ORIGINAL ARTICLE: ENVIRONMENT AND EPIDEMIOLOGY

The prevalence of migraines in adolescents with endometriosis

Jerri A. Miller, B.S.,[a,b] Stacey A. Missmer, Sc.D.,[a,c,d,e] Allison F. Vitonis, Sc.M.,[a,f] Vishnudas Sarda, M.S.,[a,c] Marc R. Laufer, M.D.,[a,f,g] and Amy D. DiVasta, M.D., M.M.Sc.[a,c,g]

[a] Boston Center for Endometriosis, Boston Children's Hospital and Brigham and Women's Hospital; [c] Division of Adolescent and Young Adult Medicine and [g] Division of Gynecology, Boston Children's Hospital and Harvard Medical School; [f] Department of Obstetrics, Gynecology, and Reproductive Biology, Brigham and Women's Hospital and Harvard Medical School; and [d] Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts; [b] Bryant University Physician Assistant Program, Smithfield, Rhode Island; and [e] Department of Obstetrics, Gynecology, and Reproductive Biology, College of Human Medicine, Michigan State University, Grand Rapids, Michigan

Objective: To determine the prevalence and experience of migraines in adolescents with surgically confirmed endometriosis compared with those without endometriosis.
Design: Cross-sectional study conducted within The Women's Health Study: From Adolescence to Adulthood—an ongoing longitudinal cohort.
Setting: Boston Center for Endometriosis.
Patient(s): Adolescent females enrolled November 2012 through November 2016. The case group included adolescents surgically diagnosed with endometriosis. The control group included adolescents without endometriosis, recruited from the local community and clinics.
Intervention(s): Not available.
Main Outcome Measure(s): An extensive online health questionnaire regarding medical history, lifestyle, medication use, anthropometrics, and symptom experience and treatments. Migraine diagnosis was self-reported. Migraine pain and noncyclic pelvic pain severity were rated using an 11-point numerical rating scale. Cyclic pelvic pain was categorized.
Result(s): Adolescents with endometriosis were more likely to experience migraines (69.3%) than those without endometriosis (30.7%) (multivariable odds ratio = 4.77, 95% confidence interval 2.53, 9.02). For each 1-point increase in the migraine numerical rating scale, the odds of endometriosis increased by 22% (multivariable odds ratio = 1.22, 95% confidence interval 1.03, 1.44; $P_{trend} = .02$). Among those with endometriosis, age of menarche was associated inversely with the odds of migraines. Participants with endometriosis and migraines have more dysmenorrhea than those without migraines.
Conclusion(s): Adolescents with endometriosis are more likely to experience migraines than adolescents without endometriosis. A linear relationship exists between migraine pain severity and the odds of endometriosis, suggesting heightened pain sensitivity for adolescents with endometriosis. Due to the strong correlation, patients who present with either condition should be screened for comorbidity to maximize the benefits of care. (Fertil Steril® 2017;■:■–■. ©2017 by American Society for Reproductive Medicine.)
Key Words: Endometriosis, adolescents, migraines, pain sensitization, WERF EPHect

Discuss: You can discuss this article with its authors and other readers at https://www.fertstertdialog.com/users/16110-fertility-and-sterility/posts/28637-24996

Endometriosis is a gynecological disease in which endometrium-like tissue grows in locations outside of the uterus, primarily in the pelvic cavity. Notable symptoms include pelvic pain, dysmenorrhea, menorrhagia, and infertility (1, 2). Migraine is another pain disorder that involves headaches, frequently accompanied by nausea, fatigue, phonophobia, and photophobia (1, 3). Both disorders can impede productivity and cause moderate-to-severe pain that intensifies through routine physical activity (1).

In adults, these two pain disorders have been linked, as migraines appear to occur more commonly in patients with endometriosis than in the general population (1,3–5). This association may be because women with chronic pelvic pain (CPP) often have hypersensitivity to pain, known as central sensitization (6–8). Pain sensitivity may be heightened for those patients with endometriosis compared with those without. Similar studies exploring endometriosis and migraine co-occurrence have not yet been replicated within the adolescent population.

