entered by SG and then checked by HG to ensure accuracy and reproducibility of the dataset.

Inclusion criteria included age between 18 and 50 years, and first clinic appointment between 1st February 2015 – 31st December 2016. This time period was chosen to encompass the study time of the 'Persistent Pelvic Pain' study which explores the outcomes of women referred for pelvic pain as previously published.[10,11]

Women who had multiple surgeries during the study period (n=25), were only included once. Patients without formal referrals in their file were excluded from the study (n= 8), as were women who had had a hysterectomy prior to their initial consult (n=2).

Ethics approval was granted by the Mercy Health Human Research Ethics Committee (reference HREC 2020-020) on 9th June 2020.

Statistical analyses

Statistical analyses were performed using Stata 15. Linear regression analyses were performed to determine 1) if there was an association between age and stage of endometriosis, and 2) whether initially presenting with ovarian cysts or masses was associated with severity of disease. Using Stages I-IV as categorical variables, a logistic regression analysis was performed to determine whether patients with severe disease were more likely to present with pain.

Results

There were 300 cases of endometriosis identified at laparoscopy that met inclusion criteria. Of these, 90 patients (30%) were found to have severe (Stage IV) endometriosis (see Table 1).

Women were a mean [SD] age of 33.1 [7.6] years of age at the time of admission, with the majority of women (76.7%) initially reviewed in the General Gynaecology OPD.

The most common reasons for initial referral were pain (37.0%), infertility / subfertility (17.0%), and a combination of pain and/or infertility and/or ovarian cyst and/or irregular bleeding and/or bowel symptoms (23.3%) (see Table 2). 38.3% (n=115) of the cohort did not have any mention of pain in their referring GP letter, including 36.7% of patients with Grade IV disease.

"Other" reasons for referral (n=9) included removal/reinsertion of Mirena (n=1), suspected pre-malignant / malignant condition (n=7), and pelvic organ prolapse (n=1).

Among women who were reported as experiencing pain (n=185) in their GP referral letter, there was often limited information to characterise the pain (Figure 1). 23.8% of women were reported as experiencing dysmenorrhoea alone, while 28.6% experienced two or more pain symptoms (including chronic pelvic pain, dyspareunia, dysmenorrhoea, painful defaecation, pain on urination).

No patient was referred with bowel symptoms alone, but 18 patients (6.0%) of the total cohort reported some degree of bowel symptoms (bloating, dyschezia, painful defaecation) in conjunction with other symptoms. Eight of these 18 patients had Stage IV endometriosis.

Among the 33 patients (17.8%) referred with dyspareunia, the vast majority (n=23) had mild (Stage I-II) disease.

Women referred in with ovarian cysts or masses were more likely to have severe disease (regression coefficient 0.69; 95% CI: 0.37-1.01, p<0.01). Among patients with severe endometriosis, 16.7% had repeat procedures, compared with 4.5% of patients with mild disease. Women with severe disease were not more likely to be referred in with pain than those with less-severe disease (regression coefficient 1.17; 95% CI: 0.65-2.12, p=0.601).

Women with Stage IV disease were older, with a mean [SD] age of 36.3 [7.4] years, compared with 30.5 [6.5] years among patients with Stage I disease (regression coefficient 0.05; 95% CI: 0.03-0.07, p<0.01).

Discussion

The most recent NICE Guidelines propose that pain – specifically dysmenorrhoea, CPP, dyspareunia, painful defecation and/or micturition make up five of the six presenting symptoms of endometriosis.[19] And yet, this study has found that more than one in three women with Grade IV disease did not have pain as part of their reason for referral to the gynaecology OPD as documented by their GP.

