

Factors associated with deep infiltrating endometriosis, adenomyosis and ovarian endometrioma

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ABSTRACT

Introduction: To compare epidemiological features and clinical presentations of deep infiltrating endometriosis with endometrioma and adenomyosis, as well as to identify risk factors for the respective histologically confirmed conditions.

Method: Patients undergoing index surgery at the National University Hospital, Singapore for endometriosis or adenomyosis over a 7-year period—from 2015 to 2021—were identified from hospital databases using the Table of Surgical Procedures coding. Social and epidemiological features of cases with histologically confirmed diagnoses of endometrioma only, adenomyosis only, and deep infiltrating endometriosis were compared. Significant variables from univariate analysis were entered into 3 binary multivariate logistic regression models to obtain independent risk factors for: deep infiltrating endometriosis versus endometrioma only, deep infiltrating endometriosis versus adenomyosis only, and adenomyosis only versus endometrioma only.

Results: A total of 258 patients were included with 59 ovarian endometrioma only, 47 adenomyosis only, and 152 deep infiltrating endometrioses. Compared to endometrioma only, deep infiltrating endometriosis was associated with higher rates of severe dysmenorrhoea (odds ratio [OR] 2.80, 95% confidence interval [CI] 1.02–7.70) and out-of-pocket private surgical care (OR 4.72, 95% CI 1.85–12.04). Compared to adenomyosis only, deep infiltrating endometriosis was associated with a higher fertility desire (OR 13.47, 95% CI 1.01–180.59) and a lower body mass index (OR 0.89, 95% CI 0.79–0.99). In contrast, heavy menstrual bleeding was the hallmark of adenomyosis, being less common in patients with endometriosis.

Conclusion: Deep infiltrating endometriosis is associated with severe dysmenorrhoea, pain related to urinary and gastrointestinal tracts, higher fertility desire and infertility rate. Patients with pain symptomatology and subfertility should be referred early to a tertiary centre with the capability to diagnose and manage deep infiltrating endometriosis.

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INTRODUCTION

Endometriosis is a chronic inflammatory gynaecologic disease marked by the presence of endometrial-like tissue outside the uterus.¹ Debilitating chronic pelvic pain, dysmenorrhoea, and subfertility in women of reproductive age are commonly associated with endometriosis. The disease is estimated to affect about

1 in every 10 women of reproductive age, and half of infertile women.²⁻⁴ The condition imposes a substantial economic burden on society, and the annual healthcare costs for endometriosis in selected European countries is estimated to be €3,113 per affected woman, which is similar to the costs for other chronic conditions such as type 2 diabetes, Crohn's disease and rheumatoid

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CLINICAL IMPACT

What is New

- This is the first and largest study in Singapore on histologically proven deep infiltrating endometriosis.
- Compared to endometrioma, deep infiltrating endometriosis was associated with higher rates of severe dysmenorrhoea and out-of-pocket private surgical care.
- Compared to adenomyosis, deep infiltrating endometriosis was associated with a higher childbearing desire and a lower body mass index.
- Heavy menstrual bleeding was the hallmark of adenomyosis.

Clinical Implications

- Patients with pain symptomatology and subfertility should be referred early to a tertiary centre with the capability to diagnose and manage deep infiltrating endometriosis.

arthritis.⁵ The costs of care to manage symptoms, including chronic pelvic pain, dysmenorrhoea, deep dyspareunia, dysuria, dyschezia, tenesmus, fatigue, and infertility, are much greater. These symptoms affect physical, mental, sexual, and social well-being, resulting in the need for prolonged medical therapy, repeated surgical treatments, and the indirect costs associated with a reduced quality of life and work productivity.^{4,6}