Received September 12, 2017; revised November 25, 2017; accepted December 13, 2017.
J.A.M. has nothing to disclose. S.A.M. has nothing to disclose. A.F.V. has nothing to disclose. V.S. has nothing to disclose. M.R.L. has nothing to disclose. A.D.D. has nothing to disclose.
Supported by the J. Willard and Alice S. Marriott Foundation, Bethesda, MD.
Data collection was facilitated by and conducted in compliance with the World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonization Project (WERF EPHect).
Reprint requests: Amy D. DiVasta, M.D., M.M.Sc., Division of Adolescent Medicine, Boston Children's Hospital, 333 Longwood Avenue, Boston, Massachusetts, 02115 (E-mail: amy.divasta@childrens.harvard.edu).

Fertility and Sterility® Vol. ■, No. ■, ■ 2018 0015-0282/$36.00

https://doi.org/10.1016/j.fertnstert.2017.12.016

The current study was conducted to determine the prevalence of migraines in adolescents with surgically confirmed endometriosis compared with those without endometriosis. We hypothesized that the prevalence of migraines would be higher in those with endometriosis. In addition, we hypothesized that among participants with migraines, those with endometriosis would have worse migraine pain than participants who did not have endometriosis. We also sought to determine whether adolescents suffering from both endometriosis and migraines experienced more severe pelvic pain than those with only endometriosis.

MATERIALS AND METHODS

This cross-sectional study was set within an ongoing longitudinal cohort study, The Women's Health Study: From Adolescence to Adulthood, enrolling premenopausal females aged $\geq$7 years with and without surgically confirmed endometriosis. This study is conducted within the Boston Center for Endometriosis, which is a joint initiative between Boston Children's Hospital and Brigham and Women's Hospital, with the primary aim of investigating endometriosis across the lifespan. Participants are recruited from the two tertiary care centers, as well as from the surrounding community by local advertisements, online postings, and word of mouth. The participants completed an extensive baseline questionnaire and annual follow-up questionnaires. Our extensive online health questionnaire is an expanded version of the World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonization Project (WERF EPHect) standard clinical questionnaire (9). Surveys are collected and managed using REDCap electronic data capture tools. The study was approved by the Boston Children's Hospital Institutional Review Board on behalf of Boston Children's Hospital and Brigham and Women's Hospital. Informed consent with obtained, with parental consent/participant assent for girls $<$18 years.

The analytic population for the current study included female adolescents who were enrolled from November 2012 through November 2016, and completed the baseline questionnaire. Participants who had been surgically diagnosed with endometriosis at the hospital of enrollment comprised the case group (10). Participants in the control group included healthy individuals and those with other medical comorbidities who were recruited from the local Boston community and from clinics at Boston Children's Hospital and Brigham and Women's Hospital. The control subjects were not undergoing evaluation for endometriosis and had no surgical diagnosis of endometriosis. As part of study enrollment, participants were asked to complete a survey soliciting information regarding menstrual history (including age at menarche), medical history, lifestyle, medication, anthropometric, and environmental exposures, as well as symptom experience and treatments. Those participants who failed to complete the pelvic pain symptom portions of the questionnaire were excluded from this analysis (n = 16). The remaining participants were restricted to those who were children and adolescents (aged $\leq$21 years) at enrollment (n = 391).

The primary characteristics of interest included having ever experienced migraines, with or without a diagnosis from a physician, age at migraine diagnosis, migraine pain severity, and the presence and severity of cyclic and noncyclic pelvic pain, as well as lower general abdominal pain. Migraine pain and noncyclic pelvic pain severity were rated using an 11-point numerical rating scale anchored with 0 = no pain and 10 = worst imaginable pain. Cyclic pelvic pain severity was categorized as no pain, mild (medication never or rarely needed), moderate (medication usually needed), or severe cramping (medication and bed rest needed). Information was also collected regarding the age of pelvic pain and/or migraine pain onset, age at diagnosis of endometriosis and/or migraine, hormonal medications ever used, and smoking history. In addition collected covariates from the questionnaire included participants' demographic data such as age, race, body mass index (BMI), and educational level.

We initially calculated crude odds ratios (ORs) and 95% confidence intervals (CIs) using univariate unconditional logistic regression. We then used adjusted models, first including covariates for age (continuous), race (white, black, Asian, other/missing), and whether or not the participant ever used hormonal medication (never/ever). Second adjusted models also included terms for the presence and degree of menstrual pain (none/mild or moderate/severe) and for the presence of general, noncyclic pelvic pain (yes/no). We examined the association between endometriosis and risk of migraine overall and the association between migraine symptoms (pain severity and age at diagnosis) and risk of endometriosis. Pain severity and age at menarche were modeled categorically and continuously. In addition, we examined the association between age at menarche, pelvic pain, and migraine risk, separately in endometriosis cases and noncases. To examine heterogeneity in the relation between age at menarche or pelvic pain and migraine risk by endometriosis status, we ran logistic regression models and calculated likelihood ratio tests comparing models fit with and without interaction terms. Analyses were completed with SAS version 9.4 (SAS Institute).

