Risk factors associated with endometriosis: importance of study population for characterizing disease in the ENDO Study

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Abstract

OBJECTIVE—We sought to identify risk factors for endometriosis and their consistency across study populations in the Endometriosis: Natural History, Diagnosis, and Outcomes (ENDO) Study.

STUDY DESIGN—In this prospective matched, exposure cohort design, 495 women aged 18–44 years undergoing pelvic surgery (exposed to surgery, operative cohort) were compared to an age- and residence-matched population cohort of 131 women (unexposed to surgery, populationcohort). Endometriosis was diagnosed visually at laparoscopy/laparotomy or by pelvic magnetic resonance imaging in the operative and population cohorts, respectively. Logistic regression estimated the adjusted odds ratios (AORs) and 95% confidence intervals (CIs) for each cohort.

RESULTS—The incidence of visualized endometriosis was 40% in the operative cohort (11.8% stage 3–4 by revised criteria from the American Society for Reproductive Medicine), and 11% stage 3–4 in the population cohort by magnetic resonance imaging. An infertility history increased the odds of an endometriosis diagnosis in both the operative (AOR, 2.43; 95% CI, 1.57–3.76) and population (AOR, 7.91; 95% CI, 1.69–37.2) cohorts. In the operative cohort only, dysmenorrhea (AOR, 2.46; 95% CI, 1.28–4.72) and pelvic pain (AOR, 3.67; 95% CI, 2.44–5.50) increased the odds of diagnosis, while gravidity (AOR, 0.49; 95% CI, 0.32–0.75), parity (AOR, 0.42; 95% CI,

0.28–0.64), and body mass index (AOR, 0.95; 95% CI, 0.93–0.98) decreased the odds of diagnosis. In all sensitivity analyses for different diagnostic subgroups, infertility history remained a strong risk factor.

CONCLUSION—An infertility history was a consistent risk factor for endometriosis in both the operative and population cohorts of the ENDO Study. Additionally, identified risk factors for endometriosis vary based upon cohort selection and diagnostic accuracy. Finally, endometriosis in the population may be more common than recognized.

Keywords

Body mass index; dysmenorrhea; endometriosis; epidemiology; infertility; laparoscopy; magnetic resonance imaging; risk factors

Endometriosis has been clinically recognized since 1860.[1] The prevalence of endometriosis in women varies widely: 0.7–11% in populations presenting for health care,[2–7] 2–22% when undergoing surgical sterilization,[8–11] 17–47% among infertile women,[11–14] and 2–74% in women with chronic pelvic pain.[15,16] Recently, we reported that the incidence of endometriosis varied by a magnitude of 2 depending upon the study population and diagnostic criteria employed in the Endometriosis: Natural History, Diagnosis, and Outcomes (ENDO) Study.[17] The variability in the reported prevalence and incidence of endometriosis raises questions regarding the consistency of risk factors for an endometriosis diagnosis or for informing about its etiology. Reports to date have largely relied upon a single study cohort/sample, which precludes assessment of the consistency/validity of so-called risk factors across different cohorts.

Prior studies identified a variety of endometriosis risk factors including abnormal or heavy bleeding, cyclic gastrointestinal/urinary symptoms, dyschezia, dysmenorrhea, dyspareunia, dysuria, and pelvic pain.[18–21] Increasing age, alcohol use, early menarche, family history of endometriosis, infertility, intercourse during menses, low body weight, prolonged menstrual flow, and short cycle interval are also alleged risk factors.[19,20,22–25] Endometriosis has been negatively associated with exercise and smoking.[22] Recently, red hair,[26] blue or green eyes, and freckles have been reported to increase the odds of diagnosis.[27] The plethora of risk factors for endometriosis may reflect varying methodologies such as study populations, definitions utilized for risk factors, and diagnostic accuracy. Our aim is to assess previously reported risk factors for endometriosis and their consistency across study cohorts in the ENDO Study to identify variations in risk factors, and how they may inform regarding etiology.

Materials and Methods

Study design and populations

The ENDO Study was specifically designed and implemented to identify environmental (nongenetic) determinants for endometriosis including persistent environmental chemicals and lifestyle in the context of somatic signs and symptoms. A prospective matched (with surgery being the exposure) cohort design was utilized to assess the robustness of findings across study populations and diagnostic methods. The operative cohort comprised 495