Endometriosis is diagnosed conclusively through surgical visualisation and biopsy specimens indicating the presence of endometrium-like epithelium and/or stroma outside the endometrium and myometrium. Broadly, 2 major endometriotic phenotypes are encountered clinically, namely ovarian endometrioma and deep infiltrating endometriosis.^{7,8} Endometriomas are ovarian cysts containing endometrium-like tissue and dark blood-stained fluid, the colour and consistency of which give rise to the name “chocolate cysts”. Deep infiltrating endometriosis where endometriotic deposits exist below the peritoneum has been increasingly recognised to be responsible for disabling pain, poor quality of life and sexual dysfunction in many women.^{9,10} It is also considered to be the most aggressive form of endometriosis.^{11,12} There is no robust evidence of whether ovarian endometriomas and deep

infiltrating endometriosis share similar risk factors.⁴ Many studies consider endometriosis to be a single disease without differentiating between ovarian endometriomas and deep infiltrating endometriosis.¹³ Some studies indicate that these 2 phenotypes have similar risk factors,^{14,15} while others suggest that deep infiltrating endometriosis should be considered a specific disease with mechanisms of disease progression distinct from endometriomas.^{9,16} Despite huge advances in our understanding of endometriosis, knowledge of the epidemiology and symptomatology of endometrioma compared to deep infiltrating endometriosis is considered rudimentary, leading to controversy about the epidemiology and development of these phenotypes.⁹ Epidemiological studies underpinned by histopathologically verified cases would contribute to a better understanding of these 2 endometriotic phenotypes.

Another condition commonly associated with intense pelvic pain and subfertility is adenomyosis. It is diagnosed by the presence of endometrial glands and stroma within the myometrium. In severe adenomyosis, the pathological diagnosis is straightforward, with disease evident at both gross and microscopic examinations. However, the diagnosis may be difficult in those with more limited disease, leading to extreme variations in the prevalence of adenomyosis, which ranges from 10–88%.¹⁷ Although adenomyosis was previously considered a disease of older multiparous women, the advent of transvaginal ultrasound as another diagnostic tool for adenomyosis has added a layer of uncertainty to the epidemiology and symptomatology of the condition.^{18,19} The heterogeneity of diagnostic criteria for endometriosis and adenomyosis has led to some confusion on the presenting symptomatology and epidemiology of endometriomas, deep infiltrating endometriosis and adenomyosis.²⁰ There is a need to clarify the epidemiology, symptomatology and risk profiles of ovarian endometrioma, adenomyosis and deep infiltrating endometriosis, using the gold standard histopathological diagnostic criteria.

The objective of our study is to further clarify the epidemiology of deep infiltrating endometriosis, compared to patients who have only ovarian endometrioma or only adenomyosis, using cases that were confirmed by histological examination. The surgical logs for a tertiary referral centre for deep infiltrating endometriosis were examined and consecutive cases with either deep infiltrating endometriosis, ovarian endometrioma only, or adenomyosis only were identified, and their presentations and epidemiological features compared.

METHOD

Patients

The case logs of patients undergoing the index surgery for endometriosis or adenomyosis from 1 January 2015 to 30 September 2021 in the Department of Obstetrics and Gynaecology, National University Hospital, Singapore were identified and examined (Fig. 1). The study was reviewed by the Domain Specific Review Board of the National Healthcare Group, Singapore (Reference number: 2021/00498), and exemption from individual consent was granted.

Index operations were searched, and consecutive cases identified using the inpatient Table of Surgical Procedures (TOSP) codes for endometriosis or adenomyosis surgery from the Ministry of Health, Singapore:²¹ SI702P, SI715U, SI726U, SI802O, SI803O, SI805O, SI806O and SI812U (online Supplementary Table S1). Electronic case records of cases identified by the TOSP search were examined and cases with confirmed histological diagnosis of endometriosis or adenomyosis during the period of 2015–2021 were selected (Fig. 1). These patients were then classified into 3 groups based on diagnostic confirmation by histopathological examination: ovarian endometrioma only, adenomyosis only, and deep infiltrating endometriosis. Cases in which both endometrioma and adenomyosis were present were not included in this analysis.

