

Accepted Manuscript

Spectrum Of Symptoms In Women Diagnosed With Endometriosis During
Adolescence Versus Adulthood

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PII: S0002-9378(17)32482-1

DOI: [10.1016/j.ajog.2017.12.007](https://doi.org/10.1016/j.ajog.2017.12.007)

Reference: YMOB 11976

To appear in: *American Journal of Obstetrics and Gynecology*

Received Date: 17 August 2017

Revised Date: 9 November 2017

Accepted Date: 6 December 2017

Please cite this article as: DiVasta AD, Vitonis AF, Laufer MR, Missmer SA, Spectrum Of Symptoms In Women Diagnosed With Endometriosis During Adolescence Versus Adulthood, *American Journal of Obstetrics and Gynecology* (2018), doi: 10.1016/j.ajog.2017.12.007.

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1 SPECTRUM OF SYMPTOMS IN WOMEN DIAGNOSED WITH ENDOMETRIOSIS DURING
2 ADOLESCENCE VERSUS ADULTHOOD

3
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3
4 Abstract word count: 354

5
6 Manuscript word count: 2998

7
8 Funding Sources: Study financial support was provided by the J. Willard and Alice S. Marriott
9 Foundation. The sponsor had no role in the study design, conduct of the study or data analysis,
10 writing of the report, or decision to submit the article for publication.

11
12 Conflicts of Interest Statement: The authors have no conflicts of interest relevant to this article
13 to disclose. The authors have no financial relationships relevant to this article to disclose.

14
15 Study findings were presented as an oral platform presentation at the North American Society
16 of Pediatric and Adolescent Gynecology Annual Meeting, Toronto, Canada, April 7-9, 2016.

17
18 Abbreviations: WERF EPHeCT, World Endometriosis Research Foundation Endometriosis

19 Phenome and Biobanking Harmonization Project

20 BCH, Boston Children's Hospital

21 BWH, Brigham and Women's Hospital

22 BMI, Body mass index

1

2 **Condensation of the Paper:**

3

4 Presenting symptoms of endometriosis, including non-cyclic pelvic pain, do not differ based
5 upon age at diagnosis, although more adolescents reported debut at menarche and nausea.

6

7 **Short Title:**

8 Symptoms of Endometriosis during Adolescence versus Adulthood

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Abstract

BACKGROUND:

Endometriosis symptoms often start at a young age, and the time between symptom onset and endometriosis diagnosis can be several years. It is not clear if symptoms experienced by adolescents differ from adults. Better understanding may shorten the often lengthy delay in diagnosis.

OBJECTIVE:

To further elucidate the symptom presentation of adolescents as compared to adults to determine if differences existed based upon age at surgical diagnosis that could impact time to diagnosis.

STUDY DESIGN:

This investigation was a cross-sectional study at enrollment within a longitudinal cohort of adolescents and women with endometriosis. The population-based cohort was recruited from two tertiary care centers and the surrounding communities. Participants included adolescents (diagnosed ≤ 18 y, n=295) and adults (diagnosed >18 y, n=107) with surgically-confirmed endometriosis who were enrolled into The Women's Health Study: From Adolescence to Adulthood. Participants completed an expanded version of the World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonization Project (WERF EPHeCt) standard clinical questionnaire including items regarding menstrual history, associated

1 symptoms, and pain. Chi-square or Fisher's exact tests were applied to categorical data, and
2 Wilcoxon rank sum tests to continuous data.

3

4 **RESULTS:**

5 Most participants (90%) experienced moderate-severe menstrual pain. On average, 3 doctors
6 were seen before diagnosis, regardless of age at presentation (range 0-25). Time from
7 symptoms to diagnosis averaged 2y for adolescents and 5y for adults ($p<0.001$). More
8 adolescents (50%) than adults (33%) reported pain starting at menarche ($p=0.002$) and nausea
9 accompanying pain (69% vs. 53%, $p=0.01$). Non-cyclic, general pelvic pain was prevalent. Half of
10 participants reported relief of their general pelvic pain after a bowel movement. Pain interfered
11 with work/school, daily activities, exercise, and sleep to a moderate-extreme degree; difficulties
12 were similar by age at diagnosis.

13

14 **CONCLUSIONS:**

15 Pelvic pain was severe, non-cyclical, and negatively impacted quality of life. At our tertiary care
16 centers, symptoms of endometriosis did not differ between women surgically diagnosed during
17 adolescence compared to those diagnosed as adults. Adolescents had more nausea and
18 symptom onset at menarche. Multi-year delays in diagnosis were common. Clinicians should be
19 aware of these alternate symptom patterns, and include endometriosis in their differential
20 diagnosis for both adolescent and young adult women experiencing non-cyclic pelvic pain and
21 nausea.