currently menstruating women, aged 18–44 years, who underwent a diagnostic and/or therapeutic laparoscopy or laparotomy at 1 of 5 participating surgical facilities located in the Salt Lake City area (n = 432) or 1 of 9 sites in the San Francisco area (n = 63) in 2007 through 2009.[17] Exclusion criteria included: previous laparoscopic diagnosis of endometriosis; currently breast-feeding 6 months (because of its likely impact lowering concentrations of environmental chemicals); history of cancer other than nonmelanoma skin cancer; use of injectable hormonal therapy within the past 2 years that may affect somatic presentation; and inability to communicate in Spanish or English. Any surgical indication was acceptable and included pelvic pain (n = 206, 42%), pelvic mass (n = 74, 15%), menstrual irregularities (n = 60, 12%), fibroids (n = 49, 10%), tubal ligation (n = 48, 10%), and infertility (n = 35, 7%).[17] The population cohort was matched to the surgical cohort on both age and residence within a 50-mile geographic catchment area for the participating clinical centers, and included 131 currently menstruating women without a history of surgically confirmed endometriosis. Sampling frameworks for defining the population cohorts included the Utah Population Database and the InfoUSA California directory to ensure both cohorts arose from the same geographic referent population. The population cohort was defined to be at risk for endometriosis (currently menstruating) and opportunity for diagnosis (residence in the clinical catchment area) in an attempt to overcome key methodologic challenges underlying endometriosis research that requires adherence to the gold standard of visualized disease.[28,29] More complete details regarding the design and methodology of the ENDO Study are provided elsewhere.[17]

Data collection

All women were given a study packet introducing the study prior to enrollment. Research assistants subsequently screened and recruited women by telephone or in person. Briefly, the standardized data collection protocol included a computer-assisted interview administered at baseline, an anthropometric assessment including body mass index (BMI) and skin-fold measurements,[17,30] and biospecimen collection for quantification of environmental chemicals. Women were queried regarding sociodemographic characteristics, medical and reproductive history, pain, and lifestyle. The protocol was administered prior to surgery for the operative cohort and at the earliest convenience for the population cohort (approximately 2 months before surgery or magnetic resonance imaging [MRI]). Completion rates were 95% and 98% for the operative and population cohorts, respectively.

Surgeons completed a standardized operative report immediately following surgery to capture gynecologic pathology and endometriosis diagnosis and staging using the revised criteria from the American Society for Reproductive Medicine (rASRM).[29] A computerized algorithm was also developed for the automatic calculation of severity and categorized as stage 1 (minimal) to 4 (severe) disease.

Magnetic resonance imaging

All women in the population cohort (without prior surgery) underwent a pelvic MRI to assess visceral fat distribution and any gynecologic pathology including endometriosis. Using Food and Drug Administration–approved protocol for pelvic imaging, 1 radiologist

supervised and evaluated all MRI. All findings were confirmed by a second radiologist with special expertise in gynecologic imaging.

Human subjects and monitoring

Remuneration was provided for time and travel. Full human subjects' approval was awarded by all participating research institutions; all women provided written informed consent prior to any data collection.

Operational definitions

Endometriosis diagnoses were derived from visualization by the surgeon in the operative cohort and from MRI in the population cohort. Histologically confirmed endometriosis required the presence of endometrial glands and/or stroma and/or hemosiderin-laden macrophages. MRI-visualized endometriosis comprised primarily ovarian endometriomas, but also included nodular implants. rASRM staging was categorized as: stage I, minimal (scores 1–5); stage II, mild (scores 6–15); stage III, moderate (scores 16–40); or stage IV, severe (scores >40).[29]

Statistical analysis

The analysis was conducted in 2 phases with separate analyses for each cohort. First, descriptive analyses were undertaken to inspect the completeness and consistency of data, and to identify risk factors associated with endometriosis diagnosis for both cohorts. Potential risk factors were identified a priori based on prior literature and these were included in the ENDO instruments. Significance was estimated using either the χ^2 statistic or the Student *t* test for categorical and continuous variables, respectively. In the analytic phase, unadjusted odds ratios (ORs) and accompanying 95% confidence intervals (CIs) were estimated for all risk factors observed to be significant in the descriptive phase of research using logistic regression. We conservatively estimated ORs rather than relative risks, given our uncertainty about the timing of onset for incident endometriosis. Subsequently, a logistic regression model was specified to include all significant ORs along with age (in years) and clinical site (Utah or California) to account for potential residual confounding. Separate models were run for each cohort. To assess the robustness of findings, several sensitivity analyses were undertaken by restricting endometriosis to be visually and histologically confirmed disease, restricting to moderate or severe disease (stages 3 and 4), or restricting the comparison group of women to those with a postoperative diagnosis of a "normal pelvis." Twenty-two (4%) women in the operative cohort had no diagnostic information, given cancellations of their surgeries. Also, 4 (3%) women in the population cohort had unreadable MRIs. The absence of diagnostic information for these 26 women necessitated their removal from analyses. All statistical analyses were conducted using SAS, version 9.1 (SAS Institute, Cary, NC).

Results

The incidence of surgically visualized endometriosis in the operative cohort was 40% (190/473 with 11.8% [56/473] moderate/severe and 28.3% [134/473] minimal/mild) and 11% (14/127) in the population cohort based on MRI.[17] MRI-visualized endometriosis in

the population cohort consisted of primarily ovarian endometriomas, and included nodular implants (stage 3–4 by rASRM).