Diagnosis of endometrioma, adenomyosis and deep infiltrating endometriosis

Adenomyosis was defined as the presence of endometrial glands and stroma in the myometrium of cases with myometrium specimens. Ovarian endometrioma was confirmed by histology. Deep infiltrating endometriosis was defined as endometriosis infiltrating the peritoneum by >5mm and confirmed by intraoperative histology, located at or involving one of the following sites: recto-vaginal septum and related subperitoneal spaces; retroperitoneal spaces in the pouch of Douglas; subperitoneal involvement of fibromuscular pelvic structures such as the uterosacral and utero-ovarian ligaments; urinary tract including ureters, bladder, urethra; or digestive tract, especially colorectal sites. The presence of endometriosis at other sites did not affect the definition of deep infiltrating endometriosis.

Data collection

Sociodemographic characteristics, reproductive status, menstrual patterns, pain symptomatology, previous

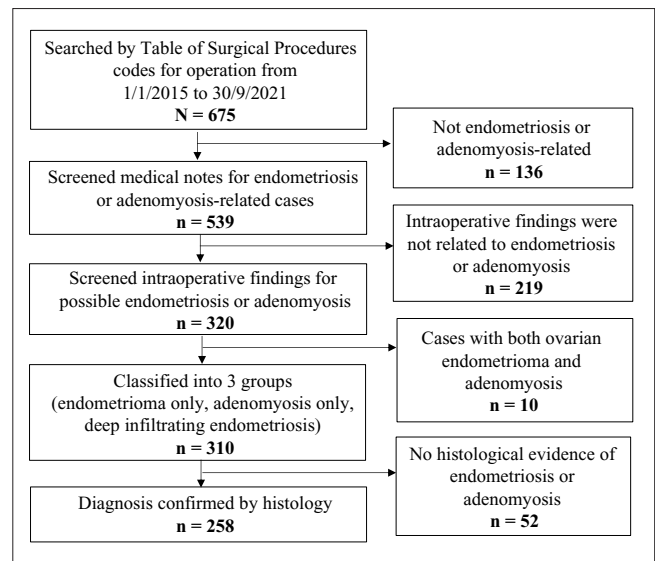


Fig. 1. Search strategy to identify cases of ovarian endometrioma only, adenomyosis only, or deep infiltrating endometriosis, confirmed by histopathological examination.

medical and surgical treatments prior to the index surgery, and the class of ward were retrieved from the patients' medical records and stored in a secured database on our hospital intranet. Reproductive data recorded included sexual activity, fertility desire, previous diagnosis of infertility, obstetric history and the serum level of anti-Müllerian hormone (AMH) prior to the index operation. Menstrual regularity was classified as frequent (≤ 23 days), regular (24–35 days), oligomenorrhoea (> 35 days) or amenorrhoea (> 1 year). Abnormal menstrual bleeding patterns such as heavy bleeding or intermenstrual bleeding were also recorded. Patterns of chronic pain recorded included dysmenorrhoea, dyspareunia, dyschezia, tenesmus, constipation or diarrhoea, dysuria, or urinary frequency.

Statistical analysis

Anonymised data were analysed with the SPSS Statistics software version 28.0 (IBM Corp, Armonk, US). Univariate analysis for continuous variables across the 3 groups (endometrioma only, adenomyosis only, and deep infiltrating endometriosis) were compared using a one-way analysis of variance and Pearson's chi-square test for categorical variables. Significant variables from the univariate analysis were entered into 3 binary multivariate logistic regression models (deep infiltrating endometriosis versus endometrioma only, deep infiltrating endometriosis versus adenomyosis only, and adenomyosis only versus endometrioma only). The following were not entered into the regression models: pain score before the index operation due to collinearity

with pain symptomatology; weight being collinear with body mass index (BMI); and duration between age at first endometriosis diagnosis and age at index operation. Odds ratios (OR) with its corresponding 95% confidential interval (CI) were presented. $P < 0.05$ was considered statistically significant.

