GENERAL GYNECOLOGY

Early menstrual characteristics associated with subsequent diagnosis of endometriosis

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OBJECTIVE: The aim of this study was to investigate the association between early menstrual characteristics, before symptom onset, and later diagnosis of endometriosis.

STUDY DESIGN: This was a case-control study of 268 Australian women with surgically confirmed moderate-to-severe endometriosis (cases) and 244 women without endometriosis (controls). Early menstrual cycle characteristics, before age at symptom onset, were analyzed.

RESULTS: Menarche after age 14 years was strongly and inversely associated with endometriosis (odds ratio, 0.3; 95% confidence interval, 0.1–0.6). A history of dysmenorrhea was associated with subsequent

endometriosis (odds ratio, 2.6; 95% confidence interval, 1.1–6.2). Despite a suggestive trend, shorter menstrual cycle length was not associated with endometriosis. Duration of natural menstruation and heaviness of flow were not associated with subsequent risk of endometriosis; neither was the reported type of sanitary protection used nor history of sexual intercourse during menstruation.

CONCLUSION: There is a decreased risk of endometriosis with late age at menarche and an increased risk in women who report an early history of dysmenorrhea.

Key words: dysmenorrhea, early menstrual characteristics, endometriosis, etiology, menstruation

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Endometriosis is a common benign gynecologic disorder, defined as endometrial tissue occurring outside its normal location in the uterus.¹ Pelvic endometriosis is the most common form of the disease, and it mostly affects women during their reproductive life.² The prevalence of endometriosis is thought to approach 10–15% in the general female population and up to 35–50% in women who experience pelvic pain, infertility, or both.³

The pathogenesis of endometriosis is commonly described using Sampson's theory, which proposes that ectopic en-

dometrium and potentially viable, steroid-sensitive cells are fluxed backward through the fallopian tubes into the peritoneal cavity during menses.⁴ The popularity of this theory has meant that much of the existing epidemiologic research on endometriosis has focused on menstrual cycle characteristics.^{5–7} In particular, increased exposure to menstruation in terms of short cycle length, long duration of flow, and low parity have frequently been identified as possible risk factors.⁸ However, the epidemiologic findings have been inconsistent, with ef-

fect estimates varying widely.^{5,9–11} Furthermore, it has been postulated that many of the supposed menstrual risk factors for endometriosis are in fact consequences of the disease,¹² because the disease is often characterized by symptoms of severe dysmenorrhea, dyspareunia, menorrhagia, and irregular menses.^{13,14}

A major shortfall in studies of endometriosis that have evaluated potentially causative exposures that change over time, such as menstrual cycle length, is that only recent menstrual characteristics have been collected rather than adolescent or early adulthood menstrual characteristics preceding disease occurrence in affected women.¹² The potential role of menstrual cycle characteristics in the actual development of endometriosis therefore remains an open question. The aim of the current study was to further examine the role of atypical menstrual history and symptoms in the development of endometriosis, with particular emphasis on the timing of potential causal exposures. We hypothesized that women with endometriosis would more likely have had an early age at menarche, shorter cycle lengths, and heavier menstrual flow compared with women without endometriosis. We also hypothe-

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sized that a prior history of longer menses, tampon use, and sexual intercourse during menstruation were risk factors for endometriosis.

Our detailed data collection allowed for the analysis of early exposure data, before the onset of symptoms rather than diagnosis, because the magnitude of the average delay between onset of symptoms and diagnosis of endometriosis is in the order of 5–7 years.^{15,16}

MATERIALS AND METHODS

Study population and sample

This Australian case-control study included women aged between 18–55 years with surgically confirmed endometriosis; full study details of study design and participant recruitment have been reported previously.¹⁷ The cases were initially recruited largely through media campaigns between 1996–2002 for a genetic study of endometriosis.¹⁸ Although the primary objective of the genetic study was to recruit affected sibling pairs for linkage studies, the extensive media exposure for this study resulted in recruitment of approximately 970 surgically diagnosed women who had no affected sibling. From this group of women we identified those with moderate/severe disease (rAFS stages III/IV) and no first-degree relative who had endometriosis diagnosed, and this made up the pool from which eligible cases were drawn for this study.^{19,20} A total of 310 potential cases were randomly selected and all were invited to participate. Of these, 2 were found to be ineligible, as they were residing overseas at the time of contact, and an additional 7 were unable to be contacted. Of the remaining 301 eligible cases who were contacted, 268 agreed to participate (89%).