Only a few significant differences in reproductive history were observed by endometriosis status, with some difference by cohort (Table 1). Women with endometriosis had lower mean gravidity (1.7 ± 2.0) than unaffected women (2.3 ± 2.1), and lower parity (ie, 1.8 ± 1.3 and 2.2 ± 1.4, respectively) in the operative cohort. While not significant, a reverse pattern for gravidity and parity was observed in the population cohort. A higher percentage of women with endometriosis reported prior infertility treatment than women without endometriosis in both the operative (34% and 17%, respectively) and population (29% and 5%, respectively) cohorts (Table 1). With regard to menstruation history, women in the operative cohort with endometriosis reported more pelvic pain or dysmenorrhea in the past year than women without endometriosis (Table 2).

Logistic regression identified only one consistent risk factor across both cohorts–a history of infertility (Table 3). An infertility history increased the odds of an endometriosis diagnosis >2-fold in the operative cohort (adjusted odds ratio [AOR], 2.43; 95% CI, 1.57–3.76), and >7-fold in the population cohort (AOR, 7.91; 95% CI, 1.69–37.2), even after adjusting for age and study site. Other risk factors either decreased or increased the odds of an endometriosis diagnosis in the operative cohort only, as follows (Table 3). Specifically, odds were decreased for gravidity (AOR, 0.49; 95% CI, 0.32–0.75), parity (AOR, 0.42; 95% CI, 0.28–0.64), and BMI (AOR, 0.95; 95% CI, 0.93–0.98). Factors that increased the odds of diagnosis included: college education (AOR, 1.83; 95% CI, 1.12–3.00), older age at first sex (AOR, 1.06; 95% CI, 1.01–1.12), pelvic pain as a surgical indication for laparoscopy (AOR, 3.67; 95% CI, 2.44–5.50), and dysmenorrhea (OR, 2.46; 95% CI, 1.28–4.72). We found no relationship to endometriosis for any aspect of menstrual history other than dysmenorrhea in either cohort.

Multiple sensitivity analyses assessed the robustness of our findings. As summarized in Tables 4–7, infertility was a consistent risk factor across all analyses irrespective of cohort. When restricting to histologically confirmed endometriosis (Table 4) and endometriosis stages 3 and 4 (Table 5), college education and history of pelvic pain were not significant. Dysmenorrhea (AOR, 3.11; 95% CI, 0.94–10.3) was not significant in the model restricted to histologically confirmed disease (Table 4). The effect for BMI (AOR, 0.97; 95% CI, 0.93–1.01) was nonsignificant, but the effects for parity (AOR, 0.19; 95% CI, 0.10–0.37), age at first sex (AOR, 1.11; 95% CI, 1.03–1.19), and surgical indication (AOR, 4.47; 95% CI, 2.39–8.38) were significant when restricting endometriosis to stages 3 and 4 in the operative cohort (11.8%, or 56/473 of the operative cohort) (Tables 4 and 5). All of the previously noted risk factors were significantly associated with endometriosis when restricting the comparison group in the operative cohort to women with a surgically visualized normal pelvis (Table 6). In the population cohort, 11% (14/127) of women were diagnosed with probable moderate/severe endometriosis detected with MRI compared to 11.8% (56/473) in the operative cohort. Significant differences across both cohorts and in all sensitivity analyses are summarized in Table 7.

Comment

In this novel study utilizing a prospective matched surgical exposure cohort design, we found infertility to be a consistent risk factor for endometriosis in both the operative and population cohorts. To our knowledge, infertility has not been previously reported in a clinically independent, population-based cohort diagnosed with endometriosis. An intriguing aspect of the infertility history is the comparable gravidity and parity of women with and without endometriosis in the population cohort. This may be explained by resolution of infertility in affected women who achieve a pregnancy irrespective of the time to pregnancy. Additionally, a history of infertility without treatment lends support to the finding that not all women reporting infertility seek medical care, as noted in the National Survey for Family Growth.[31] Thus, for clinicians, a reproductive history that includes both time to pregnancy and infertility treatment may provide useful clues suggestive of endometriosis in both operative candidates and the general population.

Of notable clinical interest is the 11% (14/127) incidence of probable moderate/severe endometriosis diagnosed by MRI in the population cohort. This mirrors the 11.8% (56/473) moderate/severe incidence of visually staged moderate/severe endometriosis found in the operative cohort. MRI is unable to reliably diagnose minimal/mild endometriosis. If the true incidence of stage 1–2, minimal/mild endometriosis in the population cohort is similar to that of the operative cohort (28.3% [134/473]), one might speculate that endometriosis in the operative cohort could be analogous to the visible portion of an iceberg with the population cohort forming a large invisible and unmeasured volume of un-diagnosed endometriosis. Furthermore, if minimal/mild endometriosis could have been reliably diagnosed in the population cohort the significant risk factors identified potentially could change, thus, emphasizing the importance of cohort selection and diagnostic accuracy.

Our study affirms previous clinical study findings in women seeking medical care and/or undergoing laparoscopy. These findings included a reduction in the odds of an endometriosis diagnosis for higher gravidity, parity,[11–14] and BMI.[30] Despite the documented relationship between endometriosis and infertility, causality remains uncertain. For example, it is not clear whether endometriosis and infertility share a common cause or if endometriosis is in the etiologic pathway to infertility. Why some affected women are able to resolve their infertility, either spontaneously or through treatment, remains to be established. Suppression of endometriosis by the progesterone-dominant hormonal milieu of pregnancy may explain a portion of the decreased incidence associated with gravidity and/or parity.