RESULTS

The participants in this study included 296 cases and 95 controls, comprised of 205 adolescents with both endometriosis and migraines, 91 adolescents with only endometriosis, 30 adolescents with only migraines, and 65 adolescents with neither endometriosis nor migraines. On average, the participants were primarily in school with an average age of 17.4 years (SD = 2.3; Table 1). In all four categories, most participants were of normal BMI category (compared with underweight, overweight. or obese). Most participants were of white race (79.8%), although there was a higher ratio of black, Asian, and other races among those participants with only migraines or neither disorder. As would be expected due to clinical history, 92.2% of adolescent participants with endometriosis had ever taken hormonal medication compared with 54.7% of adolescents without endometriosis. There was an increased prevalence of anxiety and mood disorders among those with compared with those without endometriosis.

TABLE 1

Demographics of adolescents by surgically confirmed endometriosis and migraine status at enrollment.

Demographics	Endometriosis and migraines (N = 205)	Endometriosis only (N = 91)	Migraines only (N = 30)	Neither (N = 65)
Age (y)				
Median (min, max)	17.0 (12.0, 21.0)	17.0 (13.0, 21.0)	19.0 (15.0, 21.0)	19.0 (13.0, 21.0)
Mean (SD)	17.0 (2.3)	17.1 (2.3)	18.6 (1.9)	18.9 (1.8)
BMI category (kg/m^2)[a]				
Underweight	3 (1.5)	1 (1.2)	0 (0.0)	3 (4.6)
Normal	137 (67.2)	62 (71.3)	16 (53.3)	40 (61.5)
Overweight	51 (25.0)	19 (21.8)	12 (40.0)	13 (20.0)
Obese	13 (6.4)	5 (5.8)	2 (6.7)	9 (13.9)
Race[b]				
White	176 (88.4)	84 (93.3)	13 (48.2)	39 (61.9)
Black	4 (2.0)	0 (0.0)	4 (14.8)	3 (4.8)
Asian	1 (0.5)	0 (0.0)	3 (11.1)	15 (23.8)
Other	18 (9.1)	6 (6.7)	7 (25.9)	6 (9.5)
Ethnicity				
Not Hispanic	181 (91.4)	87 (96.7)	23 (76.7)	58 (90.6)
Hispanic	17 (8.6)	3 (3.3)	7 (23.3)	6 (9.4)
Ever used hormonal medication				
Never	14 (6.8)	9 (9.9)	11 (36.79)	32 (49.2)
Ever	191 (93.2)	82 (90.1)	19 (63.3)	33 (50.8)
In school				
No	7 (3.4)	5 (5.5)	2 (6.7)	6 (9.4)
Yes	197 (96.6)	86 (94.5)	28 (93.3)	58 (90.6)
Amount of sleep on average per night (h)				
<6	24 (11.8)	6 (6.6)	3 (10.0)	7 (10.8)
6–8	137 (67.2)	69 (75.8)	23 (76.7)	51 (78.5)
≥9	43 (21.1)	16 (17.6)	4 (13.3)	7 (10.8)
Anxiety disorder				
No	152 (74.2)	71 (78.0)	29 (96.7)	58 (89.2)
Yes	53 (25.9)	20 (22.0)	1 (3.3)	7 (10.8)
Mood disorder				
No	167 (81.5)	80 (87.9)	28 (93.3)	60 (92.3)
Yes	38 (18.5)	11 (12.1)	2 (6.7)	5 (7.7)
Smoking history				
Never	200 (98.0)	91 (100.0)	28 (93.3)	64 (98.5)
Ever	4 (2.0)	0 (0.0)	2 (6.7)	1 (1.5)

Note: BMI = body mass index.
[a] For women aged ≥20 years, participants were categorized as underweight (BMI <18.5 kg/m^2), normal weight (BMI 18.5–24.9 kg/m^2), overweight (BMI 25–29.9 kg/m^2), or obese (BMI ≥30 kg/m^2) according to World Health Organization (WHO) criteria (11). For those <20 years, the age- and gender-specific BMI z-score was calculated and participants were categorized as underweight (z-score ≤ -2), normal weight (z-score > -2 to <1), overweight (z-score 1–2), or obese (z-score >2).
[b] Participants who reported more than one race were categorized as "Other."