RESULTS

Initial screening using TOSP codes identified 675 index operations. Cases unrelated to endometriosis or adenomyosis, cases with both conditions, and those without histological confirmation were excluded. Only 258 index cases with histologically confirmed endometriosis or adenomyosis were used in the present analysis (Fig. 1). Table 1 shows their epidemiological features. About half were of Chinese ethnicity, a fifth were Malay and 10% were Indian. Almost 70% were married, 60% were nulliparous, 40% expressed a desire for children, and a quarter of all patients having been diagnosed with infertility. Some 40% reported heavy menstrual bleeding and severe dysmenorrhoea. Their mean age at the time of index operation was 38.1 ± 8.2 years, the mean BMI was 24.4 ± 5.3 , and the mean duration between diagnosis of the condition and index surgery was 2.7 ± 4.0 years.

Unadjusted differences between endometrioma, adenomyosis and deep infiltrating endometriosis

Our analytical cohort consisted of ovarian endometrioma only ($n=59$), adenomyosis only ($n=47$), and deep infiltrating endometriosis ($n=152$) (Table 1). Subjects with deep infiltrating endometriosis were the youngest at the time of index operation (35.7 ± 7.2 years), followed by endometrioma only (37.9 ± 8.1 years) and adenomyosis only (45.9 ± 6.7 years). Subjects with endometrioma only had the shortest duration between diagnosis and the index operation (1.6 ± 2.8 years) whereas adenomyosis only had the longest (3.6 ± 5.3 years). Consequently, cases with adenomyosis only were the oldest (42.6 ± 9.7 years) at the time of first diagnosis. Cases with deep infiltrating endometriosis were most likely to be private patients compared to those with adenomyosis and endometrioma only (52.6% versus 44.7% vs 30.5%).

Cases with deep infiltrating endometriosis were most likely to be nulliparous (65.8% vs 29.8% vs 64.0%), expressed the highest desire for fertility (55.3% vs 4.3% vs 35.6%) and received a diagnosis of subfertility (32.2% vs 14.9% vs 18.6%) compared to cases of adenomyosis and endometrioma only.

Cases of adenomyosis were most likely to present with heavy menstrual bleeding compared to cases with

endometrioma only and deep infiltrating endometriosis (78.7% vs 25.4% vs 37.5%).

Among patients reporting severe dysmenorrhoea, deep infiltrating endometriosis had the highest pain symptomatology with a 55.9% rate compared to 31.1% for adenomyosis and 20.3% for endometrioma only. Cases with deep infiltrating endometriosis also reported increased rates of dyspareunia, dyschezia and tenesmus of 17.8–24.3% compared to about 10% in patients with adenomyoma, and 5% in patients with endometrioma only. Preoperative pain scores were also highest at 5.3 ± 4.2 compared to 3.2 ± 4.4 and 2.8 ± 3.8 for cases of adenomyosis and endometrioma only. Cases of deep infiltrating endometriosis were also most likely to have undergone previous surgery for endometriosis compared to adenomyosis and endometrioma only (27.0% vs 17.0% vs 11.9%).

The BMI of patients with deep infiltrating endometriosis was the lowest (23.2 ± 4.5) and those with adenomyosis only was the highest (27.5 ± 6.3). When comparing the 3 different groups based on diagnosis, no statistically significant differences were observed in ethnicity, marital status, sexual activity status, history of ectopic pregnancy, menstrual regularity, constipation, urinary symptoms and preoperative AMH levels.

Adjusted risk factors for deep infiltrating endometriosis

Significant univariate factors from Table 1 were entered into 3 binary multivariate logistic regression models that compared deep infiltrating endometriosis versus endometrioma only, deep infiltrating endometriosis versus adenomyosis only, and adenomyosis only versus endometrioma only (Table 2). Compared to ovarian endometrioma only, patients with deep infiltrating endometriosis suffered significantly more severe dysmenorrhoea (OR 2.80, 95% CI 1.02–7.70) and also opted for private surgical care (OR 4.72, 95% CI 1.85–12.04). Compared to adenomyosis only, patients with deep infiltrating endometriosis had 13.47 times (95% CI 1.01–180.59) higher fertility desire, a lower BMI (OR 0.89, 95% CI 0.79–0.99), and reported fewer complaints of heavy menstrual bleeding (OR 0.22, 95% CI 0.05–0.91). Overall, patients with adenomyosis had a higher risk of heavy menstrual bleeding compared to endometriosis, whether endometrioma only or deep infiltrating endometriosis.