Potential control participants were same-sex female twin pairs enrolled with the Australian Twin Registry. They reported never having endometriosis diagnosed in earlier twin studies.²¹ Controls were randomly selected from women frequency-matched to the cases on age (5-year groups) and geographic location (urban/rural). In all, 511 women were contacted. Of these, 40 were ineligible, because they were residing overseas (n =

11) or had a new diagnosis of endometriosis (n = 29), and a further 39 were unable to be contacted. Of the 432 eligible women, 244 (57%) agreed to participate and returned a questionnaire.

Data collection and exposures

Information was collected using a self-administered questionnaire, which included questions about demographic, hormonal; and reproductive factors; physical characteristics; and lifestyle habits. To determine the influence of the timing of relevant exposures, data were collected in prespecified age bands: before age 10 years, 10–19 years, 20–29 years, 30–39 years, and 40+ years. The early menstrual cycle characteristics of interest included age at menarche, cycle length, heaviness of flow, duration of natural menstruation (not while using oral contraceptives), and pelvic pain in association with menstruation. In addition, we collected information about the type, frequency, and timing of sanitary protection, as well as information about sexual intercourse during menstruation. Data for some menstrual cycle characteristics were incomplete, because some women could not remember details of their menstrual cycles in past years. In addition, it was difficult to distinguish menstrual characteristics from disease symptoms for some affected women, because symptoms of endometriosis started in the 10–19 year age range, which is the typical age range for onset of menstruation. Those women for whom menstrual characteristics and symptom onset were both recorded in the 10–19 year age range were excluded from this analysis.

Ethics approval for the study was obtained from the Queensland Institute of Medical Research (QIMR) Human Research Ethics Committee (ref: H0005-00-016), the Australian Twin Registry (ref: 96-007-3), and the University of Queensland's Medical Research Ethics Committee (ref: H313).

Statistical analysis

Unconditional logistic regression was used to calculate odds ratios (ORs) with 95% confidence intervals (CIs) for the association between menstrual charac-

teristics and endometriosis risk. The analyses of exposure before onset of symptoms were conducted using self-reported age of onset of endometriosis as the cutoff. For controls, the self-reported age of onset of endometriosis of their matching case was used as the corresponding cutoff point. Multivariable logistic models were used to adjust for potential confounders, including state of residence; age at menarche; body size (at 10 years and 16 years); and menstrual cycle characteristics, such as length, regularity, and heaviness of menstrual flow. For consistency in the multivariate analysis, the same period of exposure was used for both the exposure of interest and other confounding variables included in the model (eg, ORs calculated for a particular exposure relating to the time before onset of symptoms were adjusted for confounding variables also related to the period before onset of symptoms). Power calculations based on a 1:1 case control design and a 2-sided alpha of .05, using our recruitment figures of 268 cases, indicate a power of 93% to detect an OR of 2.0 and a power of 79% to detect an OR of 1.75, for an exposure prevalence of 20% in the control group. The SPSS statistical package version 12.0 was used for all data analysis (SPSS, Inc, Chicago, IL).

RESULTS

Two hundred sixty-eight women with moderate-to-severe endometriosis and 244 controls were included in the study. Cases were more likely to have been residing in the state of Queensland, where the study was based, whereas controls were mainly based in Victoria, where the Australian Twin Registry is based, and nearby Tasmania ($P < .001$) (Table 1). A higher proportion of cases were of Asian, African, and Southern and Eastern European descent ($P = .04$), and cases were less likely to have completed 15 or more years of schooling ($P = .002$) compared with controls. Cases did not differ from controls with regard to marital status, religion, smoking status, or alcohol consumption (Table 1).

Table 2 shows the association between menstrual cycle characteristics and en-

ometriosis. The average age at menarche for cases was 12.6 years (standard deviation [SD] ± 1.4 years) compared with 13.0 years (SD ± 1.4 years) for controls ($P = .003$). Women who reported being age 14 or more at menarche were less likely to develop endometriosis than women with earlier menarche (OR, 0.3; 95% CI, 0.1–0.6). Adjustment for body size at age 10 years made no material difference to effect estimates. There was a suggestion of a positive trend between shorter natural menstrual cycle length and risk of endometriosis ($P = .008$); however, the categorized odds were not significant, possibly because of the small numbers. There was no association between endometriosis and duration of natural menstruation.