Miller. Migraines in teens with endometriosis. Fertil Steril 2017.

Adolescents with endometriosis were more likely to report having migraines (69.3%) than those without endometriosis (30.7%), with nearly fivefold greater odds of migraines among those with endometriosis compared with those without (multivariable odds ratio [aOR] = 4.77, 95% CI 2.53,9.02) (Table 2). When restricting the migraine cases to only include those with physician diagnosed migraines, the association remained the same (aOR = 4.18) (data not shown). When we evaluated chronic pelvic pain (CPP) as a potential confounder, the magnitude of this association was similar

TABLE 2

The prevalence of migraines among 391 adolescents with and without endometriosis.

Characteristics	With migraines	Without migraines	Crude OR (95% CI)[a]	Adjusted model 1 OR (95% CI)[b]	Adjusted model 2 OR (95% CI)[c]
Endometriosis					
No	30 (12.8)	65 (41.7)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Yes	205 (87.2)	91 (58.3)	4.88 (2.97, 8.03)	4.77 (2.53, 9.02)	3.90 (1.78, 8.53)

Note: CI = confidence interval; OR = odds ratio.
[a] Univariate unconditional logistic regression.
[b] Adjusted for age (continuous), race (white, black, Asian, other/missing), ever used hormones (never, ever).
[c] In addition adjusted for period pain (none/mild, moderate/severe) and general pelvic pain (no, yes).

Miller. Migraines in teens with endometriosis. Fertil Steril 2017.

after adjustment for cyclic and noncyclic pelvic pain. Among participants who reported migraines, the average migraine numerical rating scale for those with endometriosis was 6.2 (SD = 2.6); for those without endometriosis, the average severity score was 4.9 (SD = 3.0) (Table 3). For each 1-point increase in the migraine numerical rating scale, the odds of endometriosis increased by 22% (aOR = 1.22, 95% CI 1.03, 1.44; P_{trend} = .02). When restricted to adolescents with endometriosis, the odds of migraines was nearly two times higher for participants reporting severe pelvic pain compared with those reporting mild pelvic pain. However, this association was not statistically significant (aOR = 1.90, 95% CI 0.64, 5.66) (Table 4).

Among participants with endometriosis, early age of menarche (≤11 years old) was reported by 51.2% of participants who had migraines and 39.6% of participants who did not have migraines. We observed almost a 70% reduction in the odds of migraines among those with late age at menarche (≥14 years old) compared with those with early menarche [aOR = 0.33, 95% CI 0.12, 0.92). However, among participants without endometriosis, there was no evidence of a relation between age at menarche and odds of migraines.

Participants with both endometriosis and migraines had more pain with periods compared with those without migraines. For those with endometriosis and migraines, 4.9% reported no pain or mild cramps, 27.8% reported moderate cramps, and 67.3% reported severe cramps. With endometriosis, but among participants with endometriosis, there was a twofold greater odds of migraines among those with severe dysmenorrhea compared with those with no or mild pain with periods. However, this association was not statistically significant (95% CI 0.64, 5.66) (Table 4).

DISCUSSION

In this large sample of adolescents, we found that participants with endometriosis more commonly experience migraines compared with those without endometriosis. We also demonstrated a linear relationship between the severity of migraine pain and the odds of endometriosis. Among adolescents with endometriosis, those girls with migraines trended toward experiencing worse pelvic pain during periods than those girls without migraines.

Our current findings are consistent with most previous research conducted in adults that has demonstrated a comorbid relationship between endometriosis and migraines (1, 3, 4). In a large population-based cohort study involving data abstraction from outpatient and inpatient records from 2000 to 2007, Yang et al. (1) found that among 20,220 participants with clinically diagnosed endometriosis and 263,767 participants without endometriosis, migraines were 1.7 times more prevalent in women with endometriosis than in those without endometriosis. Similarly, a study by Nyholt et al. (3), which included a large sample of families containing multiple women with surgically confirmed endometriosis, found a significantly increased risk of migraine headache in women with endometriosis compared with those without endometriosis (OR 1.57, 95% CI 1.12–2.21; P=.009). Attempting to consider pain and endometriosis distinctly, Karp et al. (12) concluded that migraines were more common in women with CPP independent of an endometriosis diagnosis. We investigated the role of CPP as a confounder (Table 2) and as the exposure of interest (Table 4). Our findings remained consistent after adjustment, indicating that those with migraines are at higher odds for endometriosis even after adjusting for pelvic pain.