DISCUSSION

Our study, based on histologically confirmed cases, indicates significant differences in the epidemiology

Table 1. Characteristics of patients with endometrioma only, adenomyosis only, and deep infiltrating endometriosis

Variables	All patients (n=258)	Endometrioma only (n=59, 22.9%)	Adenomyosis only (n=47, 18.2%)	Deep infiltrating endometriosis (n=152, 58.9%)	P value
Ethnicity, no. (%)					
Chinese	136 (52.7)	36 (61.0)	18 (38.3)	82 (53.9)	0.148
Malay	48 (18.6)	12 (20.3)	13 (27.7)	23 (15.1)	
Indian	26 (10.0)	4 (6.8)	7 (14.9)	15 (9.9)	
Others	48 (18.4)	7 (11.9)	9 (19.1)	32 (21.1)	
Reproductive factors, no. (%)					
Marital status					0.131
Single	69 (26.7)	22 (37.3)	8 (17.0)	39 (25.7)	
Married	177 (68.6)	33 (55.9)	37 (78.7)	107 (70.4)	
Divorced	12 (4.7)	4 (6.8)	2 (4.3)	6 (3.9)	
Virgo intacta (VI) status					0.452
Non-VI	213 (82.6)	46 (78.0)	41 (87.2)	126 (82.9)	
VI	45 (17.4)	13 (22.0)	6 (12.8)	26 (17.1)	
Parity					<0.001
Nulliparous	152 (58.9)	38 (64.0)	14 (29.8)	100 (65.8)	
Parous	106 (41.1)	21 (35.6)	33 (70.2)	52 (34.2)	
Previous vaginal delivery	70 (27.1)	12 (20.3)	27 (57.4)	31 (20.4)	<0.001
Previous caesarean section	40 (15.5)	9 (15.3)	9 (19.1)	22 (14.5)	0.740
Fertility desire ^a	107 (41.5)	21 (35.6)	2 (4.3)	84 (55.3)	<0.001
Previous diagnosis of infertility ^b	67 (26.0)	11 (18.6)	7 (14.9)	49 (32.2)	0.021
Menstrual pattern, no. (%)					
Menstrual regularity					0.374
Regular (24–35 days)	225 (87.2)	51 (86.4)	38 (80.9)	135 (88.8)	
Frequent (≤ 23 days)	4 (1.6)	1 (1.7)	2 (4.3)	1 (0.7)	
Oligomenorrhea (> 35 days)	17 (6.6)	3 (5.1)	4 (8.5)	10 (6.6)	
Amenorrhea (> 1 year)	9 (3.5)	2 (3.4)	3 (6.4)	4 (2.6)	
Heavy menstrual bleeding	109 (42.2)	15 (25.4)	37 (78.7)	57 (37.5)	<0.001
Intermenstrual bleeding	36 (14.0)	5 (8.5)	11 (23.4)	20 (13.2)	0.081
Pain symptomatology, no. (%)					
Pain score before index operation, mean $\pm$ SD	4.3 $\pm$ 4.3	2.8 $\pm$ 3.8	3.2 $\pm$ 4.4	5.3 $\pm$ 4.2	0.005
Dysmenorrhoea					<0.001
Mild	53 (20.5)	19 (32.2)	9 (18.0)	25 (16.4)	
Moderate	17 (6.6)	4 (6.8)	1 (2.0)	12 (7.9)	
Severe	111 (43.0)	12 (20.3)	14 (31.1)	85 (55.9)	
Dyspareunia	30 (11.6)	3 (5.1)	0	27 (17.8)	0.002

Table 1. Characteristics of patients with endometrioma only, adenomyosis only, and deep infiltrating endometriosis (Cont'd)