22

1

2 **KEY WORDS:**

3 Adolescents

4 Diagnosis

5 Endometriosis

6 Pelvic Pain

7

8

ACCEPTED MANUSCRIPT

1 Introduction

2 Endometriosis is an estrogen-dependent chronic inflammatory condition affecting 6%-10% of
3 women during the reproductive years.¹ While prevalence rates in the general population are
4 unknown due to the need for laparoscopic diagnosis, 50%-60% of females with pelvic pain and
5 ~50% of women with infertility suffer from endometriosis.² Nearly two-thirds of adolescents
6 with chronic acyclic pelvic pain have laparoscopic evidence of endometriosis.³

7
8 Definitive diagnosis of endometriosis requires laparoscopy, and multi-year diagnostic delays are
9 common.⁴⁻⁶ Although symptoms usually begin during adolescence^{7,8}, delays frequently result
10 between presentation of symptoms to a clinician and referral to a gynecologist⁶, often including
11 visits with non-gynecologic specialists and misdiagnoses.^{6,9,10} Diagnostic delays may lead to
12 central sensitization¹¹, chronic pain, scarring, and compromised fecundability.¹²

13
14 Delays may be due to adolescents lacking the experience and influence to advocate for their
15 own diagnosis and treatment.¹² However, we hypothesized that delays would also occur if
16 presenting symptoms of adolescents differed from those of adults. Small studies suggest that
17 only 9.4% of adolescents present with “classic” symptoms of cyclic pain only during menses.¹³
18 We sought to further elucidate the symptom presentation of adolescents as compared to adults.

20 Materials and Methods

21 This cross-sectional study was set within an ongoing longitudinal cohort study, The Women’s
22 Health Study: from Adolescence to Adulthood, enrolling premenopausal females aged ≥ 7 years

1 with and without endometriosis. This joint project between Boston Children's Hospital (BCH)
2 and Brigham and Women's Hospital (BWH) has the overall aim of investigating endometriosis
3 across the lifespan. Participants are recruited from the two tertiary care centers and from the
4 surrounding community. They complete an extensive baseline questionnaire and annual
5 follow-up questionnaires. The initial version of our baseline questionnaire included questions
6 on medical history, lifestyle, medication, anthropometric, and environmental exposures as well
7 as symptom experience and treatments. In January 2014, we adopted an expanded version of
8 the World Endometriosis Research Foundation Endometriosis Phenome and Biobanking
9 Harmonization Project (WERF EPHeCt) standard clinical questionnaire¹⁴. Surveys are collected
10 and managed using REDCap electronic data capture tools hosted at BWH¹⁵. The study was
11 approved by the BCH Institutional Review Board on behalf of both BCH and BWH. Informed
12 consent was obtained, with parental consent/participant assent for girls <18 years at
13 enrollment.

14
15 The endometriosis symptoms included in our analysis were self-reported pain and details of
16 acyclic (not associated with menses) and/or cyclic (associated with menses) pain of the
17 abdomen and/or pelvis over the lifetime and at varying time points over the last 12 months¹⁴
18 including age of pain onset, impact of pain, and care-seeking behaviors. Pain severity was
19 graded on an 11-point numeric rating scale anchored with 0=no pain and 10=worst imaginable
20 pain. Participants reported the severity of typical cramps with menses (dysmenorrhea), age of
21 dysmenorrhea onset, and associated physician visits and diagnoses. Urinary or bowel
22 movement habit changes during menses were characterized, including gastrointestinal

1 symptoms experienced over the preceding year, activities that worsened or helped pain, and
2 medications utilized to relieve pain.

3

4 Additional exposures included participants' demographic data and reproductive history. Body
5 mass index (BMI, kg/m^2) was calculated from self-reported weight and height. For women aged
6 ≥ 20 years, participants were categorized as underweight ($\text{BMI} < 18.5 \text{ kg}/\text{m}^2$), normal-weight
7 ($\text{BMI} 18.5\text{-}24.9 \text{ kg}/\text{m}^2$), overweight ($\text{BMI} 25\text{-}29.9 \text{ kg}/\text{m}^2$), or obese ($\text{BMI} \geq 30 \text{ kg}/\text{m}^2$) per World
8 Health Organization criteria.¹⁶ For adolescents, the age-and gender-specific BMI Z-score was
9 calculated, and categorized as underweight (Z-score ≤ -2), normal-weight (Z-score > -2 to $< 1e$),
10 overweight (Z-score 1 to 2), or obese (Z-score > 2).¹⁷ All self-reports of a diagnosis of
11 endometriosis were verified by review of the participants' operative reports stating that
12 endometriosis had been visualized.

13

14 Chi-square or Fisher's exact tests were applied to categorical data. Continuous data were
15 compared by Wilcoxon rank sum test. All hypothesis tests were two-sided. Data were analyzed
16 using SAS statistical software version 9.4 (Cary NC, USA).

17

18 **Results**

19 From November 2012 to March 2016, we enrolled 984 participants. Participants were excluded
20 if they never began the baseline questionnaire ($n=225$), or if they left more than 20% of it blank
21 after beginning ($n=68$). The sample then included $n=268$ controls (no diagnosis of
22 endometriosis) and $n=423$ cases (females who self-reported a diagnosis of endometriosis),

1 among whom 10 were subsequently excluded because they did not have an operative report
2 that confirmed endometriosis diagnosis. We restricted the sample to cases, and excluded those
3 omitting items on cyclic/general pelvic pain (n=11) for a final sample of 402 endometriosis
4 cases. Among these participants, 202 completed the first version of the questionnaire and 200
5 completed the expanded WERF EPHeCT standard clinical questionnaire. Participants ranged in
6 age from 12 to 49 years at enrollment (median age=19 years; Table 1). We divided the cohort
7 based upon age at diagnosis of endometriosis. “Adolescents” were defined as participants ≤ 18
8 years old at the time of surgical diagnosis; they comprised 73% (295/402) of the total sample.
9 “Adults” were defined as participants >18 years old at surgical diagnosis. Most participants self-
10 identified as White (88%) and non-Hispanic (93%). Most participants had menarche between
11 11-14 years old. Twelve adolescents and 10 adults were gravid prior to enrollment; 14 (3%) of
12 the participants reported having tried >6 months to become pregnant without success.

