

GYNECOLOGY

Premenstrual spotting of ≥ 2 days is strongly associated with histologically confirmed endometriosis in women with infertility

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OBJECTIVE: The purpose of this study was to assess the prevalence of endometriosis in women with premenstrual spotting and to determine the predictive value of this symptom in the diagnosis of endometriosis.

STUDY DESIGN: We conducted a retrospective cohort study of 80 consecutive women who presented to the infertility clinic for evaluation and who subsequently underwent laparoscopic assessment for infertility with or without pelvic pain. Our main outcome measure was the presence or absence of histologically confirmed endometriosis in women with and without premenstrual spotting.

RESULTS: Endometriosis was significantly more prevalent in subfertile women who reported premenstrual spotting for ≥ 2 days relative to women without this symptom (89% [34/38 women] vs 26% [11/42 women]; $P < .0001$). Multinomial logistic regression analysis

demonstrated the presence of premenstrual spotting for ≥ 2 days to be associated significantly with the presence of endometriosis (odds ratio, 16; 95% confidence interval, 3.9–65.4; $P < .01$) and red vesicular lesion type (odds ratio, 52.6; 95% confidence interval, 8.6–323.1; $P < .001$).

CONCLUSION: In this cohort of women with infertility, premenstrual spotting of ≥ 2 days was associated strongly with histologically confirmed endometriosis and a better predictor than dysmenorrhea or dyspareunia of finding endometriosis at laparoscopy. Premenstrual spotting of at least 2 days was also associated strongly with both higher stage disease and the red vesicular peritoneal endometriosis phenotype.

Key words: endometriosis, infertility, menstrual cycle, premenstrual spotting, progesterone

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Endometriosis is a debilitating gynecologic condition classically defined as the presence of endometrial glands and

stroma in ectopic locations. Affecting 6–10% of reproductive-aged women, endometriosis is associated with pain and infertility.¹ Currently, this disorder can be reliably diagnosed only by visual inspection of the abdomen and pelvis with histologic confirmation of biopsied lesions.² Although laparoscopy is a relatively safe minimally invasive approach, the procedure poses surgical risk to patients. In addition, laparoscopy is expensive in terms of both procedural cost and convalescence-associated absence from work. Despite the association of endometriosis with well-characterized pain symptoms, nearly one-half of women with chronic pelvic pain are found to have no identifiable disease at laparoscopy.^{3,4} These considerations highlight the importance of research toward minimizing negative laparoscopies with accurate preoperative identification of patients with endometriosis.

The requirement for invasive surgery for the diagnosis of peritoneal implants

contributes to an average latency of 6.7 years from onset of symptoms to definitive diagnosis.⁵ Delayed diagnosis and treatment may have significant consequences, as endometriosis is more advanced in women whose surgical evaluation is delayed, suggesting progression of disease over time.⁶ Consequently, the discovery of a nonsurgical biomarker for the diagnosis of endometriosis is considered a main priority⁷ and an area of active research.

To date, an accurate, noninvasive diagnostic test for endometriosis is unavailable, and decisions to perform laparoscopy are based on clinical judgment with the use of medical history, pelvic examination, and ultrasound scanning. In women with an endometrioma, ultrasound scanning is very accurate in the preoperative prediction of endometriosis but rather limited when only peritoneal disease is present.⁸ A previous study reported only 38% of cases of nonovarian endometriosis were

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predicted accurately by the combination of symptoms, pelvic examination, and ultrasound scanning.⁹ Of note, this study did not include irregular bleeding of any type in the preoperative assessment.

Several groups have reported an association between shorter menstrual cycle length and endometriosis.¹¹ However, these studies do not comment on whether premenstrual spotting abbreviated the interval. Compared with women with luteal phase defect, a higher prevalence of endometriosis was observed in women with premenstrual spotting of ≥ 3 days.¹²⁻¹⁴ Herein, we sought to determine whether the symptom of premenstrual spotting has predictive value in the diagnosis of endometriosis in women with infertility. If correlated, inclusion of this clinical symptom in the menstrual history may assist in the identification of the most appropriate surgical candidates.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of the Madigan Healthcare System. The records of all consecutive women who underwent laparoscopy for infertility with or without pelvic pain from March 2009 to March 2011 at a single tertiary care center were reviewed. All women were reproductive age with regular menses

in terms of cycle length and at least unilateral tubal patency at hysterosalpingogram or chromopertubation. The latter stipulation was maintained in view of abundant evidence that supported retrograde menstruation in the pathogenesis of endometriosis.