A linear relationship was found between migraine pain severity and the odds of endometriosis, supporting the hypothesis of central sensitization for adolescents with CPP (6–8). Stratton et al. (7) determined that pain sensitivity was heightened for those patients with endometriosis compared with those without. In contrast, As-Sanie et al. (6) found that this hypersensitivity was located among all participants with CPP, not just those suffering from endometriosis when compared with a group of pain-free healthy women.

Our study suggests that adolescents with more severe migraine pain have greater odds of endometriosis. It is important to note that when our results were further adjusted for (i.e., independent of) pelvic pain, the association was attenuated. However, there remained a nearly twofold greater odds of endometriosis among those reporting the most severe migraine pain. If we hypothesize that the central sensitization

TABLE 3

The association between migraine symptoms and odds of surgically confirmed endometriosis among 235 adolescents.

Characteristics	With endometriosis (N = 205)	Without endometriosis (N = 30)	Crude OR (95% CI)[a]	Adjusted model 1 OR (95% CI)[b]	Adjusted model 2 OR (95% CI)[c]
Migraine pain severity score					
0–3	34 (16.8)	10 (33.3)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
4–6	67 (33.0)	9 (30.0)	2.19 (0.81, 5.90)	3.03 (0.88, 10.4)	1.12 (0.20, 6.19)
7–10	102 (50.3)	11 (36.7)	2.73 (1.07, 6.68)	3.35 (1.04, 10.8)	1.95 (0.34, 11.3)
Mean (SD)	6.2 (2.6)	4.9 (3.0)	1.19 (1.04, 1.37)	1.22 (1.03, 1.44)	1.16 (0.90, 1.49)
Age at migraine diagnosis					
≤Median	34 (64.2)	4 (66.7)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
>Median	19 (35.8)	2 (33.3)	1.12 (0.19, 6.68)	2.27 (0.28, 18.5)	2.29 (0.19, 28.2)
Mean (SD)	13.3 (3.3)	13.3 (4.0)	1.00 (0.77, 1.28)	1.06 (0.79, 1.42)	1.10 (0.75, 1.61)

Note: CI = confidence interval; OR = odds ratio.
[a] Univariate unconditional logistic regression.
[b] Adjusted for age (continuous), race (white, black, Asian, other/missing), ever used hormones (never, ever).
[c] In addition adjusted for period pain (none/mild, moderate/severe) and general pelvic pain (no, yes).

Miller. Migraines in teens with endometriosis. Fertil Steril 2017.

TABLE 4

The association between age at menarche, pelvic pain symptoms, and the odds of migraines by surgically confirmed endometriosis status.

	Endometriosis				No endometriosis				
Characteristics	Migraine (N = 205)	No migraine (N = 91)	OR (95% CI)[a]	*P* value	Migraine (N = 30)	No migraine (N = 65)	OR (95% CI)[a]	*P* value	*P* value[b]
Age at menarche (y)									
≤11	105 (51.2)	36 (39.6)	1.00 (Ref)		14 (46.7)	19 (29.2)	1.00 (Ref)		.34
12–13	91 (44.4)	46 (50.6)	0.71 (0.41, 1.21)	.21	11 (36.7)	37 (56.9)	0.45 (0.15, 1.35)	.15	
≥14	9 (4.4)	9 (9.9)	0.33 (0.12, 0.92)	.03	5 (16.7)	9 (13.9)	0.69 (0.15, 3.09)	.63	
P trend				.05				.27	
Pain with periods									.86
None–mild	10 (4.9)	7 (7.7)	1.00 (Ref)		20 (66.7)	49 (75.4)	1.00 (Ref)		
Moderate	57 (27.8)	30 (33.0)	1.47 (0.48, 4.53)	.50	7 (23.3)	11 (16.9)	1.58 (0.49, 5.15)	.45	
Severe	138 (67.3)	54 (59.3)	1.90 (0.64, 5.66)	.25	3 (10.0)	5 (7.7)	0.99 (0.18, 5.41)	.99	
P trend				.08				.98	
Pelvic pain in general									.37
No	74 (36.1)	32 (35.2)	1.00 (Ref)		26 (86.7)	54 (83.1)	1.00 (Ref)		
Yes	131 (63.9)	59 (64.8)	0.98 (0.58, 1.65)	.93	4 (13.3)	11 (16.9)	0.51 (0.13, 1.99)	.33	
Severity of pelvic pain in general in the past year									.74
0–3	19 (15.0)	12 (20.7)	1.00 (Ref)		2 (50.0)	5 (45.5)	1.00 (Ref)		
4–6	29 (22.8)	9 (15.5)	2.40 (0.82, 7.01)	.11	1 (25.0)	5 (45.5)	0.53 (0.02, 14.1)	.70	
7–10	79 (62.2)	37 (63.8)	1.52 (0.63, 3.63)	.35	1 (25.0)	1 (9.1)	3.83 (0.02, 644)	.61	
P trend				.63				.85	