While it cannot be assumed that these patients are pain-free, it does suggest that pain is not the most significant symptom in their presentation. This is in keeping with previous research by Vercellini et al that found an inconsistent relationship between severity of pain symptoms and stage of endometriosis.[20]

Comparatively however, when women with endometriosis were surveyed, 70.3% (Singh et al)[21], 90% (Divasta et al)[22] and even 100% (Markham et al)[23] self-reported experiencing dysmenorrhoea, suggesting that there is perhaps a discrepancy between medical practitioners' and patients' perceptions of symptoms of the disease. However, these pain symptoms are not necessarily related to a diagnosis of endometriosis, considering the prevalence of dysmenorrhoea among young Australian women (with or without endometriosis) is estimated to be 80%.[24]

This current study is unique in that it identifies reasons for initial referral among patients later diagnosed as having endometriosis. Pain is not a reason for referral for many of these patients nor does it seem to be a predictor of severe disease.

The increasing recognition of the role of central sensitisation,[15] the questioning of the effectiveness of intervention for superficial peritoneal disease,[6] combined with these findings where the majority of women with severe disease did not have pain symptoms does suggest that the emphasis on pain as a symptom of endometriosis needs to be questioned.

The 6% of patients who experienced bowel symptoms as reported by their GP is a far lower rate than Maroun et al reported in a cohort of 290 women with endometriosis, where 90% experienced some degree of bowel symptoms.[25] GP referral letters are often incomplete,[26] and perhaps bowel symptoms have not been volunteered by the patient or omitted by the referring clinician, believing they relate to a different disease process.

Ultrasound has been shown to reliably predict mild endometriosis,[27] as well as severe disease.[28] Specifically, Banerjee et al have demonstrated that endometriomas are a useful marker for deep

infiltrative endometriosis,[29] and in a similar vein, this current study has shown that patients referred with an ovarian cyst or mass are more likely to be subsequently diagnosed with severe endometriosis.

Strengths and Limitations

This is a large cohort study from a major tertiary hospital, unique in that it retrospectively assesses symptoms at first referral for many patients, rather than following an established diagnosis.

There is however a potential for error inherent in all database-based research. Grading of endometriosis is subjective, and there is a possibility that intraoperative findings were incompletely or incorrectly documented on operation reports. However, the accuracy of grading was maximised with each report reviewed by a gynaecologist who has undergone training in advanced laparoscopic techniques.

Further, as suggested by the literature, it is possible that GP referral letters include some but not all of a patient's presenting symptoms.[26] Accordingly, there may be an underestimation of the scope of ways in which endometriosis may present, and a potential that pain and bowel symptoms may be underrepresented. Specific pain symptoms, namely throbbing and dyschezia, have been shown to be related to endometriosis, as compared with CPP.[30] Although outside the scope of this paper, were gynaecology notes reviewed, further information would likely be available as to pain symptoms. GP referral letters, by comparison, provide a unique insight into patients' primary presenting problems, where pain seems to be less prevalent that what one might expect.

While pelvic pain is not a good predictor for a diagnosis of endometriosis, it remains a common symptom among women with the disease. However, more than a third of patients with Grade IV disease were referred without any mention of pain symptoms, encouraging clinicians to adopt a broader approach to endometriosis.

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Appendix

[1] ICD codes

N80.0 Endometriosis of uterus
N80.1 Endometriosis of ovary
N80.2 Endometriosis of fallopian tube
N80.3 Endometriosis of pelvic peritoneum
N80.4 Endometriosis of rectovaginal septum and vagina
N80.5 Endometriosis of intestine
N80.6 Endometriosis of cutaneous scar
N80.8 Other endometriosis
N80.9 Endometriosis unspecified