In contrast to past studies,[20,21,23,24] we found no relationship between endometriosis and menstrual cycle history, including age at menarche, average cycle length, and number of menstrual cycles in the past 12 months. However, >80% of the women in all groups in this study had a history of oral contraceptive use. This contraceptive use may have altered both recent menstrual cycle patterns, or possibly the presence or absence of endometriosis. We would expect use of oral contraceptives to reduce any differences in the natural menstrual cycle of women with or without endometriosis. Women in the operative cohort with endometriosis reported more pelvic pain or dysmenorrhea in the past year than women

without endometriosis. While many report menstrual cycle characteristics as risk factors for endometriosis, they may be proxy markers of disease onset or progression and not etiologic risk factors.

There are a number of possible explanations for infertility being identified as the sole significant risk factor for endometriosis in both cohorts (Table 3). These explanations could include: (1) a multifactorial etiology for endometriosis that manifests differently for varying levels of symptoms (including no symptoms), especially when utilizing true population cohorts rather than clinically derived population cohorts; (2) lower gravidity and parity may be consequences not antecedents of disease; (3) alternatively, lower gravidity and parity may be antecedents as women whose menstruation is not interrupted by pregnanc(ies) and postpartum amenorrhea have more cycles of exposure and potentially more severe disease expression; (4) residual confounding in the operative cohort based upon surgical indication or other relevant somatic symptoms; (5) reduced statistical power as the population cohort was a priori powered for our chemical exposures rather than clinical risk factors; (6) MRI is not sufficiently sensitive to detect minimal-mild endometriosis; (7) endometriomas may not contribute significantly to the dysmenorrhea and/or pelvic pain that may be typically associated with milder stages of endometriosis; and finally (8) relationships with menstrual cycles, pain, or dysmenorrhea may also be reduced by oral contraceptives. Clearly, sample size of the population cohort and the insensitivity of MRI for the diagnosis of minimal/mild endometriosis are significant limitations. We suggest that future studies be designed to discriminate among these different possibilities to the extent possible.

Our sensitivity analyses (Tables 4–7) suggest that some purported risk factors for endometriosis are specific to care-seeking behavior. This includes education that may be a proxy for health insurance or socioeconomic status. Overall, our sensitivity analyses demonstrate that the definition of the disease state along with choice of the study cohort and comparison groups has a significant impact on the identification of risk factors (Table 7). It is possible that there may not be a classic set of risk factors generic to all women with endometriosis. Rather, risk factors may need tailoring to the subgroups of women by their medical care-seeking behavior and opting in for surgical care. These findings have important implications regarding the design and analysis of future studies focusing on endometriosis. Additionally, utilizing an expanded reproductive history as a screening tool in asymptomatic women may result in a higher suspicion and, possibly, utilization of targeted diagnostic options.

In summary, our operative cohort findings confirm a number of risk factors for endometriosis such as gravidity, parity, pelvic pain, and infertility history. Identifying asymptomatic endometriosis in the general population remains challenging but critical to our understanding of the true spectrum of the disease. A unique set of risk factors such as self-reported infertility or increased time to pregnancy in such subgroups of affected women may shed new insight on the general population incidence, potential etiologies and associations, and the natural history of endometriosis. Inclusion of appropriate populations controls and sensitive and specific noninvasive tests to diagnose minimal/mild endometriosis in future studies will assist in clarifying our understanding about endometriosis and in the

development of appropriate metrics to diagnosis, stage, determine risk factors by cohort, and evaluate the efficacy of various interventions.

Acknowledgments

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TABLE 1

Reproductive history by cohort and endometriosis diagnosis, ENDO Study (n = 600)