Women who reported experiencing dysmenorrhea were more likely to have endometriosis develop than women reporting never or seldom experiencing pain during menstruation (OR, 2.6; 95% CI, 1.1–6.2) (Table 3). There was also a significant trend of increasing risk of endometriosis with increasing reported frequency of pain associated with menstruation ($P = .03$). We found no association between endometriosis and pelvic pain occurring during ovulation. Heavy (vs average) menstrual flow was not associated with endometriosis ($P = .4$).

We found no association between endometriosis and the use of any particular type of sanitary protection (sanitary pads, tampons, or both), nor was there any association with use of tampons at night (Table 4). Sexual intercourse during menstruation was not associated with endometriosis.

COMMENT

We offer new insights into the possible etiologic role of menstrual characteristics in the development of endometriosis from this Australian case-control study. The most interesting and novel finding of this study is that early (presymptom onset age) dysmenorrhea is associated with subsequent development of endometriosis. We also found a significantly decreased risk of endometriosis associated with later age (≥ 14 years) at men-

TABLE 1
Selected demographic, personal, and lifestyle characteristics of cases and controls

Characteristics	Cases ^a (n = 268)	Controls ^a (n = 244)	P value
Age, y (mean $\pm$ SD)	36.4 $\pm$ 7.1	36.3 $\pm$ 7.6	.61
State of residence			
Queensland, n (%)	117 (44)	35 (14)	
New South Wales, n (%)	61 (23)	50 (21)	
Victoria/Tasmania, n (%)	54 (20)	113 (46)	
South Australia/Northern Territory, n (%)	13 (5)	25 (10)	
Western Australia, n (%)	23 (8)	21 (9)	< .001
Ethnicity, n (%)			
Australia/New Zealand, n (%)	242 (90)	222 (91)	
North/West Europe, n (%)	12 (5)	18 (7)	
Other, n (%) ^b	14 (5)	4 (2)	.04
Marital status			
Married/defacto, n (%)	197 (74)	182 (75)	
Never married, n (%)	38 (14)	44 (18)	
Divorced/separated, n (%)	32 (12)	17 (7)	.11
Education			
<15 y, n (%)	56 (21)	26 (11)	
≥ 15 y, n (%)	210 (79)	214 (89)	.002
Religion			
No religion, n (%)	67 (25)	76 (31)	
Catholic, n (%)	77 (29)	61 (25)	
Anglican, n (%)	60 (22)	44 (18)	
Other, n (%)	64 (24)	63 (26)	.29
Smoking status			
Lifelong nonsmoker, n (%)	139 (52)	147 (61)	
Current smoker, n (%)	52 (19)	46 (19)	
Ex-smoker, n (%)	77 (29)	50 (21)	.08
Alcohol consumption			
Never/occasional, n (%)	39 (15)	47 (19)	
Infrequent, n (%)	164 (61)	150 (62)	
Regular, n (%)	65 (24)	47 (19)	.21

SD, standard deviation.

^a Numbers may not sum to total, because some data are missing; ^b Other includes Asia, Africa, Southern and Eastern Europe.

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arche. There may be limited clinical significance of the reduced risk associated with later age at menarche. Perhaps a menarche later than 14 years may help to guide diagnostic and therapeutic strategy if other symptoms suggest endometriosis as a possible diagnosis. Other

putative menstrual risk factors for endometriosis, such as duration and heaviness of flow, the type and frequency of sanitary protection, and sexual intercourse during menstruation, were not associated with the development of endometriosis.

TABLE 2

Association between endometriosis and early menstrual cycle characteristics in cases and matched controls

Characteristics	Cases, ^a n (%)	Controls, ^a n (%)	Adjusted ^b OR (95% CI)	P trend
Age at menarche, y ^c				
<12	61 (23)	31 (13)	1.3 (0.5–3.4)	
12–13	143 (53)	126 (53)	1.0	
≥14	64 (24)	83 (35)	0.3 (0.1–0.6)	.003
Cycle length, d ^d				
≤24	15 (15)	9 (11)	5.0 (0.8–30.6)	
25–29	66 (66)	42 (51)	3.8 (0.8–18.8)	
30–34	15 (15)	22 (27)	1.0 (0.2–5.7)	
≥35	4 (4)	9 (11)	1.0	.008
Length of natural menses, d ^e				
≤4	17 (16)	12 (13)	0.3 (0.03–2.6)	
5–6	55 (51)	53 (58)	1.0	
≥7	35 (33)	27 (29)	1.0 (0.2–5.1)	.48

CI, confidence interval; OR, odds ratio.