Variables	All patients (n=258)	Endometrioma only (n=59, 22.9%)	Adenomyosis only (n=47, 18.2%)	Deep infiltrating endometriosis (n=152, 58.9%)	P value
Pain symptomatology, no. (%)					
Dyschezia	36 (14.0)	1 (1.7)	3 (6.4)	32 (21.1)	<0.001
Tenesmus	45 (17.4)	3 (5.1)	5 (10.6)	37 (24.3)	0.002
Diarrhoea	29 (11.2)	1 (1.7)	3 (6.4)	25 (16.4)	0.005
Constipation	26 (10.1)	3 (5.1)	7 (14.9)	16 (10.5)	0.251
Dysuria or urinary frequency/ urgency	20 (7.8)	2 (3.4)	3 (6.4)	15 (9.9)	0.277
Endometriosis/adenomyosis, no. (%)					
Age at first diagnosis of endometriosis, mean $\pm$ SD, years	35.5 $\pm$ 8.7	36.3 $\pm$ 8.6	42.6 $\pm$ 9.7	33.0 $\pm$ 7.2	<0.001
Previous endometriosis operation	56 (21.7)	7 (11.9)	8 (17.0)	41 (27.0)	0.040
Previous hormonal treatment	105 (40.7)	16 (27.1)	23 (48.9)	66 (43.4)	0.043
Analgesia required before index operation (i.e. NSAIDs)	52 (20.2)	5 (8.5)	11 (23.4)	36 (23.7)	0.039
Previous abdominal/pelvic operation (non-endometriosis related)	70 (27.1)	15 (25.4)	16 (34.0)	39 (25.7)	0.499
Index operation, mean $\pm$ SD					
Age at index operation, years	38.1 $\pm$ 8.2	37.9 $\pm$ 8.1	45.9 $\pm$ 6.7	35.7 $\pm$ 7.2	<0.001
Height, m	1.6 $\pm$ 0.1	1.6 $\pm$ 0.1	1.6 $\pm$ 0.1	1.6 $\pm$ 0.1	0.322
Weight before index operation, kg	61.7 $\pm$ 13.4	63.4 $\pm$ 13.9	68.5 $\pm$ 15.3	58.9 $\pm$ 11.7	<0.001
BMI before index operation, kg/m ²	24.4 $\pm$ 5.3	24.9 $\pm$ 5.5	27.5 $\pm$ 6.3	23.2 $\pm$ 4.5	<0.001
Duration between age at first endometriosis diagnosis and age at index operation, mean $\pm$ SD, years	2.7 $\pm$ 4.0	1.6 $\pm$ 2.8	3.6 $\pm$ 5.2	2.8 $\pm$ 3.9	0.041
AMH level before index operation, mean $\pm$ SD, pmol/L	19.8 $\pm$ 20.8	17.8 $\pm$ 11.6	No data ^c	20.4 $\pm$ 22.5	0.729
Admission class, no. (%)					0.015
Subsidised	139 (53.9)	41 (69.5)	26 (55.3)	72 (47.4)	
Private	119 (46.1)	18 (30.5)	21 (44.7)	80 (52.6)	

AMH: anti-Müllerian hormone; BMI: body mass index; NSAIDs: nonsteroidal anti-inflammatory drugs; SD: standard deviation

All results were analysed using Pearson's chi-square test or one-way analysis of variance.

Missing data were present for the following variables: AMH level before index operation (n=161), pain score before index operation (n=118), dyspareunia (n=42), dysmenorrhoea (n=4), height and BMI before index operation (n=2), heavy menstrual bleeding, dyschezia, tenesmus, diarrhoea, constipation, dysuria, age at first diagnosis of endometriosis, weight before index operation, and duration between age at first endometriosis diagnosis and age at index operation (n=1).

^a Fertility desire refers to whether the patient is considering future pregnancies.

^b Previous diagnosis of infertility is defined as not being able to conceive after 12 months (or longer) of unprotected sex.