Note: CI = confidence interval; OR = odds ratio.
[a] Unconditional logistic regression adjusted for age (continuous), race (white, black, Asian, other/missing), ever used hormones (never, ever); *P* values are two-sided Wald tests.
[b] *P* value, likelihood ratio test of heterogeneity.

Miller. Migraines in teens with endometriosis. Fertil Steril 2017.

theory for CPP contributes to the increased odds of endometriosis when experiencing severe migraine pain, removing pelvic pain from this association would negate this important correlation. In addition, in our sample, only 10 participants with endometriosis reported mild or no pelvic pain. Therefore, this result is likely due to confounding by indication. A surgical diagnosis of endometriosis was required for inclusion as a "case" within our cohort. In adolescence, the indication for surgical evaluation for possible endometriosis is thus the presence of pain, whereas adults may seek surgical treatment due to infertility or be diagnosed through incidental surgery such as tubal ligation or cholecystectomy. Therefore, we conclude that adolescents with endometriosis suffer more frequently from migraines than those without, and that there is an increased odds of endometriosis for those adolescents with worse severity of migraine pain.

Earlier age at menarche was associated with greater odds of migraines, but only among the participants with endometriosis. There was no association observed between age at menarche and migraines among those without endometriosis. Aegidius et al. (13) found that an earlier menarche did increase the likelihood of headaches among adolescents and adults. Specifically, it was noted that when a female experienced menarche at age ≤12 years, headaches were more likely to be present. Furthermore, Pakalnis and Gladstein (14) studied the relationship between hormones and migraines in adolescent and young adult females to reveal that the fluctuations in the levels of estrogen (E) can play a significant factor in the presence of headaches. Similarly, most (11,15,16) but not all (17) studies found that a younger age of menarche is an additional risk factor for endometriosis. Further research needs to be done to determine whether there is an association between the age of menarche and the comorbidity of endometriosis and migraines.

Our data suggest that among adolescents with endometriosis, those with migraines experienced worse pelvic pain during periods than those without migraines. Although the likelihood of migraines was double for participants with severe pelvic pain compared with those with mild pelvic pain, these findings were not statistically significant. In addition, general pelvic or lower abdominal pain was not more prevalent for participants with migraines compared with those without migraines among adolescents with or without endometriosis. Very little previous research has been conducted in this area. Further studies should replicate these investigations to conclusively determine whether or not adolescents with endometriosis have worse pelvic or lower abdominal pain when presenting with migraines compared with those adolescents with endometriosis but without migraines.

Strengths of this study include use of thorough health questionnaires, laparoscopic diagnosis of endometriosis for the case group, and the unique focus on an adolescent population. Limitations of the study include the accuracy of a self-reported migraine and the subjective nature of pain scores in research and clinical settings. However, previous research has shown nearly equivalent responses to questionnaire tools and interview measures (18). Participants in our cohort were enrolled from Boston Children's Hospital, Brigham and Women's Hospital, and the surrounding communities; our patient population and clinical practices may not be generalizable to patients not presenting to a tertiary care center, to other geographic areas, or to patients from different racial and ethnic or economic backgrounds. We acknowledge the

potential for misclassification of our control subjects. As not every adolescent in the study underwent laparoscopy, it is possible that we included in our control subjects women who have endometriosis but who have not undergone laparoscopic visualization of the disease. However, this misclassification is related to the current lack of better diagnostics for endometriosis, and would have biased our results toward the null.

