GYNECOLOGY

Spectrum of symptoms in women diagnosed with endometriosis during adolescence vs adulthood

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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 whether the symptoms that are experienced by adolescents differ from adults. Better understanding may shorten the often lengthy delay in diagnosis.

OBJECTIVE: The purpose of the study was to further elucidate the symptom presentation of adolescents as compared with adults to determine whether differences existed, based on 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 2 tertiary care centers and the surrounding communities. Participants included adolescents (diagnosed at $\leq$18 years old; n=295) and adults (diagnosed at $>$18 years old; 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 standard clinical questionnaire that included items regarding menstrual history, associated symptoms, and pain. Chi-square or Fisher's exact tests were applied to categoric data; Wilcoxon rank sum tests were applied to continuous data.

RESULTS: Most participants (90%) experienced moderate-severe menstrual pain. On average, 3 doctors were seen before diagnosis, regardless of age at presentation (range, 0-25 years). Time from symptoms to diagnosis averaged 2 years for adolescents and 5 years for adults ($P<.001$). More adolescents (50%) than adults (33%) reported pain starting at menarche ($P=.002$) and nausea accompanying pain (69% vs 53%; $P=.01$). Noncyclic, general pelvic pain was prevalent. One-half of the participants reported relief of their general pelvic pain after a bowel movement. Pain interfered with work/school, daily activities, exercise, and sleep to a moderate-extreme degree; difficulties were similar by age at diagnosis.

CONCLUSIONS: Pelvic pain was severe and noncyclic and negatively impacted quality of life. At our tertiary care centers, symptoms of endometriosis did not differ between women surgically diagnosed during adolescence compared with those diagnosed as adults. Adolescents had more nausea and symptom onset at menarche. Multi-year delays in diagnosis were common. Clinicians should be aware of these alternate symptom patterns and include endometriosis in their differential diagnosis for both adolescent and young adult women who experience noncyclic pelvic pain and nausea.

Key words: adolescents, diagnosis, endometriosis, pelvic pain

Endometriosis is an estrogen-dependent chronic inflammatory condition that affects 6−10% of women during the reproductive years.[1] Although prevalence rates in the general population are unknown because of the need for laparoscopic diagnosis, 50−60% of women with pelvic pain and approximately 50% of women with infertility experience endometriosis.[2] Nearly two-thirds of adolescents with chronic acyclic pelvic pain have laparoscopic evidence of endometriosis.[3]

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

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

Materials and Methods

This cross-sectional study was set within an ongoing longitudinal cohort study (The Women's Health Study: from Adolescence to Adulthood) that enrolled premenopausal female patients aged $\geq$7 years with and without endometriosis. This joint project between Boston Children's Hospital (BCH) and Brigham and Women's Hospital (BWH) has the overall aim of investigating endometriosis across the lifespan. Participants are recruited from the 2 tertiary care centers and from the surrounding community. They complete an extensive baseline questionnaire and annual follow-up questionnaires. The initial version of our baseline questionnaire included questions on medical history, lifestyle, medication, anthropometric and environmental exposures, symptom experience, and treatments. In January 2014, we adopted an expanded version of the World

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Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonization Project standard clinical questionnaire.[14] Surveys are collected and managed with the use of REDCap electronic data capture tools hosted at BWH.[15] The study was approved by the BCH Institutional Review Board on behalf of both BCH and BWH. Informed consent was obtained, with parental consent/participant assent for girls <18 years old at enrollment.

The endometriosis symptoms included in our analysis were self-reported pain and details of acyclic (not associated with menses) and/or cyclic (associated with menses) pain of the abdomen and/or pelvis over the lifetime and at varying time points over the last 12 months,[14] which included age of pain onset, impact of pain, and care-seeking behaviors. Pain severity was graded on an 11-point numeric rating scale anchored with 0=no pain and 10=worst imaginable pain. Participants reported the severity of typical cramps with menses (dysmenorrhea), age of dysmenorrhea onset, and associated physician visits and diagnoses. Urinary or bowel movement habit changes during menses were characterized, which included gastrointestinal symptoms experienced over the preceding year, activities that worsened or helped pain, and medications used to relieve pain.