13

14 **Diagnosis**

15 Participants surgically diagnosed with endometriosis during adolescence had symptoms start at
16 13 y on average (range 8-18y). These adolescents first saw a clinician because of pain at 14y (9-
17 19) [median (min-max)], and received a diagnosis at 16y (9-18). Women diagnosed during
18 adulthood recalled symptoms beginning at age 16y (10-36), first saw a clinician at 20y (12-37),
19 and received a surgical diagnosis at 22y (19-46). On average, adolescents waited 1y (0-7)
20 between symptom onset and first seeing any clinician for complaints of pain, and 2y (0-7)
21 between symptom onset and diagnosis of endometriosis. For women diagnosed during
22 adulthood, delays were significantly longer (Table 2). Adults waited almost 3 times longer

1 between first seeing a clinician and achieving a surgical diagnosis (3.0 ± 4.0 y vs. 1.2 ± 1.4 y,
2 $p=0.001$). Adolescents saw a median of 2 (0-20) clinicians before surgical diagnosis; adults saw
3 a median of 2.5 (0-25) clinicians. No significant differences were found in age, weight status,
4 age at menarche, or parity between women who saw 1-2, 3-4, or >5 clinicians. Women who
5 saw >5 clinicians prior to diagnosis were more likely to report that they “tried to get pregnant
6 for at least 6 months without becoming pregnant” (9.4%) than women who saw 1-2 clinicians
7 (4.5%) or 3-4 clinicians (1.0%, $p=0.04$) (data not shown).

8

9 **Menstrual symptoms**

10 Most participants (93%) experienced moderate pain (pain usually requiring medication) to
11 severe pain (pain requiring medications and bed rest) during menses over the lifetime; there
12 was no appreciable difference between groups ($p=0.52$, Table 3). Half of those diagnosed as
13 adolescents and one-third of adults reported pain starting with their very first period ($p=0.002$).
14 More adults (25%) than adolescents (12%) noted that pain began >2 y after menarche. There
15 were no differences in birth weight, race, ethnicity, or premenarchal somatotype between
16 those who experienced pain proximal to menarche or those without pain until >2 years after
17 (data not shown). Both groups were equally likely to have taken medication for menstrual pain
18 ($p=0.99$). Over the counter pain-killers were used by 70% participants. One-third tried hormone
19 medications for pain, but did not have an improvement in symptoms; the proportion did not
20 vary by age at diagnosis ($p=0.42$). Few adolescents (18%) and adults (13%) took hormones and
21 found that pain “got at least somewhat better” ($p=0.38$).

22

1 **Acyclic pain**

2 General acyclic pelvic pain over the lifetime was common for adolescents (66%) and adults
3 (77%; $p=0.04$). Over the previous 1-3 months, general pelvic pain severity was severe and
4 similar between groups, with a median score of 8.0 for both (on a 0-10 scale, where 0=no pain
5 and 10=worst imaginable pain). Many adolescents (40%) and adults (48%) complained of
6 general pelvic pain lasting for days at a time ($p=0.18$).

7
8 Participants rated the impact of pain on their normal activities on a continuum from 0="not at
9 all" to 10="extremely." General pelvic pain made it difficult to participate in work/school for
10 participants regardless of age (median score 7.0 for both groups, $p=0.95$). Pain also made
11 participation in recreational and social activities difficult (median score 7.0 for both groups,
12 $p=0.99$). General pelvic pain interfered with school or work "moderately", "quite a bit", or
13 "extremely" for almost two-thirds (61% in both adolescents and adults). Interestingly, women
14 diagnosed during adulthood were more likely to report either that general pelvic pain
15 interfered "not at all" with work/school (adults 24% vs. adolescents 13%), or that general pelvic
16 pain interfered "extremely" with work/school (adults 32% vs. adolescents 13%, $p=0.01$).

17
18 Overall, general pelvic pain interfered with daily activities at home, exercise, sleep, and social
19 activities similarly between the two age groups ($p=0.07$ to 0.41). However, many differences
20 are still notable (Table 3). General pelvic pain interfered with sleep "not at all" for twice as
21 many participants diagnosed during adolescence (23.4%) compared to adults (10%). Exercise
22 was also impacted more severely for adults. General pelvic pain interfered with exercise

1 “extremely” for 36.1% of adults, compared to 21.3% of adolescents. With social activities,
2 general pelvic pain interfered “not at all” or “slightly” for 35.9% of adolescents and 44.7% of
3 adults. The extent to which general pelvic pain interfered with these activities did not differ
4 between patients diagnosed relatively quickly (≤ 1 year between symptom onset and diagnosis)
5 and those with a protracted time until diagnosis (>5 years from symptom onset to diagnosis)
6 ($p=0.27$ to 0.92) (data not shown).