Characteristic	Operative cohort n = 473		Population cohort n = 127	
	Endometriosis n = 190 n (%)	No endometriosis n = 283 n (%)	Endometriosis n = 14 n (%)	No endometriosis n = 113 n (%)
Age, y				
<20	5 (2.6)	7 (2.5)	0 (0)	4 (3.5)
20–24	22 (11.6)	26 (9.2)	4 (28.6)	21 (18.6)
25–29	48 (25.3)	55 (19.5)	1 (7.1)	22 (19.5)
30–34	44 (23.2)	58 (20.6)	2 (14.3)	18 (15.9)
35	71 (37.4)	136 (48.2)	7 (50)	48 (42.5)
Mean (SD)	31.98 (6.75)	33.61 (7.09)[a]	33.14 (8.33)	32.07 (7.76)
Ever sexually active				
No	27 (14.2)	37 (13.2)	1 (7.1)	14 (12.4)
Yes	163 (85.8)	244 (86.8)	13 (92.9)	99 (87.6)
Age at first consenting sex				
17	92 (48.4)	157 (55.5)	4 (28.6)	55 (48.7)
18–20	50 (26.3)	67 (23.7)	6 (42.9)	38 (33.6)
21	48 (25.3)	59 (20.8)	4 (28.6)	20 (17.7)
Mean (±SD)	19.19 (4.28)	18.33 (3.83)	19.08 (2.47)	18.49 (2.99)
Ever use oral contraceptives				
No	21 (11.1)	45 (15.9)	1 (7.1)	17 (15)
Yes	169 (88.9)	238 (84.1)	13 (92.9)	96 (85)
Gravidity				
Nulligravid (0)	81 (42.6)	74 (26.3)[b]	5 (35.7)	46 (40.7)
Gravid (1)	109 (57.4)	207 (73.7)	9 (64.3)	67 (59.3)
Mean (±SD)	1.65 (1.98)	2.28 (2.12)[c]	2.21 (2.08)	1.65 (1.80)
Parity (no. of live births)				
Nulliparous	21 (19.4)	25 (12.1)	1 (11.1)	10 (14.9)
Parous	87 (80.6)	182 (87.9)	8 (88.9)	57 (85.1)
Mean (±SD)	1.81 (1.27)	2.19 (1.44)[d]	2.56 (1.59)	2.21 (1.45)
Age at first pregnancy, y				
<20	42 (38.5)	79 (38.2)	0 (0)	14 (20.9)
20–24	42 (38.5)	71 (34.3)	5 (55.6)	27 (40.3)
25–29	20 (18.3)	33 (15.9)	4 (44.4)	20 (29.9)
30–34	4 (3.7)	22 (10.6)	0 (0)	4 (6)
35–39	1 (0.9)	1 (0.5)	0 (0)	1 (1.5)
40	0 (0)	1 (0.5)	0 (0)	1 (1.5)

Characteristic	Operative cohort n = 473		Population cohort n = 127	
	Endometriosis n = 190 n (%)	No endometriosis n = 283 n (%)	Endometriosis n = 14 n (%)	No endometriosis n = 113 n (%)
Mean (±SD)	21.63 (4.19)	21.98 (5.13)	23.56 (2.79)	23.64 (4.99)
History STIs				
No	160 (84.2)	219 (77.4)	13 (92.9)	91 (80.5)
Yes	30 (15.8)	64 (22.6)	1 (7.1)	22 (19.5)
History of abnormal pap smear				
No	148 (77.9)	210 (74.2)	12 (85.7)	80 (70.8)
Yes	42 (22.1)	73 (25.8)	2 (14.3)	33 (29.2)
Ever seek infertility treatment				
No	126 (66.3)	235 (83.0)[e]	10 (71.4)	107 (94.7)[f]
Yes	64 (33.7)	48 (17.0)	4 (28.6)	6 (5.3)
Surgical indication				
Pelvic pain	120 (63.2)	86 (30.5)[g]		
Pelvic mass	26 (13.7)	48 (17.0)		
Menstrual irregularity	20 (10.5)	40 (14.2)		
Fibroids	9 (4.7)	40 (14.2)		
Tubal ligation	8 (4.2)	40 (14.2)		
Infertility	7 (3.7)	28 (9.9)		

Analysis excludes 22 women in operative cohort whose surgeries were cancelled, and 4 women in population cohort with unreadable magnetic resonance images.

STIs, sexually transmitted disease.

Peterson. Risk factors associated with endometriosis. Am J Obstet Gynecol 2013.

[a]$P = .0126$;

[b]$P = .0002$;

[c]$P = .0013$;

[d]$P = .0191$;

[e]$P = .00001$;

[f]$P = .0023$;

[g]$P = .0013$.

TABLE 2

Comparison of menarche and menstruation history by cohort and endometriosis diagnosis, ENDO Study, 2007 through 2009 (n = 600)