All laparoscopic procedures were performed by 1 of 2 surgeons (G.E.C., R.O.B.) who are experienced in the diagnosis and treatment of endometriosis. At laparoscopy, the surgeon surveyed the entire pelvis and upper abdomen. Biopsies were performed on suspected lesions, as per standard clinical practice, and read by a pathologist who is experienced in the histologic appearance of endometriosis. Any remaining endometriotic lesions were removed by either surgical resection or thermal cautery ablation. All patients had at least 1 biopsy specimen sent for histologic confirmation. The extent of endometriosis was staged according to the revised American Fertility Society (rAFS) classification system.¹⁰ Additionally, peritoneal implants were classified as either red vesicular or powder burn phenotype. Representative images of these lesional phenotypes are provided in the Figure.

The medical records of women who met the study inclusion criteria were abstracted for historic findings, ultrasound scan results, pelvic examination,

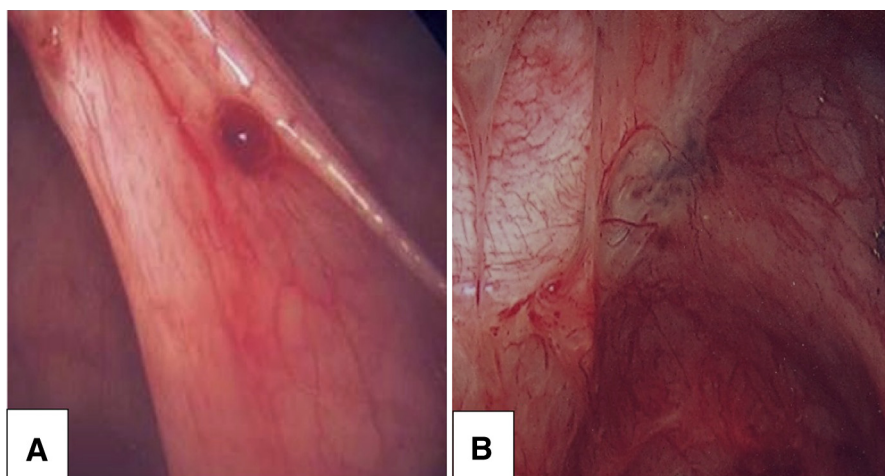
infertility history, and indication for laparoscopy; the results were correlated with surgical findings. For purposes of assessing the relative accuracy of symptoms in the prediction of endometriosis, the medical records were reviewed specifically for the presence and duration of premenstrual spotting, dysmenorrhea, and dyspareunia.

Patient history at the intake visit was collected both by written questionnaire and by physician interview. Before the initial infertility consultation, patients completed a standard 3-page infertility questionnaire that was developed by the Reproductive Endocrinology and Infertility Division. The questionnaire was reviewed by the physician with the patient at the time the history is taken. Questions specifically related to endometriosis symptoms and menstrual irregularities were included in the general infertility questionnaire. Patients were asked specifically about dysmenorrhea ("Do you have severe cramping or pelvic pain with your periods?") and dyspareunia ("Do you have pain with intercourse?"). Women who selected "Yes" on the questionnaire with corroborative documentation by the physician who obtained the verbal history at intake were considered to be affected with these symptoms. The intake survey specifically queried whether patients experienced "spotting before the onset of full menstrual flow." Likewise, physicians specifically asked and documented response to the question, "Do you experience spotting before the onset of full menstrual flow?" For women who acknowledged premenstrual spotting, the duration of spotting was recorded. We defined *premenstrual spotting* as bleeding on the order of spotting before the onset of full menstrual flow. To eliminate confounding by normal variants in menstrual onset and other conditions that may result in brief premenstrual spotting, the symptom was considered significant only if the reported duration was at least 2 days.

The demographic parameters of age, gravidity, parity, and body mass index were compared between groups with the use of the Student *t* test. The chi-square statistic was used to calculate the significance of the association between

FIGURE

Endometriosis lesion phenotypes encountered at laparoscopy



A, Red vesicular phenotype. B, Powder burn phenotype.