7

8 **Urinary and gastrointestinal symptoms**

9 Nausea was a frequent complaint. Within the 12 months prior to survey completion, more
10 adolescents (70%) than adults (51%) reported nausea accompanying general pelvic pain
11 ($p=0.004$). Only 20% reported vomiting in conjunction with pain; no difference between groups
12 occurred ($p=0.15$). Bowel symptoms were less frequent (Table 4). One third of participants
13 reported more frequent bowel movements when period pain started ($p=0.74$), while 21%
14 reported less frequent bowel movements when the period pain started ($p=0.62$). Looser stools
15 accompanying pain onset were more common with dysmenorrhea than general pelvic pain
16 (Table 4). While changes in bowel habits did not often accompany the onset of general pelvic
17 pain, half of participants had general pelvic pain relief “sometimes”, “often”, “most of the time”,
18 or “always” after a bowel movement.

19

20 Participants diagnosed as adults were more likely to report more frequent urination when
21 experiencing menstrual pain (57%) compared to adolescents (32%, $p=0.05$) (Table 4). Pain with
22 urination during menstrual pain occurred in half the sample and was similar between the two

1 groups ($p=0.38$). The prevalence of pain with urination was slightly less with general pelvic pain
2 (adolescents 37% vs. adults 40%, $p=0.56$).

3

4 **Discussion**

5 Dysmenorrhea and acyclic, general pelvic pain are common symptoms of endometriosis
6 regardless of age at diagnosis. Contrary to our original hypothesis, pain patterns were similar
7 between females diagnosed with endometriosis during adolescence compared to adulthood.
8 Pain significantly impaired the women's daily lives, was frequently associated with nausea, and
9 frequently improved following a bowel movement.

10

11 Unlike adult endometriosis that is typically diagnosed on the basis of either pelvic pain or
12 infertility, adolescents are driven to seek medical care almost solely through life-impacting pain
13 symptoms. Dysmenorrhea and the pattern of pelvic pain in adolescents with endometriosis
14 were thought to differ from adults.^{12,18} In a previous small case series of 46 adolescents with
15 endometriosis, 9.4% had solely cyclic pain with menses, whereas 62.5% had both acyclic and
16 cyclic pain and 28.1% had acyclic pain only.¹⁹ We similarly found a high prevalence of acyclic
17 pain (66%) during adolescence and in the adult cohort (76%), suggesting that endometriosis-
18 associated pain may remain acyclic and perhaps even become more acyclic as patients get
19 older. Symptom patterns may change over time due to changes in the type of endometriosis
20 lesions found at laparoscopy that differ between adolescents and adults, or due to the
21 increased prevalence of deep infiltrating endometriosis as women age.¹⁹ Our findings may also
22 be related to the population studied. Our cohort includes a large proportion of adolescents and

1 young women who present with symptoms of pain and at surgical diagnosis were observed to
2 have stage I and II endometriosis, and is positioned to compare symptoms of adults and
3 adolescents. The sample does not reflect the adults presenting with infertility or more
4 advanced ASRM stage disease.^{6,20}

5

6 Dysmenorrhea not responding to medical therapy with non-steroidal anti-inflammatory drugs
7 and/or combined oral contraceptive pills is suggestive of endometriosis among adolescents.^{3,13}

8 More than 90% of our participants reported > 6 months of moderate-severe cramping during
9 menstruation not relieved by over-the-counter medications. One-third of participants took
10 hormone medications for pain without symptom improvement, regardless of age at diagnosis.
11 This result likely reflects the lowered responsiveness of endometriosis-associated pain to
12 hormonal therapies. These historical details should be considered markers of potential
13 endometriosis and prompt clinicians to consider further evaluation. However, the higher risk of
14 endometriosis being observed at diagnostic surgery among women with acyclic or hormone-
15 resistant pain may also be confounding by indication. If symptoms had been satisfactorily
16 treated by hormones or if pain negatively impacted quality of life solely during menses, these
17 women may have never undergone surgery to obtain a laparoscopic diagnosis. Our data
18 regarding response to hormonal treatment reflect this likelihood as well.

19

20 Early onset of dysmenorrhea is another characteristic of endometriosis among
21 adolescents.^{8,21,22} Pain most commonly started within two years following menarche. Twice as
22 many women diagnosed during adulthood than during adolescence did not start having pain

1 until >2 years after menarche. These women did not differ on measured premenarchal
2 characteristics. Since endometriosis is a progressive disease, early diagnosis and treatment are
3 particularly important for younger sufferers,^{18,23} particularly since endometriosis is a major
4 cause of disability and compromised quality of life.¹² In our sample, participants described
5 inhibition of normal daily activities due to pain, as well as a substantial negative impact on
6 academic or work success, exercise, and sleep. Recreational/social activities were slightly less
7 impacted than these other areas, hypothesized to perhaps be due to the potential
8 inactive/passive nature of many social activities and the more physical/active nature of the
9 others.