Additional exposures included participants' demographic data and reproductive history. Body mass index (BMI) was calculated from self-reported weight and height. 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) per World Health Organization criteria.[16] For adolescents, the age-and gender-specific BMI Z-score was calculated and categorized as underweight (Z-score, ≤ −2), normal-weight (Z-score, > −2 to <1), overweight (Z-score, 1–2), or obese (Z-score, >2).[17] All self-reports of a diagnosis of endometriosis were verified by review of the participants' operative reports stating that endometriosis had been visualized.

Chi-square or Fisher's exact tests were applied to categoric data. Continuous data were compared by Wilcoxon rank sum test. All hypothesis tests were 2-sided. Data were analyzed with SAS statistical software (version 9.4; SAS Institute Inc, Cary, NC).

Results

From November 2012 to March 2016, we enrolled 984 participants. Participants were excluded if they never began the baseline questionnaire (n=225) or if they left >20% of it blank after beginning (n=68). The sample then included 268 control subjects (no diagnosis of endometriosis) and 423 cases (female participants who self-reported a diagnosis of endometriosis), among whom 10 were excluded subsequently because they did not have an operative report that confirmed endometriosis diagnosis. We restricted the sample to cases and excluded those who omitted items on cyclic/general pelvic pain (n=11), for a final sample of 402 endometriosis cases. Among these participants, 202 completed the first version of the questionnaire, and 200 completed the expanded World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonization Project standard clinical questionnaire. Participants ranged in age from 12–49 years old at enrollment (median age, 19 years; Table 1). We divided the cohort based on age at diagnosis of endometriosis. "Adolescents" were defined as participants ≤18 years old at the time of surgical diagnosis; they comprised 73% (295/402) of the total sample. "Adults" were defined as participants >18 years old at surgical diagnosis. Most participants self-identified as white (88%) and non-Hispanic (93%). Most adolescents had menarche from 11–14 years old. Twelve adolescents and 10 adults were gravid before enrollment; 14 of the participants (3%) reported having tried >6 months to become pregnant without success.

Diagnosis

Participants who had been diagnosed surgically with endometriosis during adolescence had symptoms start at 13 years old on average (range, 8–18 years old). These adolescents first saw a clinician because of pain at 14 years old (9-19; median [min-max]) and received a diagnosis at 16 years old (9-18). Women diagnosed during adulthood recalled symptoms beginning at 16 years old(10-36), first saw a clinician at 20 years old (12-37), and received a surgical diagnosis at 22 years old (19-46). On average, adolescents waited 1 year (0-7) between symptom onset and first seeing any clinician for complaints of pain and 2 years (0-7) between symptom onset and diagnosis of endometriosis. For women diagnosed during adulthood, delays were significantly longer (Table 2). Adults waited almost 3 times longer between first seeing a clinician and achieving a surgical diagnosis (3.0±4.0 vs 1.2±1.4 years; P=.001). Adolescents saw a median of 2 (0-20) clinicians before surgical diagnosis; adults saw a median of 2.5 (0-25) clinicians. No significant differences were found in age, weight status, age at menarche, or parity between women who saw 1–2, 3–4, or >5 clinicians. Women who saw >5 clinicians before diagnosis were more likely to report that they "tried to get pregnant for at least 6 months without becoming pregnant" (9.4%) than women who saw 1–2 clinicians (4.5%) or 3–4 clinicians (1.0%; P=.04; data not shown).

Menstrual symptoms

Most participants (93%) experienced moderate pain (pain usually requiring medication) to severe pain (pain requiring medications and bed rest) during menses over the lifetime; there was no appreciable difference between groups (P=.52; Table 3). One-half of those diagnosed as adolescents and one-third of adults reported pain starting with their very first period (P=.002). More adults (25%) than adolescents (12%) noted that pain began >2 years after menarche. There were no differences in birthweight, race, ethnicity, or premenarchal somatotype between those who experienced pain proximal to menarche or those without pain until >2 years after (data not shown). Both groups were equally likely to have taken