^a Numbers may not sum to total, because some data are missing; ^b Adjusted for state of residence; ^c Additionally adjusted for painful menses, days, and heaviness of flow (natural menses), all before symptom onset; ^d Additionally adjusted for variation in menstruation and pelvic pain from menarche, weight at 10 y, and age at menarche; ^e Additionally adjusted for days of flow, painful menses, and variation in menstrual flow.

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TABLE 3

Association between endometriosis and early pelvic pain during menstruation and ovulation and menstrual flow in cases and in matched controls

Characteristics	Cases, ^a n (%)	Controls, ^a n (%)	Adjusted ^b OR (95% CI)	P trend
Dysmenorrhea ^c				
Never/seldom	35 (30)	54 (48)	1.0	
Sometimes	20 (16)	19 (17)	1.7 (0.6–5.1)	
Often	65 (54)	39 (35)	2.6 (1.1–6.2)	.03
Pelvic pain during ovulation ^d				
No	83 (67)	87 (78)	1.0	
Yes	40 (33)	25 (22)	0.9 (0.4–2.0)	
Menstrual flow ^e				
Light	12 (11)	12 (12)	1.0 (0.3–3.9)	
Average	59 (52)	63 (63)	1.0	
Heavy	42 (37)	25 (25)	1.6 (0.6–3.9)	.40

CI, confidence interval; OR, odds ratio.

^a Numbers may not sum to total, because some data are missing; ^b Adjusted for state of residence; ^c Additionally adjusted for age at menarche, cycle length, and pelvic pain during bowel movements; ^d Additionally adjusted for painful menses and pelvic pain during bowel movements, age at menarche; ^e Additionally adjusted for days of flow (natural menses), age at menarche, and regularity of menstrual cycle.

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The majority of studies to date have reported that early menarche (<11 years) increases the risk of endometriosis.^{5,7,9–11,22,23} Most of these results have, however, been based on small sample sizes, and a significant linear trend has not always been found. Interestingly, in a recent analysis of 1721 women with no past history of infertility who participated in the Nurses' Health Study, Missmer et al⁷ found a linear association between age at menarche and rate of laparoscopically confirmed endometriosis (*P* test for trend .001).

Although our results showed a significant trend of increasing risk of endometriosis with an early history of shorter menstrual cycle length, none of the results within categories of cycle length was significant, so the apparent trend could simply be a chance finding. Previous studies have found that a shorter cycle length is associated with an increased risk of endometriosis, but none of these studies has specifically examined this association before the onset of symptoms.^{7,10,24} We found no association between heavy menstrual flow and risk of endometriosis, even though heavy flow has been purported to be associated with endometriosis in other studies.^{24,25} To our knowledge, the association between heavy flow and endometriosis has not previously been examined when restricted to age before symptom onset. This may suggest that heavy flow develops later as part of the natural history of the disorder.

Pelvic pain is often used as a diagnostic tool for endometriosis, with dysmenorrhea being the most commonly reported symptom.^{26–28} Although it is widely believed that pain during menses is a consequence of endometriosis, it has been proposed that that this pain could be indicative of pelvic abnormality that might predispose women to endometriosis via retrograde menstruation.⁵ Some studies in the physiology of dysmenorrhea point to the relationship between strength of uterine contraction and amount of pain. Thus, if more severe dysmenorrhea is associated with increased contractility and expulsion of endometrial tissue into the peritoneal cavity, severe cramps may indicate predisposition to the disease.²⁴

Our data do indicate that dysmenorrhea is associated with a 2.5-fold increased risk of subsequent endometriosis; however, it is still possible that this is an early symptom of endometriosis but women have not yet identified it as such. Overall, these findings lend support to Sampson's theory of retrograde menstruation, where women who have menstrual characteristics offering greater opportunities for contamination of the peritoneal cavity by menstrual debris are at increased risk of endometriosis.⁶

The 2 main theories linking tampon use to endometriosis are that either their use limits menstrual flow, thus increasing the amount of retrograde menstruation, or that tampons contain levels of dioxins that are harmful,²⁹ although the latter hypothesis has recently been refuted.^{29,30} Tampon use was not associated with elevated risk in our data, adding weight to previous reports showing no association between lifetime tampon use and risk of endometriosis.^{31,32} Interestingly, after we adjusted for menstrual factors, the crude associations with tampon use and risk were negated, suggesting that the type of sanitary protection used is probably an indication of the type of menstrual history a woman experiences. It has also been postulated that sexual intercourse during menstruation may cause endometrial tissue to be forced into the peritoneal cavity; however, we found no evidence of increased risk.³³