10
11 Despite the enormous impact of these symptoms, delays in diagnosis and treatment of
12 endometriosis were common. Females diagnosed during adolescence suffered with pain for a
13 year on average before seeing a clinician, and for two years between symptom onset and
14 diagnosis. It took almost 3 times longer for women diagnosed during adulthood to receive their
15 diagnosis. Adults experienced longer time from symptom onset to first seeing a clinician, and
16 then again from first seeing a clinician to a diagnosis. This “double delay” implies that it is not a
17 delay in care-seeking that prolongs the time to diagnosis, but that other factors are contributing.
18 We speculate that these factors may include normalization of menstrual pain²⁴, fear of
19 stigmatization regarding a gynecological complaint²⁵, lack of parental advocacy as young
20 women transition into adulthood, and issues with health insurance coverage.²⁶ Additional
21 reasons may include comorbidities or false diagnoses that lead to confusion regarding the
22 endometriosis diagnosis.²⁴ Although our sample represents the experience of women

1 presenting with pain symptoms, our data are consistent with previous reports of adults
2 diagnosed on the basis of either pelvic pain or subfertility.²⁶ Educating not only medical
3 professionals, but also patients and their caregivers regarding the nature of adolescent
4 pathologic pelvic pain is critical to promote appropriate care-seeking behaviors and decrease
5 diagnostic delays in endometriosis.^{12,13,27-29}

6

7 Endometriosis has been consistently associated with dyspareunia, dysuria, and gastrointestinal
8 symptoms.^{2,3,13,30} We similarly observed that these symptoms were prevalent. However,
9 contrary to our hypothesis, we demonstrated no appreciable differences in the prevalence of
10 vomiting, constipation, frequent bowel movements, or urinary frequency between adolescents
11 and adults. Interestingly, nausea was the most common complaint in both groups, although
12 significantly greater among adolescents. The prevalence of nausea in adolescents with
13 endometriosis is higher than that previously described with primary dysmenorrhea (55%)³¹.
14 While not a well-recognized hallmark of endometriosis, the high prevalence in our sample
15 compared to other populations of adolescents with menstrual pain without endometriosis
16 suggests that nausea in association with pelvic pain should perhaps be considered a marker to
17 raise suspicion for endometriosis.

18

19 As a cross-sectional baseline analysis of our longitudinal cohort, our study has many strengths.
20 Our cohort includes a large number of adolescents with endometriosis, more than double that
21 of the case series and cross-sectional studies frequently referenced, and required a surgical
22 diagnosis for inclusion. We also have collected standardized³², validated, detailed information

1 regarding self-reported and clinically evaluated symptoms across a variety of pain types,
2 locations, and patterns. Study limitations should also be acknowledged. The analytic group
3 includes women who presented primarily with pain symptoms; this cohort is undersampled for
4 women presenting with infertility, ASRM Stage III/IV disease, or deep infiltrating
5 endometriosis.⁶ This selection bias may have led to our findings of similar clinical
6 symptomatology between the two groups. Participants in our cohort were enrolled from BCH,
7 BWH, and the surrounding communities; our patient population and clinical practices may not
8 be generalizable to patients not presenting to a tertiary care center, to other geographic areas,
9 nor to patients from different racial and ethnic or economic backgrounds. However, both age
10 groups were recruited from the same geographic and demographic catchment population,
11 making the comparison between these two age groups internally valid. Additionally, we
12 designated those patients who were diagnosed by age 18 years as “adolescents”. Based upon
13 this determination, the window of time within which one could first experience symptoms and
14 achieve a surgical diagnosis is by definition truncated, compared to the adults who could not be
15 diagnosed before age 18 until into their 40s. Our cohort of adult women was relatively young,
16 with a median age of 24 years; a cohort of adult women with an older median age may
17 demonstrate a greater difference in symptoms compared to adolescents. Despite this fact,
18 older adult women might have greater recall bias when reporting time-dependent variables
19 such as age at onset of dysmenorrhea or length of time with abdominal/pelvic pain compared
20 to adolescents.

21

1 In summary, our case-specific baseline analysis of our large, prospective cohort study has
2 demonstrated that adolescents diagnosed with surgically-confirmed endometriosis have similar
3 patterns of pain as do women diagnosed as adults. Patients commonly present with hormone-
4 resistant acyclic pain, rather than the stereotypical menstrual-cycle related pain reported in
5 textbooks. Nausea accompanying pain was extremely common, particularly among adolescents.
6 Interference with school or work, daily activities, exercise, and sleep is common, as are
7 associated gastroenterological symptoms. Pediatricians and gynecologists should be aware of
8 these important and common symptoms to avoid unnecessary diagnostic delays, and include
9 endometriosis in the differential diagnosis for both teens and adults experiencing such pain. A
10 more complete understanding of the presentation of endometriosis will enable clinicians to
11 improve care and treatment for these young women with chronic pain.

14 **Acknowledgements**

15 Supported by the J. Willard and Alice S. Marriott Foundation and the Division of Adolescent and
16 Young Adult Medicine at Boston Children's Hospital. The authors thank our patients and their
17 families, who made this research possible. Data collection was facilitated by and conducted in
18 compliance with the World Endometriosis Research Foundation Endometriosis Phenome and
19 Biobanking Harmonization Project (WERF EPHeCT).