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endometriosis presence/absence and premenstrual spotting presence/absence. The sensitivity, specificity, positive and negative predictive values, and accuracy (percentage correct) were calculated for the symptoms of dysmenorrhea, dyspareunia, and premenstrual spotting. Relationships between each variable (premenstrual spotting, dysmenorrhea, dyspareunia, dyschezia, age, parity, and body mass index) and each outcome (presence/absence of endometriosis, rAFS stage, lesional phenotype) were indicated by the phi-coefficient; nominal/multinomial logistic regression was used to determine their odds ratio, both unadjusted and adjusted, in contributing to the outcome. Unweighted kappa analysis was performed to evaluate the variability between self-reported premenstrual spotting and histologic findings. Statistical analysis was performed using SPSS software (version 18; SPSS Inc, Chicago, IL). Probability values of $< .05$ were considered statistically significant.

RESULTS

Of the 80 consecutive patients who met inclusion criteria, 38 women reported premenstrual spotting of ≥ 2 days, and 42 women denied premenstrual spotting on both intake questionnaire and during menstrual history. All patients initially were seen for infertility, which was the primary indication for surgery in all but 3 patients for whom chronic pelvic pain was the primary indication. However, these 3 patients also were seen for infertility evaluation and were maintained in the analysis. Women who reported ≥ 2 days of premenstrual spotting were older than those women without this history. Otherwise, there were no significant differences between the 2 groups with respect to gravidity, parity, or body mass index (Table 1).

In the group of women without premenstrual spotting, 26% of the women (11/42 women) were diagnosed with endometriosis at laparoscopy. Of note, all cases were staged as minimal (rAFS stage I) biopsy-proven disease (Table 2). On the other hand, 89% of the women (34/38 women) with premenstrual spotting were found to have biopsy-proven

TABLE 1
Characteristics of women with and without premenstrual spotting

Characteristics	Premenstrual spotting (n = 38)	No premenstrual spotting (n = 42)	P value ^a
Age, y ^b	30.7 \pm 0.8 (22–40)	28.2 \pm 0.8 (20–40)	.03
Gravidity, n ^b	0.6 \pm 0.1 (0–3)	0.8 \pm 0.2 (0–8)	NS
Parity, n ^b	0.2 \pm 0.1 (0–1)	0.3 \pm 0.1 (0–3)	NS
Body mass index, kg/m ^{2b}	24.6 \pm 0.6 (19.5–33.0)	25.7 \pm 0.7 (19.0–35.6)	NS
Preoperative diagnosis, n			
Unexplained	30	21	
Tubal factor	2	17	
Uterine septum	4	1	
Chronic pain	2	3	

NS, not significant.

^a Student *t* test with significance, $P < .05$; ^b Data are given a mean \pm SEM (range).

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endometriosis at laparoscopy (89% vs 26%; $P < .0001$). Furthermore, in 85% of these cases (29/34 women), advanced stage disease (defined as greater than rAFS stage I) was documented at surgery. In women with premenstrual spotting affected with endometriosis, 85% (23/27 women) had lesions of red vesicular type. In contrast, only 27% of affected women (3/11 women) without premenstrual spotting evidenced red vesicular lesions ($P < .001$).

Compared with presurgical symptoms of dysmenorrhea and dyspareunia, premenstrual spotting demonstrated the highest positive predictive value and a negative predictive value very near that of dysmenorrhea (Table 3). Of the 3 symptoms, premenstrual spotting was the most accurate in correctly identifying women with and without endometriosis: 81% compared with 76% accuracy for dysmenorrhea and 58% accuracy for dyspareunia. Unweighted kappa analysis also demonstrated accuracy between self-reported spotting and histologic findings ($\kappa = 0.63$; 95% confidence interval [CI], 0.46–0.80). Only 6% of the biopsy specimens (3/48 women) were negative for endometriosis, which demonstrated high accuracy for biopsy determination at laparoscopy.

Univariate regression analyses demonstrated premenstrual spotting for ≥ 2

days (odds ratio [OR], 24; 95% CI, 6.9–83; $P = .001$), dysmenorrhea (OR, 15.5; 95% CI, 4.3–43; $P = .001$) and dyspareunia (OR, 3.2; 95% CI, 1.2–9.3; $P = .03$) to be correlated significantly with the presence of endometriosis at laparoscopy. Premenstrual spotting of ≥ 2 days was associated with both red vesicular lesional phenotype (OR, 71.4; 95% CI, 14.3–333.3; $P = .001$) and powder burn lesion type (OR, 9; 95% CI, 2–41.7; $P = .005$). Dysmenorrhea was associated with both the red vesicular (OR, 15.1; 95% CI, 3.8–58.8; $P = .001$) and powder burn lesion type (OR, 9.3; 95% CI, 1.9–47.6; $P = .008$).