In conclusion, adolescents with endometriosis are more likely to experience migraines than adolescents without endometriosis, independent of pelvic pain. Furthermore, a linear relationship exists between migraine pain severity and the odds of endometriosis, suggesting heightened pain sensitivity for adolescents with endometriosis. Most important, due to the strong correlation of migraines and endometriosis, patients who present with either condition need to be screened by their physicians for comorbidity to receive proper care.

Acknowledgments: The authors thank The Women's Health Study: From Adolescence to Adulthood (A2A) cohort participants and their families who made this research possible.

REFERENCES

1. Yang M-H, Wang P-H, Wang S-J, Sun W-Z, Oyang Y-J, Fuh J-L. Women with endometriosis are more likely to suffer from migraines: a population-based study. PLoS One 2012;7:e33941.
2. Zannoni L, Del Forno S, Paradisi R, Seracchioli R. Endometriosis in adolescence: practical rules for an earlier diagnosis. Pediatr Ann 2016;45:e332–5.
3. Nyholt DR, Gillespie NG, Merikangas KR, Treloar SA, Martin NG, Montgomery GW. Common genetic influences underlie comorbidity of migraine and endometriosis. Genet Epidemiol 2009;33:105–13.
4. Ferrero S, Pretta S, Bertoldi S, Anserini P, Remorgida V, Del Sette M, et al. Increased frequency of migraine among women with endometriosis. Hum Reprod 2004;19:2927–32.
5. Morotti M, Remorgida V, Buccelli E, Venturini PL, Ferrero S. Comparing treatments for endometriosis-related pain symptoms in patients with migraine without aura. J Comp Eff Res 2012;1:347–57.
6. As-Sanie S, Harris RE, Harte SE, Tu FF, Neshewat G, Clauw DJ. Increased pressure pain sensitivity in women with chronic pelvic pain. Obstet Gynecol 2013;122:1047–55.
7. Stratton P, Khachikyan I, Sinaii N, Ortiz R, Shah J. Association of chronic pelvic pain and endometriosis with signs of sensitization and myofascial pain. Obstet Gynecol 2015;125:719–28.
8. Ferreira Gurian MB, Poli Neto OB, Rosa e Silva JC, Nogueira AA, Candido dos Reis FJ. Reduction of pain sensitivity is associated with the response to treatment in women with chronic pelvic pain. Pain Med 2015;16:849–54.
9. Rahmioglu N, Fassbender A, Vitonis AF, Tworoger SS, Hummelshoj L, D'Hooghe TM, et al. World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonization Project: III. Fluid biospecimen collection, processing, and storage in endometriosis research. Fertil Steril 2014;102:1233–43.
10. Practice Committee of the American Society for Reproductive Medicine. Treatment of pelvic pain associated with endometriosis: a committee opinion. Fertil Steril 2014;101:927–35.
11. Saha R, Kuja-Halkola R, Tornvall P, Marions L. Reproductive and lifestyle factors associated with endometriosis in a large cross-sectional population sample. J Women's Heal 2017;26:152–8.
12. Karp BI, Sinaii N, Nieman LK, Silberstein SD, Stratton P. Migraine in women with chronic pelvic pain with and without endometriosis. Fertil Steril 2011;95:895–9.
13. Aegidius KL, Zwart J-A, Hagen K, Dyb G, Holmen TL, Stovner LJ. Increased headache prevalence in female adolescents and adult women with early menarche. The Head-HUNT Studies. Eur J Neurol 2011;18:321–8.
14. Pakalnis A, Gladstein J. Headaches and hormones. Semin Pediatr Neurol 2010;17:100–4.
15. Missmer SA, Hankinson SE, Spiegelman D, Barber RL, Malspeis S, Willett WC, et al. Reproductive history and endometriosis among premenopausal women. Obstet Gynecol 2004;104(5 Pt 1):965–74.
16. Signorello LB, Harlow BL, Cramer DW, Spiegelman D, Hill JA. Epidemiologic determinants of endometriosis: a hospital-based case-control study. Ann Epidemiol 1997;7:267–74.
17. Cramer DW, Wilson E, Stillman RJ, Berger MJ, Belisle S, Schiff I, et al. The relation of endometriosis to menstrual characteristics, smoking, and exercise. JAMA 1986;255:1904–8.
18. Field AE, Taylor CB, Celio A, Colditz GA. Comparison of self-report to interview assessment of bulimic behaviors among preadolescent and adolescent girls and boys. Int J Eat Disord 2004;35:86–92.