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Table 1. Demographics, anthropometrics, and menstrual history of participants with surgically-confirmed endometriosis, stratified by age at time of surgical diagnosis (n=402)

	<i>Adolescents at diagnosis (n=295)</i>	<i>Adults at diagnosis (n=107)</i>
Age at enrollment, y		
Median (min-max)	17 (12 - 46)	24 (17 - 49)
Race		
White	260 (88.1%)	96 (89.7%)
Black	6 (2.0%)	5 (4.7%)
Other/Unknown	29 (9.8%)	6 (5.6%)
Ethnicity		
Non-Hispanic	270 (94.1%)	95 (90.5%)
Hispanic	17 (5.9%)	10 (9.5%)
In school at study enrollment		
No	43 (14.6%)	66 (61.7%)
Yes	252 (85.4%)	41 (38.3%)
Height, cm		
Median (min-max)	162.6 (130-191)	165.1 (142-180)
Weight, kg		
Median (min-max)	61.2 (43-133)	63.5 (43-110)
BMI, kg/m ²		
Median (min-max)	23.0 (16-45)	23.5 (18-43)
BMI category		
Underweight	2 (0.7%)	2 (1.9%)
Normal weight	190 (65.3%)	65 (61.3%)
Overweight	74 (25.4%)	22 (20.8%)
Obese	25 (8.6%)	17 (16.0%)
Age at menarche, y		
Median (min-max)	12.0 (8-15)	12.0 (8-15)
Early menarche, <11 y	58 (19.7%)	11 (10.3%)
Typical menarche, 11-14 y	230 (78.0%)	89 (83.2%)
Delayed menarche, >14 y	7 (2.4%)	7 (6.5%)
Ever pregnant		
No	282 (95.9%)	88 (89.8%)
Yes	12 (4.1%)	10 (10.2%)

BMI: body mass index; BMI categories were defined using World Health Organization criteria for participants ≥ 20 years old, and using age-specific Center for Disease Control BMI z-scores for those <20 years old.

Table 2: Pathways to surgical diagnosis of endometriosis for females diagnosed during adolescence (age ≤ 18 years) and during adulthood (age >18 years)

	Adolescents at diagnosis (n=270*)	Adults at diagnosis (n=101*)	p-value†
Symptoms prompting the diagnosis of endometriosis			
Pain	259 (95.9%)	95 (94.1%)	0.85
Infertility	1 (0.4%)	4 (4.0%)	0.02
Age at first symptoms, y			
Median (min – max)	13 (8 - 18)	16 (10 - 36)	<0.0001
Age when first saw any clinician about symptoms, y‡			
Median (min – max)	14 (9 - 19)	20 (12 - 37)	<0.0001
Time between symptom onset and clinician visit, y‡			
Median (min – max)	1.0 (0 - 7)	1.0 (0 - 17)	0.007
0 years	69 (41.1%)	27 (34.6%)	<0.0001
≤ 1 year	41 (24.4%)	15 (19.2%)	
>1 to 3 years	45 (26.8%)	12 (15.4%)	
>3 years	13 (7.7%)	24 (30.8%)	
Time between symptom onset and surgical diagnosis, y			
Median (min – max)	2.0 (0 - 7)	5.0 (0 - 26)	<0.0001
0 years	37 (14.0%)	8 (8.0%)	<0.0001
≤ 1 year	66 (25.0%)	8 (8.0%)	
>1 to 3 years	86 (32.6%)	19 (18.0%)	
>3 years	75 (28.4%)	65 (65.0%)	
Age surgically diagnosed with endometriosis, y			
Median (min – max)	16 (9 – 18)	22 (19 - 46)	<0.0001
Number of clinicians seen for symptoms before surgical diagnosis of endometriosis			
Median (min – max)	2.0 (0 – 20)	2.5 (0 – 25)	0.37

*31 participants who completed the questionnaire before their surgical diagnosis did not answer questions regarding diagnosis and symptom onset and are excluded from this table.

†2-sided p-values from Chi-square or Fisher's exact tests for categorical variables and from Wilcoxon rank sum tests for continuous variables

‡ 124 participants completed the earliest version of the questionnaire (participants enrolled between 11/2012 and 6/2013) where age when first saw clinician about symptoms was not queried.

Table 3. Dysmenorrhea and general pelvic pain among females with endometriosis diagnosed during adolescence (age ≤ 18y) or during adulthood (age >18y)

	Adolescents at diagnosis N=295	Adults at diagnosis N=107	p-value*
MENSTRUAL PAIN			
Do you experience pain with periods?			
No pain	3 (1.0%)	2 (1.9%)	0.52
Mild cramps (medication seldom needed)	20 (6.8%)	5 (4.7%)	
Moderate cramps (medication usually needed)	86 (29.2%)	26 (24.3%)	
Severe cramps (medication and bed rest needed)	186 (63.1%)	74 (69.2%)	
When did you start having pain with your periods?			
With my very first period	144 (49.7%)	35 (34.0%)	0.002
Within 2 years of my first period	111 (38.3%)	42 (40.8%)	
More than 2 years after my first period	35 (12.1%)	26 (25.2%)	
How long has it been since your last period?			
≤3 months	159 (57.8%)	62 (61.4%)	0.49
4-6 months	34 (12.4%)	13 (12.9%)	
7-12 months	20 (7.3%)	3 (3.0%)	
>12 months	62 (22.5%)	23 (22.8%)	
During the time in life when menstrual pain was the worst...			
Did you take any medication for the pain? †			
No	8 (5.7%)	3 (5.0%)	0.99
Yes	133 (94.3%)	57 (95.0%)	
Did you take prescription pain-killers? †			
No	98 (69.5%)	41 (68.3%)	0.87
Yes	43 (30.5%)	19 (31.7%)	
Did you take over-the-counter pain-killers? †			
No	41 (29.1%)	17 (28.3%)	0.92
Yes	100 (70.9%)	43 (71.7%)	
Did you take hormonal medication, but the pain did not get better? †			
No	88 (62.4%)	41 (68.3%)	0.42
Yes	53 (37.6%)	19 (31.7%)	
Did you take hormonal medication, and the pain got at least somewhat better? †			
No	115 (81.6%)	52 (86.7%)	0.38
Yes	26 (18.4%)	8 (13.3%)	
ACYCLIC PELVIC PAIN			
Did you ever experience general pelvic pain?			
No	101 (34.2%)	25 (23.4%)	0.04
Yes	194 (65.8%)	82 (76.6%)	
How long did this pelvic pain last?			
Minutes	20 (10.5%)	13 (16.0%)	0.18
Up to 1 hour	29 (15.3%)	8 (9.9%)	
Hours	64 (34.2%)	21 (25.9%)	
Days	74 (40.0%)	39 (48.1%)	
How difficult did the pain make it to participate in school/work? †			