In multivariate regression that was controlled for other variables, premenstrual spotting (OR, 16; 95% CI, 3.9–65.4; $P = .001$) and dysmenorrhea (OR, 8.63; 95% CI, 1.9–38.8; $P = .005$) remained significant for the finding of histologically confirmed endometriosis at laparoscopy. Premenstrual spotting of ≥ 2 days was associated strongly with red vesicular lesional phenotype (OR, 52.6; 95% CI, 8.6–323.1; $P = .001$), but not for powder burn lesions (OR, 5.1; 95% CI, 0.99–31.5; $P = .06$). Dysmenorrhea remained significant for both red vesicular lesions (OR, 12.3; 95% CI, 1.7–74.9; $P = .01$) and powder burn lesions (OR, 6.8; 95% CI, 1.1–41.7; $P = .04$). Results of the

TABLE 2
Surgical findings in women with (n = 38) vs without (n = 42) premenstrual spotting

Finding	Premenstrual spotting, n (%)	No premenstrual spotting, n (%)	P value ^a
No endometriosis	4 (11)	31 (74)	
Endometriosis	34 (89)	11 (26)	< .0001
Stage			
I	5 (15)	11 (100)	
II	11 (32)	0	
III	13 (38)	0	
IV	5 (15)	0	
Lesion phenotype			
Red vesicular	27 (79)	3 (27)	< .001
Powder burn	7 (21)	8 (73)	

^a χ^2 statistic with significance, $P < .05$.

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regression analyses are provided in Table 4.

COMMENT

Our results demonstrate a striking association between premenstrual spotting of at least 2 days and the finding of endometriosis at surgery in women with infertility. Interestingly, this symptom was associated with both advanced (rAFS, >stage I) disease and red vesicular lesion phenotype. Premenstrual spotting predicted presence or absence of endometriosis with 81% accuracy and outperformed the symptoms of dysmenorrhea and dyspareunia in this regard.

Wentz¹¹ was the first to report on a potential association between premenstrual spotting and endometriosis. Spotting of ≥ 3 days was observed in 35% of patients (8/23 women) who were confirmed to have endometriosis at laparoscopy. A cohort of patients with luteal phase defect, as determined by a timed late luteal phase endometrial biopsy, served as the comparison group; premenstrual spotting of ≥ 3 days was reported in only 6% of the patients (2/32 women). The weaker association between endometriosis and premenstrual spotting in this study may be consequent to the longer duration of spotting used to qualify inclusion. Several studies have reported an association between shorter

menstrual cycle length and endometriosis.¹²⁻¹⁴ Although premenstrual spotting was not specifically evaluated in any of these studies, the shorter cycle duration reported by women may have resulted from premenstrual spotting abbreviating the cycle interval.

In a review article, Jansen¹⁵ cited his own unpublished results regarding prevalence of endometriosis in women with premenstrual spotting. Among 1350 consecutive patients with infertility or reversal of sterilization, 101 women (8%) reported premenstrual spotting that was defined as spotting of at least 1-day duration. Among these women, 83% (84/101 women) were found to have endometriosis at laparoscopy. By comparison, premenstrual spotting was present in 4% of fertile women (3/70 women) who were examined for reversal of tubal sterilization. The high prevalence of endometriosis in women with premenstrual spotting is similar to our observed rate of 89%. In view of the well-accepted theory of retrograde menstruation, patent tubes are necessary for the development of endometriosis; thus, a cohort of women with a history of tubal sterilization may not represent the optimal comparison group.

Interestingly, the red vesicular lesion phenotype in cases of endometriosis correlated with premenstrual spotting. Conversely, in the few cases of endometriosis observed in women without premenstrual spotting, stage I powder burn-type lesions were the observed phenotype. This association suggests a hormonal or inflammatory relationship between the red vesicular lesion and premenstrual spotting. The red vesicular lesion is considered to be the earliest and most hormonally active type of endometriotic lesion.¹⁶ A previous study demonstrated that red vesicular endometriotic implants produce higher amounts of prostaglandin F (PGF_{2 α}) than typical powder-burn implants.¹⁷ Prostaglandins are known to exert a luteolytic effect on the corpus luteum in the absence of pregnancy. Red vesicular lesions therefore may indirectly result in premenstrual spotting because of insufficient progesterone to support the maintenance of endometrial lining by

TABLE 3
Classification of women before surgery according to presence or absence of endometriosis at laparoscopy

Symptom	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Percent correct (accuracy) ^a
Dysmenorrhea	0.87	0.63	0.75	0.79	0.76
Dyspareunia	0.38	0.83	0.74	0.51	0.58
Premenstrual spotting	0.76	0.90	0.96	0.74	0.81

^a Diagnostic accuracy refers to the percentage of correctly predicted surgical findings (presence or absence of endometriosis).