^c No data as n=1 in this group.

and clinical presentations of deep infiltrating endometriosis, endometriomas and adenomyosis. Severe dysmenorrhoea was highest in patients with deep infiltrating endometriosis and was associated with higher rates of out-of-pocket private surgical care. Compared to adenomyosis only, deep infiltrating endometriosis was associated with a higher fertility desire and a lower BMI. In contrast, heavy menstrual

bleeding was the hallmark of adenomyosis, being less common in patients with endometriosis.

The most prominent hallmark of deep infiltrating endometriosis was pain. Compared to endometrioma only or adenomyosis only, cases of deep infiltrating endometriosis suffered more severe dysmenorrhoea, dyspareunia, dyschezia, tenesmus and diarrhoea. Their mean pain score before the index operation was also the

Table 2. Independent risk factors of deep infiltrating endometriosis (compared to endometrioma and adenomyosis) and of adenomyosis (compared to endometrioma)

Variables	Deep infiltrating endometriosis (versus endometrioma only)	Deep infiltrating endometriosis (vs adenomyosis only)	Adenomyosis (vs endometrioma only)
	OR (95% CI)		
Reproductive factors			
Parity			
Parous	1.35 (0.37, 4.93)	1.76 (0.25, 12.24)	0.40 (0.04, 4.58)
Previous vaginal delivery	2.34 (0.60, 9.10)	0.52 (0.09, 3.16)	5.64 (0.69, 46.14)
Fertility desire	1.59 (0.41, 6.17)	13.47 (1.01, 180.59)	0.05 (0.00, 4.77)
Previous diagnosis of infertility	1.70 (0.55, 5.25)	0.10 (0.01, 0.81)	6.40 (0.32, 128.25)
Menstrual pattern			
Heavy menstrual bleeding	1.61 (0.65, 3.98)	0.22 (0.05, 0.91)	12.29 (2.41, 62.69)
Pain symptomatology			
Dysmenorrhoea			
Severe	2.80 (1.02, 7.70)	2.24 (0.45, 11.13)	16.59 (0.65, 421.72)
Dyspareunia	2.78 (0.53, 14.51)	ND	ND
Dyschezia	5.31 (0.60, 47.17)	ND	ND
Tenesmus	1.17 (0.24, 5.65)	1.79 (0.17, 18.56)	1.56 (0.02, 135.63)
Endometriosis/adenomyosis			
Age at first diagnosis of endometriosis (years)	1.03 (0.87, 1.23)	0.96 (0.77, 1.19)	0.90 (0.59, 1.38)
Previous endometriosis operation	3.58 (0.67, 19.13)	0.38 (0.03, 5.07)	0.21 (0.00, 18.62)
Previous hormonal treatment	2.28 (0.78, 6.61)	0.81 (0.15, 4.24)	5.71 (0.70, 46.27)
Analgesia required before index operation (i.e. NSAIDs)	3.17 (0.66, 15.25)	0.50 (0.07, 3.38)	0.56 (0.01, 23.47)
Index operation			
Age at index operation	0.94 (0.78, 1.13)	0.88 (0.70, 1.10)	1.33 (0.87, 2.03)
BMI before index operation	0.91 (0.82, 1.01)	0.89 (0.79, 0.99)	0.98 (0.88, 1.09)
Admission class			
Private	4.72 (1.85, 12.04)	1.13 (0.32, 3.93)	1.33 (0.32, 5.58)

BMI: body mass index; CI: confidence interval; ND: no data (numbers were too few for analysis); NSAIDs: nonsteroidal anti-inflammatory drugs; OR: odds ratio

Results were analysed using binary logistic regression. Significant univariate factors were entered into the model except pain score before index operation, diarrhoea, weight, and duration between age at first endometriosis diagnosis and age at index operation.

highest. Our findings differ from a study in a Chinese population where multivariate logistic regression analysis indicated that gastrointestinal symptoms during menstruation, rather than dysmenorrhoea, were more likely to be present in deep infiltrating endometriosis compared to ovarian endometriomas.²² This was possibly due to a comparatively larger number of deep infiltrating endometriosis subjects in our study. However, our results were consistent with previous studies,^{10,23}

which indicated that in addition to gastrointestinal symptoms, complaints of severe dysmenorrhoea, dyspareunia and lower urinary tract symptoms were also significantly associated with deep infiltrating endometriosis.