Characteristic	Operative cohort n = 473		Population cohort n = 127	
	Endometriosis n = 190 n (%)	No endometriosis n = 283 n (%)	Endometriosis n = 14 n (%)	No endometriosis n = 113 n (%)
Menarche, y				
11	37 (19.9)	48 (17.3)	2 (15.4)	18 (16.5)
12–13	87 (46.8)	146 (52.5)	5 (38.5)	61 (56.0)
14	62 (33.3)	84 (30.2)	6 (46.2)	30 (27.5)
Mean (±SD)	13.0 (1.8)	12.8 (1.6)	13.2 (1.5)	12.7 (1.5)
No. of menstrual cycles in past 12 mo				
None	5 (2.6)	13 (4.6)[a]	1 (7.1)	4 (3.6)
1–3	5 (2.6)	20 (7.1)	0 (0.0)	4 (3.6)
4–6	8 (4.2)	23 (8.2)	2 (14.3)	11 (9.8)
7–9	20 (10.6)	17 (6.0)	0 (0.0)	10 (8.9)
10–12	128 (67.7)	158 (56.2)	11 (78.6)	72 (64.3)
13	23 (12.2)	50 (17.8)	0 (0.0)	11 (9.8)
Mean (±SD)	11.0 (3.5)	11.3 (8.5)	10.1 (4.0)	11.2 (11.1)
Average cycle length in past 12 mo[b]				
<22	24 (13.2)	54 (20.3)	1 (8.3)	5 (4.7)
22–24	5 (2.7)	10 (3.8)	0 (0.0)	7 (6.6)
25–27	22 (12.1)	27 (10.1)	3 (25.0)	24 (22.6)
28–30	105 (57.7)	139 (52.3)	7 (58.3)	54 (50.9)
31–33	12 (6.6)	9 (3.4)	0 (0.0)	4 (3.8)
34	14 (7.7)	27 (10.2)	1 (8.3)	12 (11.3)
Mean (±SD)	28.1 (8.7)	31.6 (31.7)	27.4 (3.5)	30.3 (11.1)
Mean (±SD) length of shortest cycle in past 12 mo, d[b]	18.2 (10.6)	21.3 (29.6)	30.5 (18.2)	26.8 (10.9)
Mean (±SD) length of longest cycle in past 12 mo, d[b]	28.8 (22.7)	34.2 (39.4)[c]	37.7 (34.1)	33.6 (15.2)
Few periods than normal in past 12 mo?				
No	161 (85.2)	236 (84.0)	13 (92.9)	88 (78.6)
Yes, no medications	1 (0.5)	4 (1.4)	0 (0.0)	1 (0.9)
Yes, medications	27 (14.3)	41 (14.6)	1 (7.1)	23 (20.5)
Periods in past 12 mo typical of last 5 y				
Yes	83 (43.9)	95 (33.9)	4 (28.6)	58 (52.3)
No; specify	106 (56.1)	185 (66.1)	10 (71.4)	53 (47.7)
More frequent	29 (27.4)	54 (29.2)	1 (10.0)	12 (22.6)
Less frequent	17 (16.0)	32 (17.3)	3 (30.0)	14 (26.4)

Characteristic	Operative cohort n = 473		Population cohort n = 127	
	Endometriosis n = 190 n (%)	No endometriosis n = 283 n (%)	Endometriosis n = 14 n (%)	No endometriosis n = 113 n (%)
Heavier bleeding	72 (67.9)	102 (55.1)	1 (10.0)	22 (41.5)
Lighter bleeding	24 (22.6)	53 (28.6)	7 (70.0)	24 (45.3)
Bleeding more days	56 (52.8)	87 (47.0)	2 (20.0)	13 (24.5)
Bleeding fewer days	20 (18.9)	36 (19.5)	2 (20.0)	21 (39.6)
Pelvic pain >6 mo affecting normal function				
No	106 (55.8)	184 (65.2)[d]	13 (92.9)	102 (90.3)
Yes	84 (44.2)	98 (34.8)	1 (7.1)	11 (9.7)
Painful menses cramps >6 mo[b]				
No	91 (49.2)	179 (66.8)[e]	12 (92.3)	98 (89.9)
Yes; specify duration, mo	94 (50.8)	89 (33.2)	1 (7.7)	11 (10.1)
<6	8 (6.8)	6 (4.7)	1 (50.0)	2 (10.5)
6–12	24 (20.3)	31 (24.4)	0 (0.0)	1 (5.3)
13–24	25 (21.2)	20 (15.8)	1 (50.0)	3 (15.8)
>24	61 (51.7)	70 (55.1)	0 (0.0)	13 (68.4)

Peterson. Risk factors associated with endometriosis. Am J Obstet Gynecol 2013.

[a] $P = .0075$;

[b] Among women with ≥1 menstrual cycles in past 12 mo;

[c] $P = .07$;

[d] $P = .0384$;

[e] $P = .0002$.

TABLE 3

Risk factors for endometriosis by cohort, ENDO Study, 2007 through 2009 (n = 600)