Strengths of our study include its large size and its unique data collection focus on exposures occurring before symptom onset. As with all studies of endometriosis, the choice of control group is likely to influence the value of the study findings. Our control group consisted of single-sex twins who volunteered to participate in Australian Twin Registry research. Twins have been shown previously to be comparable to singletons and the general population in age at menarche,³⁴ education level,³⁵ fecundability,³⁶ menstrual symptoms,³⁷ age at menopause,³⁸ and endometriosis.²¹ Another potential limitation was the relatively low participation rate among controls (56%). To assess the possible effect of this, we compared the distribution of key variables in

TABLE 4

Association between endometriosis and sanitary protection and sexual intercourse during menstruation in cases and in matched controls

Characteristics	Cases, ^a n (%)	Controls, ^a n (%)	Adjusted OR (95% CI)
Type of sanitary protection ^b			
Sanitary pads only	43 (34)	31 (27)	1.0
Sanitary pads and tampons	69 (55)	76 (67)	0.02 (0.0–1.0)
Tampons only	14 (11)	6 (5)	0.2 (0.0–21.0)
Tampon use at night ^c			
No	24 (32)	28 (37)	1.0
Yes	52 (68)	47 (63)	0.7 (0.2–2.8)
Sexual intercourse during menstruation ^d			
Never	88 (73)	83 (78)	1.0
Seldom	20 (16)	17 (16)	0.7 (0.3–1.6)
Sometimes/often	13 (11)	6 (6)	1.6 (0.5–4.9)
			<i>P</i> trend = .81

CI, confidence interval; OR, odds ratio.

^a Numbers may not sum to total, because some data are missing; ^b Adjusted for state of residence, smoking, days of flow while on OCP, age at menarche, cycle length, heaviness of flow, and regularity of menstrual cycle; ^c Adjusted for state of residence, days of flow natural and OCP, regularity of menstrual cycle; ^d Adjusted for state of residence and painful menses.

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our participating control group with data from the nonparticipating controls. We found that the distributions of key exposures (age, state of residence, education, age at menarche, smoking status, and alcohol consumption) among participating control women was not significantly different from that in nonparticipating controls. Even though our controls were women who reported no past history of endometriosis, it is possible that women with undiagnosed disease, possibly because they were pain-free, may have been included in our control group. Our case definition was surgically diagnosed moderate-to-severe endometriosis, with or without pain or other endometriosis symptoms. Likewise, our control definition was no diagnosis of endometriosis, irrespective of any possible symptoms. As the community prevalence of more severe stages of endometriosis is less than 2%,¹⁹ an estimated maximum of 5 women with undiagnosed (more severe stage) disease may have been inadvertently included in our control group. These would be highly unlikely to influence our effect estimates. A possibly larger number of control women (eg, those reporting severe pelvic

pain or those who had no prior history of menstrual symptoms) may also have had undiagnosed minimal-to-mild endometriosis, but our disease definition excluded these women. On balance, their possible inclusion as controls is more likely to have diluted the strength of associations reported than to have inflated them.

Recall bias is also a possibility. Women were asked about menstrual symptoms many years after they had first experienced them. Although we tried to limit recall bias through the use of a highly structured questionnaire, there is potential for exposures to have been differentially recalled, leading to an exaggeration in the findings for these factors. The age of endometriosis symptom onset was self-reported by cases and would depend on the type and severity of symptoms experienced. For example, women diagnosed as a result of infertility may recall and report the onset of symptoms differently than women experiencing severe pelvic pain. Therefore, even with the time period approach we have used in this study, the actual date of disease onset is unknown, and we acknowledge the potential for some of the cases to have

had endometriosis before symptom onset. Finally, the extent to which we have adequately addressed confounding is unknown, but every effort was made to measure and adjust for all factors thought to be related to the development of endometriosis.

In summary, this study has shown that later age at menarche is inversely associated with subsequent endometriosis, and early dysmenorrhea is positively associated with endometriosis. The time period analysis indicates that these characteristics are displayed by cases before the reported onset of their endometriosis symptoms. Although considered in the past as symptoms of endometriosis, dysmenorrhea is likely to be a precursor to disease development, and shorter cycles may possibly suggest increased risk. Other menstrual characteristics are not risk factors but may be symptoms. At best they may hasten diagnosis and treatment. ■

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