Compared to endometrioma only, cases of deep infiltrating endometriosis had almost double the duration between diagnosis and surgery. They were also more likely to opt for the private class of surgery despite this

method being more expensive in Singapore, with an out-of-pocket funded healthcare system. The diagnostic delay in endometriosis is not new. The awareness of long delays in the diagnosis of endometriosis and unsatisfactory treatments were first raised in the 1980s by researchers in the US, and subsequent studies on more than 7,000 endometriosis patients showed the average time to diagnosis was 9 years.²⁴ European researchers showed similar data with an average delay of 6.7 to 11.7 years from the onset of symptoms to diagnosis of endometriosis.^{25,26} Efforts to help patients identify their symptoms and seek medical attention earlier have been made in public education and primary care consultation.²⁷⁻³⁰ The longer duration between the diagnosis of deep infiltrating endometriosis and the index operation in our study further demonstrated the delay in receiving treatments and indicated the underlying challenges in providing care for this most debilitating form of endometriosis. Patients with severe pain symptomatology should be referred to a tertiary centre with the ability to diagnose and manage deep infiltrating endometriosis as this may frequently require complicated excisions of endometriotic deposits affecting the urinary or gastrointestinal tracts.

Unlike the consensus of pain being the main symptom among patients with deep infiltrating endometriosis, their fertility desires are controversial. Previous studies reported lower fertility desire in deep infiltrating endometriosis compared to those of patients with adenomyosis or superficial endometriosis, thought to be related to the presence of pelvic pain or dyspareunia, and subsequent reduction in sexual function.³¹ In our study, fertility desire was associated with deep infiltrating endometriosis and a quarter of our patients had a previous diagnosis of infertility. A recent study on deep infiltrating endometriosis demonstrated similar data with 64.1% patients with bowel endometriosis expressing the desire to conceive.³² However, it is challenging to determine the independent impact on infertility by deep infiltrating endometriosis as deep lesions are rarely isolated and other coexisting forms of endometriosis may be the causes for subfertility. Nevertheless, early treatment for deep infiltrating endometriosis is indicated so that these patients achieve their desired family size.

Our findings need to be interpreted with the following caveats. Our series represents the most severe cases that had undergone surgery. Milder forms of endometriosis or adenomyosis that do not require surgery would not be included in our analysis. Correct identification of all cases involving endometriosis and adenomyosis

depends on the accurate entry of TOSP surgical codes. Being a retrospective study, most data fields have missing datapoints. Cases with both ovarian endometrioma and adenomyosis were excluded, which may skew the symptomatology and risk factors. We have opted to include only cases confirmed with histopathological examination, thereby excluding cases that may be diagnosed based on ultrasound and other imaging methods. However, histopathology is the most rigorous diagnostic modality, and we believe this adds to the reliability of the data. One key strength of the present analysis is the relatively large number of cases of histologically proven deep infiltrating endometriosis. We also compared deep infiltrating endometriosis with cases where only ovarian endometrioma or only adenomyosis were encountered, thereby allowing clear phenotypes to be evident. Finally, the potential generalisability of the findings to other population needs to be interpreted with caution as our data represent only a surgical case series from a single centre.

CONCLUSION

In summary, our study has identified severe dysmenorrhoea, and pain related to urinary and gastrointestinal tracts, to be associated with deep infiltrating endometriosis. The highest fertility desire and infertility rate were reported in patients with deep infiltrating endometriosis. Adenomyosis was associated with heavy menstrual bleeding. Cases with pain symptomatology and subfertility should be referred to a tertiary centre with the capability to diagnose and manage deep infiltrating endometriosis.

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