Risk factor	Operative cohort (n = 473)		Population cohort (n = 127)	
	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)
Sociodemographic				
Age, y	0.97 (0.94–0.99)	—	1.02 (0.95–1.09)	—
Above poverty level (yes/no)[b]	1.53 (0.83–2.80)	1.88 (1.00–3.52)	0.86 (0.17–4.24)	0.87 (0.17–4.53)
College educated (yes/no)	1.63 (1.00–2.64)	1.83 (1.12–3.00)	0.58 (0.11–2.98)	0.58 (0.11–3.13)
Reproductive history				
Gravid (vs nulligravid)	0.48 (0.33–0.71)	0.49 (0.32–0.75)	1.24 (0.39–3.93)	1.02 (0.27–3.78)
Parous (vs nulliparous)	0.47 (0.32–0.68)	0.42 (0.28–0.64)	1.31 (0.43–4.02)	1.06 (0.28–3.96)
Infertility history (yes/no)	2.49 (1.61–3.83)	2.43 (1.57–3.76)	7.13 (1.72–29.6)	7.91 (1.69–37.2)
Age at first consenting sex, y	1.05 (1.00–1.11)	1.06 (1.01–1.12)	1.07 (0.88–1.29)	1.05 (0.87–1.28)
Surgical indication for laparoscopy (pelvic pain vs other)	3.91 (2.65–5.76)	3.67 (2.44–5.50)	—	—
Menstruation (past 12 mo)				
Age at menarche, y	1.06 (0.95–1.18)	1.05 (0.94–1.17)	1.27 (0.87–1.87)	1.25 (0.84–1.85)
Mean no. of periods[c]	0.99 (0.95–1.02)	0.99 (0.96–1.02)	0.99 (0.91–1.08)	0.99 (0.91–1.07)
Mean cycle length, d[c]	0.99 (0.98–1.00)	0.99 (0.98–1.00)	0.95 (0.85–1.06)	0.95 (0.85–1.06)
Mean length shortest cycle, d[c]	0.99 (0.98–1.00)	0.99 (0.98–1.00)	1.02 (0.98–1.06)	1.02 (0.98–1.06)
Mean length longest cycle, d[c]	0.99 (0.99–1.00)	0.99 (0.99–1.00)	1.01 (0.98–1.04)	1.01 (0.99–1.04)
Dysmenorrhea (yes/no)	2.78 (1.46–5.29)	2.46 (1.28–4.72)	1.37 (0.28–6.58)	1.41 (0.28–7.14)
Pelvic pain (yes/no)	0.95 (0.93–0.98)	1.39 (0.95–2.04)	1.01 (0.93–1.09)	0.76 (0.09–6.54)
Body mass index, kg/m^2	0.95 (0.93–0.98)	0.95 (0.93–0.98)	1.01 (0.93–1.09)	1.01 (0.93–1.09)

Excludes 22 women in operative cohort whose surgeries were cancelled and 4 women in population cohort with unreadable magnetic resonance images.

Cl, confidence interval; *OR*, odds ratio.

Peterson. Risk factors associated with endometriosis. Am J Obstet Gynecol 2013.

[a] Adjusted for age (y) and site;

[b] Based upon 2007 Health and Human Services Poverty Guidelines accounting for numbers of persons in household for 48 contiguous states and District of Columbia;

[c] Among women with 1 menstrual cycles in past 12 mo.

TABLE 4

Risk factors for visually and histologically confirmed endometriosis, ENDO Study, 2007 through 2009 (n = 473), sensitivity analysis

Risk factor	Operative cohort	
	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)
Sociodemographic		
Age, y	0.97 (0.93–1.00)	—
Above poverty level (yes/no)[b]	0.90 (0.41–2.02)	1.07 (0.47–2.45)
College educated (yes/no)	1.25 (0.62–2.49)	1.35 (0.67–2.73)
Reproductive history		
Gravid (vs nulligravid)	0.32 (0.19–0.55)	0.31 (0.17–0.56)
Parous (vs nulliparous)	0.30 (0.17–0.52)	0.27 (0.15–0.49)
Infertility history (yes/no)	2.43 (1.40–4.20)	2.39 (1.38–4.16)
Age at first consenting sex, y	1.11 (1.04–1.18)	1.11 (1.04–1.19)
Surgical indication for laparoscopy (pelvic pain vs other)	3.01 (1.74–5.22)	2.82 (1.59–4.99)
Menstruation (past 12 mo)		
Age at menarche, y	1.05 (0.90–1.23)	1.04 (0.89–1.22)
Mean no. of periods[c]	1.01 (0.97–1.04)	1.01 (0.98–1.04)
Mean cycle length, d[c]	1.00 (0.98–1.01)	0.99 (0.98–1.01)
Mean length shortest cycle, d[c]	1.00 (0.99–1.01)	1.00 (0.99–1.01)
Mean length longest cycle, d[c]	1.00 (0.99–1.01)	1.00 (0.99–1.01)
Dysmenorrhea (yes/no)	3.49 (1.06–11.5)	3.11 (0.94–10.3)
Pelvic pain (yes/no)	1.72 (1.02–2.91)	1.63 (0.96–2.76)
Body mass index, kg/m^2	0.94 (0.90–0.98)	0.94 (0.90–0.98)

CI, confidence interval; *OR*, odds ratio.

Peterson. Risk factors associated with endometriosis. Am J Obstet Gynecol 2013.

[a] Adjusted for age (y) and site;

[b] Based upon 2007 HHS Poverty Guidelines accounting for numbers of persons in household for 48 contiguous states and District of Columbia;

[c] Among women with 1 menstrual cycles in past 12 mo.

TABLE 5

Risk factors for stages 3 and 4 endometriosis, ENDO Study, 2007 through 2009 (n = 339), sensitivity analysis