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TABLE 4

Univariate and multivariate regression analyses that compare variable clinical markers with respective outcomes

Outcome	Odds ratio	Univariate 95% CI	P value	Odds ratio	Multivariate 95% CI	P value
Endometriosis						
Premenstrual spotting ≥ 2 d	24	6.9–83	.001	16	3.9–65.4	.001
Dysmenorrhea	15.5	4.3–43	.001	8.6	1.9–38.8	.005
Dyspareunia	3.2	1.1–9.3	.031	2.3	0.5–11.1	NS
Dyschezia	1.6	0.1–18.2	NS	0.2	0.009–6.6	NS
Lesional phenotype (red vesicular)						
Premenstrual spotting ≥ 2 d	71.4	14.3–333.3	.001	52.6	8.6–323.1	.001
Dysmenorrhea	15.1	3.8–58.8	.001	12.3	1.7–74.9	.013
Dyspareunia	2.8	0.9–8.8	NS	1.4	0.2–8.3	NS
Dyschezia	1.2	0.07–19.6	NS	0.2	0.2–29.9	NS
Lesional phenotype (powder burn)						
Premenstrual spotting ≥ 2 d	9	2–41.7	.005	5.1	0.99–31.5	NS
Dysmenorrhea	9.3	1.9–47.6	.008	6.8	1.1–41.7	.04
Dyspareunia	2.8	0.7–12.5	NS	1.9	0.3–11.6	NS
Dyschezia	2.8	0.2–50	NS	1.3	0.03–8.1	NS

CI, confidence interval; NS, not significant.

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PGF_{2 α} -mediated premature luteolysis. Indeed, a significant decline in late luteal-phase serum progesterone levels in women with endometriosis-associated infertility relative to fertile women without disease has been demonstrated.¹⁸ Alternatively, a direct effect of elevated prostaglandin in the pelvic microenvironment is supported by the work of Lyneham et al,¹⁹ who demonstrated premature bleeding from the endometrium after intrauterine administration of PGF_{2 α} . These lines of evidence suggest a potential role for PGF_{2 α} in mediating the premenstrual spotting in women with hormonally active endometriosis; we currently are conducting studies at our institution to explore this possibility. Our study is strengthened by use of histologic confirmation as the reference standard in the diagnosis of endometriosis toward minimization of bias in the detection of disease.²⁰ The pathologist was blinded to the patient's premenstrual spotting status. Intraoperative images of representative lesions were reviewed for the independent validation of lesional

phenotype assessment. Also, this study is strengthened by comparison of the stage of disease and type of peritoneal endometriotic lesion that were observed at laparoscopy with premenstrual spotting toward understanding the molecular underpinnings of the observed association.

Limitations of our study include the retrospective design. Because the patients who were included in this study experienced infertility, we are not able to comment on the relationship between premenstrual spotting of ≥ 2 days and pelvic pain as the major complaint. The mechanisms behind the pathophysiologic condition of endometriosis-associated pain may prove very different from those underlying infertility. Expansion of the study criteria to include women with pelvic pain must be conducted to further evaluate whether the association holds for this subset of patients. A possible explanation for the association of premenstrual spotting and endometriosis-associated infertility is provided by the concurrence of

endometrial polyps and endometriosis.^{21,22} Endometrial polyps are a well-documented cause of irregular uterine bleeding and are associated with infertility. Unfortunately, too few patients in our study underwent endometrial cavity evaluation at the time of laparoscopy to comment reliably on this relationship.

Herein, we provide evidence for a strong association between premenstrual spotting of ≥ 2 days and histologically confirmed endometriosis, particularly advanced-stage disease and the red vesicular lesional phenotype. These findings highlight the potential value of including lesional phenotype in endometriosis staging systems toward improving their clinical correlation and emphasize the need for improved understanding of the molecular biologic condition of implants stratified by appearance. If validated in larger studies, the symptom of premenstrual spotting of ≥ 2 days may facilitate the preoperative identification of women who are most likely to benefit from laparoscopic evaluation and treatment. ■

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