	Adolescents at diagnosis <i>N=295</i>	Adults at diagnosis <i>N=107</i>	p-value*
Median (min-max)	7.0 (0-10)	7.0 (0-10)	0.95
How difficult did the pain make it to participate in recreational/social activities? †			
Median (min-max)	7.0 (0-10)	7.0 (0-10)	0.99
How severe was the pain in the last 1-3 months? †			
Median (min-max)	8.0 (0-10)	8.0 (0-10)	0.75
Did you experience nausea with your pain?			
No	57 (30.5%)	40 (48.8%)	0.004
Yes	130 (69.5%)	42 (51.2%)	
Did you experience vomiting with your pain?			
No	138 (75.4%)	66 (83.5%)	0.15
Yes	45 (24.6%)	13 (16.5%)	
<i>During the time in life when the general pelvic pain was the worst...</i>			
Did you take any medication for the pain? †			
No	13 (14.3%)	5 (10.9%)	0.58
Yes	78 (85.7%)	41 (89.1%)	
Did you take prescription pain-killers? †			
No	58 (63.7%)	33 (71.7%)	0.35
Yes	33 (36.3%)	13 (28.3%)	
Did you take over-the-counter pain-killers? †			
No	28 (30.8%)	13 (28.3%)	0.76
Yes	63 (69.2%)	33 (71.4%)	
Did you take hormonal medication, but the pain did not get better? †			
No	55 (60.4%)	34 (73.9%)	0.12
Yes	36 (39.6%)	12 (26.1%)	
Did you take hormonal medication, and the pain got at least somewhat better? †			
No	82 (90.1%)	40 (87.0%)	0.58
Yes	9 (9.9%)	6 (13.0%)	
<i>If you had pelvic pain in the last 3 months, to what extent did the general pelvic pain interfere with...</i>			
Work or school? †			
Not at all	10 (13.0%)	9 (23.7%)	0.01
Slightly	20 (26.0%)	6 (15.8%)	
Moderately	12 (15.6%)	7 (18.4%)	
Quite a bit	25 (32.5%)	4 (10.5%)	
Extremely	10 (13.0%)	12 (31.6%)	
Daily activities at home? †			
Not at all	8 (10.3%)	9 (22.5%)	0.07
Slightly	20 (25.6%)	5 (12.5%)	
Moderately	21 (26.9%)	8 (20.0%)	
Quite a bit	20 (25.6%)	8 (20.0%)	
Extremely	9 (11.5%)	10 (25.0%)	
Sleep? †			
Not at all	18 (23.4%)	4 (10.0%)	0.41
Slightly	15 (19.5%)	11 (27.5%)	

	Adolescents at diagnosis <i>N=295</i>	Adults at diagnosis <i>N=107</i>	p-value*
Moderately	16 (20.8%)	11 (27.5%)	
Quite a bit	16 (20.8%)	7 (17.5%)	
Extremely	12 (15.6%)	7 (17.5%)	
Exercise? †			
Not at all	7 (9.3%)	3 (8.3%)	0.09
Slightly	16 (21.3%)	12 (33.3%)	
Moderately	17 (22.7%)	5 (13.9%)	
Quite a bit	19 (25.3%)	3 (8.3%)	
Extremely	16 (21.3%)	13 (36.1%)	
Social activities? †			
Not at all	8 (10.3%)	6 (15.8%)	0.18
Slightly	20 (25.6%)	11 (28.9%)	
Moderately	17 (21.8%)	3 (7.9%)	
Quite a bit	22 (28.2%)	8 (21.1%)	
Extremely	11 (14.1%)	10 (26.3%)	

*2-sided p-values from Chi-square or Fisher's exact tests for categorical variables and from Wilcoxon rank sum tests for severity ratings.

†These questions were only asked on the final version of the questionnaire implemented January 2014.

‡Rated on a scale ranging from 0=no difficulty to 10=extreme difficulty.