Risk factor	Operative cohort	
	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)
Sociodemographic		
Age, y	0.99 (0.95–1.03)	—
Above poverty level (yes/no)[b]	2.70 (0.80–9.09)	2.99 (0.87–10.3)
College educated (yes/no)	1.77 (0.80–3.93)	1.93 (0.86–4.31)
Reproductive history		
Gravid (vs nulligravid)	0.33 (0.18–0.60)	0.27 (0.14–0.51)
Parous (vs nulliparous)	0.26 (0.14–0.48)	0.19 (0.10–0.37)
Infertility history (yes/no)	4.90 (2.66–9.00)	4.74 (2.57–8.75)
Age first consenting sex, y	1.11 (1.03–1.18)	1.11 (1.03–1.19)
Surgical indication for laparoscopy (pelvic pain vs other)	4.44 (2.42–8.16)	4.47 (2.39–8.38)
Menstruation (in past 12 mo)		
Age at menarche, y	1.09 (0.91–1.30)	1.07 (0.90–1.29)
Mean no. of periods[c]	0.98 (0.93–1.04)	0.99 (0.94–1.04)
Mean cycle length, d[c]	1.00 (0.99–1.01)	1.00 (0.99–1.01)
Mean length shortest cycle, d[c]	1.00 (0.99–1.01)	1.00 (0.99–1.01)
Mean length longest cycle, d[c]	1.00 (0.99–1.01)	1.00 (0.99–1.01)
Dysmenorrhea (yes/no)	3.61 (1.08–12.0)	3.43 (1.02–11.5)
Pelvic pain (yes/no)	1.63 (0.91–2.91)	1.60 (0.89–2.87)
Body mass index, kg/m^2	0.97 (0.93–1.01)	0.97 (0.93–1.01)

CI, confidence interval; *OR*, odds ratio.

Peterson. Risk factors associated with endometriosis. Am J Obstet Gynecol 2013.

[a]Adjusted for age (y) and site;

[b]Based on 2007 HHS Poverty Guidelines accounting for numbers of persons in household for 48 contiguous states and District of Columbia;

[c]Among women with 1 menstrual cycles in past 12 mo.

TABLE 6

Risk factors for endometriosis in comparison to women with normal pelvis postoperatively, ENDO Study, 2007 through 2009 (n = 320), sensitivity analysis

Risk factor	Operative cohort	
	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)
Sociodemographic		
Age, y	0.96 (0.93–0.99)	—
Above poverty level (yes/no)[b]	1.90 (0.95–3.80)	2.38 (1.15–4.92)
College educated (yes/no)	2.43 (1.39–4.24)	2.62 (1.48–4.63)
Reproductive history		
Gravid (vs nulligravid)	0.22 (0.13–0.39)	0.23 (0.13–0.42)
Parous (vs nulliparous)	0.18 (0.11–0.31)	0.18 (0.10–0.32)
Infertility history (yes/no)	2.85 (1.64–4.97)	2.91 (1.66–5.11)
Age first consenting sex, y	1.07 (1.00–1.14)	1.09 (1.02–1.16)
Surgical indication for laparoscopy (pelvic pain vs other)	3.78 (2.36–6.05)	3.76 (2.29–6.20)
Menstruation (past 12 mo)		
Age at menarche, y	1.04 (0.91–1.19)	1.04 (0.91–1.19)
Mean no. of periods[c]	0.97 (0.93–1.02)	0.98 (0.95–1.02)
Mean cycle length, d[c]	1.00 (0.98–1.01)	1.00 (0.98–1.01)
Mean length shortest cycle, d[c]	1.00 (0.99–1.02)	1.00 (0.98–1.02)
Mean length longest cycle, d[c]	1.00 (0.99–1.01)	1.00 (0.99–1.01)
Dysmenorrhea (yes/no)	3.11 (1.53–6.31)	2.96 (1.43–6.13)
Pelvic pain (yes/no)	1.82 (1.14–2.91)	1.75 (1.08–2.82)
Body mass index, kg/m^2	0.96 (0.93–0.99)	0.96 (0.93–0.99)

Analysis restricted to women reported to have normal pelvis following laparoscopy. Endometriosis defined as visualized disease.

Cl, confidence interval; *OR*, odds ratio.

Peterson. Risk factors associated with endometriosis. Am J Obstet Gynecol 2013.

[a] Adjusted for age (y) and site;

[b] Based upon 2007 HHS Poverty Guidelines accounting for numbers of persons in household for 48 contiguous states and District of Columbia;

[c] Among women with 1 menstrual cycles in past 12 mo.

TABLE 7

Consistency of risk factors for endometriosis across study cohort, definition of endometriosis, and choice of comparison group, ENDO Study (n = 600)

Risk factor	Population cohort (Table 3) (n = 127)	Operative cohort visualized disease (Table 3) (n = 600)	Operative cohort visualized and histologically confirmed disease vs no endometriosis (Table 4) (n = 473)	Operative cohort rASRM stages 3 and 4 endometriosis only vs no endometriosis (Table 5) (n = 339)	Operative cohort endometriosis vs women with normal pelvis at laparoscopy (Table 6) (n = 320)
Increased risk					
Higher income					—
College education		—			—
Infertility history	—	—	—	—	—
Older age at first sex		—	—	—	—
Surgical indication for pelvic pain		—	—	—	—
Dysmenorrhea		—		—	—
History pelvic pain					—
Decreased risk					
Higher gravidity		—	—	—	—
Higher parity		—	—	—	—
Higher body mass index		—	—		—

rASRM, revised criteria from American Society for Reproductive Medicine.

Peterson. Risk factors associated with endometriosis. Am J Obstet Gynecol 2013.