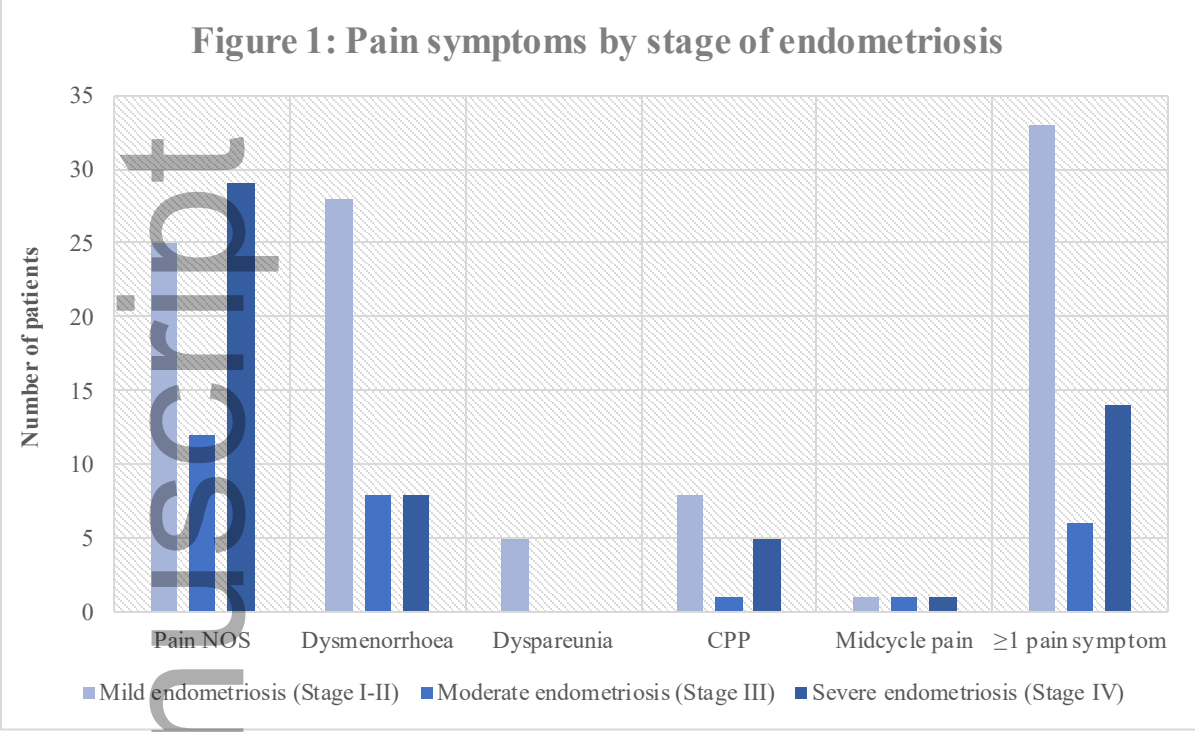
Tables

Table 1: Participant characteristics		
Age (years) (mean, [SD])		33.1 [7.6]
Severity of endometriosis, (n (%))	Stage I	94 (31.3%)
	Stage II	62 (20.7%)
	Stage III	54 (18.0%)
	Stage IV	90 (30.0%)
Specialist clinic, (n (%))	General gynaecology	230 (76.7%)
	Endosurgery	4 (1.3%)
	Oncology	11 (3.7%)
	Reproductive Medicine	54 (18.0%)
	Urogynaecology	1 (0.3%)

Table 2: Presenting symptoms of endometriosis					
		Mild (Stage I-II) endometriosis (n=156)	Moderate (Stage III) endometriosis (n=54)	Severe (Stage IV) endometriosis (n=90)	Total sample (n=300)
Reason for initial referral to clinic (N, %)	Pain (including pelvic pain, dysmenorrhoea, dyspareunia)	65 (41.7%)	13 (24.1%)	33 (36.7%)	111 (37.0%)
	Infertility / subfertility	35 (22.4%)	4 (7.4%)	12 (13.3%)	51 (17.0%)
	Non-malignant ovarian cyst / mass for investigation (no symptoms reported / asymptomatic)	7 (4.5%)	11 (20.4%)	8 (8.9%)	26 (8.7%)
	Ongoing management of known endometriosis	5 (3.2%)	2 (3.7%)	6 (6.7%)	13 (4.3%)

	without mention of specific symptoms				
	Irregular bleeding (HMB, IMB)	9 (5.8%)	5 (9.3%)	6 (6.7%)	20 (6.7%)
	Other	1 (0.6%)	2 (3.7%)	6 (6.7%)	9 (3.0%)

Figures



Abbreviations: Pain NOS (not otherwise specified)