Table 4. Urinary and bowel symptoms associated with menstrual pain and general pelvic pain in females with endometriosis diagnosed during adolescence (age \leq 18y) or during adulthood (age $>$ 18y)

	Pelvic pain with periods			General pelvic pain		
	Adolescents at diagnosis (n=82)	Adults at diagnosis (n=35)	p-value*	Adolescents at diagnosis (n=78)	Adults at diagnosis (n=40)	p-value*
<i>Urinary symptoms among those with pain in the past 3 months†</i>						
Urinated more frequently than usual						
Never/rarely	23 (28.0%)	6 (17.1%)	0.05	32 (41.6%)	12 (30.0%)	0.35
Sometimes	33 (40.2%)	9 (25.7%)		24 (31.2%)	11 (27.5%)	
Often	15 (18.3%)	8 (22.9%)		15 (19.5%)	10 (25.0%)	
Most of the time	5 (6.1%)	8 (22.9%)		3 (3.9%)	5 (12.5%)	
Always	6 (7.3%)	4 (11.4%)		3 (3.9%)	2 (5.0%)	
Pain with urination						
Never/rarely	41 (50.0%)	17 (50.0%)	0.38	49 (62.8%)	24 (60.0%)	0.56
Sometimes	25 (30.5%)	7 (20.6%)		18 (23.1%)	9 (22.5%)	
Often	6 (7.3%)	4 (11.8%)		6 (7.7%)	4 (10.0%)	
Most of the time	3 (3.7%)	4 (11.8%)		2 (2.6%)	3 (7.5%)	
Always	7 (8.5%)	2 (5.9%)		3 (3.8%)	0 (0%)	
<i>Bowel symptoms among those with pain in the past 3 months†</i>						
Pain got better or stopped after bowel movement						
Never/rarely	42 (51.9%)	16 (47.1%)	0.16	39 (50.0%)	14 (36.8%)	0.38
Sometimes	24 (29.6%)	12 (35.3%)		23 (29.5%)	17 (44.7%)	
Often	11 (13.6%)	1 (2.9%)		6 (7.7%)	1 (2.6%)	
Most of the time	3 (3.7%)	4 (11.8%)		7 (9.0%)	5 (13.2%)	
Always	1 (1.2%)	1 (2.9%)		3 (3.8%)	1 (2.6%)	
Pain got worse after bowel movement						
Never/rarely	48 (58.5%)	18 (52.9%)	0.88	48 (62.3%)	24 (61.5%)	0.94
Sometimes	22 (26.8%)	10 (29.4%)		21 (27.3%)	10 (25.6%)	

	Pelvic pain with periods			General pelvic pain		
	Adolescents at diagnosis (n=82)	Adults at diagnosis (n=35)	p-value*	Adolescents at diagnosis (n=78)	Adults at diagnosis (n=40)	p-value*
Often	6 (7.3%)	2 (5.9%)		3 (3.9%)	2 (5.1%)	
Most of the time	2 (2.4%)	1 (2.9%)		2 (2.6%)	2 (5.1%)	
Always	4 (4.9%)	3 (8.8%)		3 (3.9%)	1 (2.6%)	
More frequent bowel movements when the pain started						
Never/rarely	38 (46.9%)	18 (52.9%)	0.74	44 (57.1%)	22 (55.0%)	0.35
Sometimes	15 (18.5%)	4 (11.8%)		19 (24.7%)	6 (15.0%)	
Often	10 (12.3%)	4 (11.8%)		5 (6.5%)	7 (17.5%)	
Most of the time	11 (13.6%)	3 (8.8%)		6 (7.8%)	3 (7.5%)	
Always	7 (8.6%)	5 (14.7%)		3 (3.9%)	2 (5.0%)	
Less frequent bowel movements when the pain started						
Never/rarely	46 (56.8%)	22 (64.7%)	0.62	42 (53.8%)	26 (66.7%)	0.52
Sometimes	18 (22.2%)	5 (14.7%)		18 (23.1%)	9 (23.1%)	
Often	9 (11.1%)	2 (5.9%)		12 (15.4%)	4 (10.3%)	
Most of the time	5 (6.2%)	2 (5.9%)		3 (3.8%)	0 (0%)	
Always	3 (3.7%)	3 (8.8%)		3 (3.8%)	0 (0%)	
Stools looser when the pain started						
Never/rarely	34 (42.0%)	16 (47.1%)	0.19	40 (51.3%)	14 (35.0%)	0.34
Sometimes	22 (27.2%)	7 (20.6%)		21 (26.9%)	15 (37.5%)	
Often	11 (13.6%)	1 (2.9%)		12 (16.4%)	6 (15.0%)	
Most of the time	10 (12.3%)	9 (26.5%)		3 (3.8%)	4 (10.0%)	
Always	4 (4.9%)	1 (2.9%)		2 (2.6%)	1 (2.5%)	
Stools harder when the pain started						
Never/rarely	48 (59.3%)	21 (63.6%)	0.34	43 (55.8%)	22 (55.0%)	0.84
Sometimes	24 (29.6%)	7 (21.2%)		19 (24.7%)	13 (32.5%)	
Often	2 (2.5%)	2 (6.1%)		12 (15.6%)	5 (12.5%)	
Most of the time	4 (4.9%)	0 (0%)		2 (2.6%)	0 (0%)	
Always	3 (3.7%)	3 (9.1%)		1 (1.3%)	0 (0%)	

*2-sided p-values from Fisher's exact tests

†These questions were only asked on the final version of the questionnaire implemented January 2014.