

Epidemiology of endometriosis in UK adolescents

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ABSTRACT

Background and Purpose: To estimate the incidence of clinically diagnosed and surgically confirmed endometriosis in UK adolescents (age 10-17) from 2006-2016.

Methods: This retrospective cohort study included adolescents enrolled in the Clinical Practice Research Datalink (CPRD GOLD) during the study period. Additionally, hospital episode statistics (HES) data were linked to CPRD GOLD for eligible patients and provided surgical confirmation of endometriosis. READ and International Classification of Disease (ICD-10)/Office of Population Censuses and Surveys (OPCS) codes were used to identify cases of endometriosis in CPRD GOLD and HES, respectively. Cases of clinically diagnosed endometriosis were considered surgically confirmed if a procedure during which endometriosis could be visualized occurred within ± 1 year of the date that endometriosis codes were first entered in the patient's medical record.

Results: The most commonly reported symptoms, recorded in adolescents' medical records, in the sample of 15 to 17-year-old female adolescents were abdominal pain (3.7%) and dysmenorrhea (2.3%). The incidence per 100,000 women-years of clinically diagnosed endometriosis, in adolescents age 15-17 years was 13.65 (95% CI: 11.42-16.19), with more of the cases occurring (93%) at this range of age. The incidence of surgically confirmed endometriosis in adolescents age 15-17 years was 8.09 (95% CI: 5.86-10.90), with 98% of cases occurring in the older age group 15-17 years of age.

Conclusions: Endometriosis was infrequently diagnosed in this population-based sample of adolescents age 10-17 years in the UK and diagnosis mostly occurred in those 15-17 years or older. In accordance with clinical guidelines, there was limited surgical confirmation of endometriosis in this adolescent population. Increased diagnosis of suspected endometriosis in adolescents can lead to treatment and potentially better outcomes for young women experiencing this disease.

KEYWORDS

Endometriosis, epidemiology, diagnosis, incidence.

Introduction

Endometriosis is an inflammatory, chronic, potentially progressive disease defined by the presence of endometrial glands and stroma outside of the uterus. The pathogenesis is unknown, but theories include retrograde menstruation, altered immunity, metaplasia of the germinal epithelium, and metastatic spread^[1,2]. Endometriosis is substantially less prevalent in adolescents than adults. The incidence and prevalence of endometriosis in the adult is well-established from population-based studies^[3-13]. On the other hand, the demography in the adolescent population is less clear and the estimates are based on smaller numbers. A pattern of age-related disease incidence can be partially explained by an observed delay between development of symptoms and diagnosis of endometriosis of approximately 7-12 years^[14].

Adult endometriosis key symptoms include cyclic (severe dysmenorrhea) pelvic pain, non-cyclic pelvic pain, and infertility that impairs quality of life. In adolescents, symptoms may include cyclic and/or non-cyclic pain that poorly responds to medical therapy and irregular menstrual bleeding^[15].

Article history

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The differential diagnosis of endometriosis in adolescents is challenging, with overlapping symptoms with other conditions (e.g., primary dysmenorrhea, premenstrual syndrome, congenital obstructive Mullerian malformation, pelvic inflammatory disease, etc.)^[16]. Endometriosis is diagnosed through clinical examination. Imaging such as transvaginal ultrasound or MRI are described to support diagnosis of more advanced disease (endometrioma and deep infiltrating condition). Surgical procedures (laparoscopy or laparotomy) are used to confirm the condition and treat the macroscopic disease^[17]. In women with signs and symptoms of endometriosis, medical treatment may

be started before considering an invasive procedure (e.g. laparotomy or laparoscopy). If signs of advanced disease are not present in physical examination and imaging, physicians may choose not to perform a diagnostic laparoscopy, especially in adolescents and young adults ^[17].

Endometriosis is likely underdiagnosed in adolescents based on potential reluctance to perform invasive surgical procedures. Given an average age of menarche of 12 years, adolescents are likely to have reached adulthood by the time of their final diagnosis of endometriosis with a surgical procedure. Population based samples are useful for further understanding diagnostic patterns and potential underdiagnosis of this condition in adolescents. A recent publication by Soriano *et al.* ^[4] examined the incidence of clinically diagnosed endometriosis (not requiring evidence of surgical confirmation) in UK women, including an adolescent age group 12-19 years of age, using The Health Improvement Network (THIN) data. The current study will build upon the findings from Soriano *et al.* and will extend these findings to further understand the use of surgery for endometriosis diagnosis within a population-based sample of UK adolescents. The primary objective of this study was to estimate the incidence of surgically confirmed endometriosis and hospital data were linked to general practice data to identify eligible patients. We hypothesize, that in accordance with clinical guidelines, the use of surgical procedures in the diagnosis of endometriosis will be limited within the adolescent population.

Methods

Female adolescents 10-17 years of age enrolled in The Clinical Practice Research Datalink (CPRD GOLD) during the study period of 2006-2016, with a READ code (medical diagnosis code) for endometriosis, were selected from the CPRD GOLD database. The quality of data for each medical practice included in the study sample was assessed and participants were required to have ≥ 1 year of up-to-research-standard data available before the start of the study period. CPRD GOLD collects de-identified patient data from a network of general practitioners (GP) across the UK. Primary care data can be linked to other health related data providing a longitudinal, representative, UK population health database ^[18]. This health database contains longitudinal primary care records for approximately 13.5 million patients from 601 general practices across the UK (covering 7% of the UK population). The CPRD GOLD contains patient-level information on demographics, lifestyle data, clinical diagnoses, prescriptions and preventive care and has been found to be representative of the UK population with respect to gender, age and ethnic group ^[19].

Merck & Co., Inc. holds a multi-study annual license to CPRD GOLD data for research purposes. Quality of CPRD data is driven by the Quality and Outcomes Framework in the UK, and data are also monitored by CPRD internal processes. For more than 30 years, research using CPRD data and services has informed clinical guidance and best practice, resulting in over 2,500 peer-reviewed publications investigating drug safety, use of medicines, effectiveness of health policy, health

care delivery and disease risk factors. The study protocol was approved by CPRD's Independent Scientific Advisory Committee (ISAC), protocol number 18_321R. The data used in this study were de-identified and compliant with privacy laws. Study investigators did not have access to patient identifiable information.

Soriano *et al.* ^[4] using medical records from THIN and Hospital Episode Statistics (HES) database evaluated endometriosis incidence in the UK population utilizing a validated list of READ codes. Cases were validated by manual review of free-text comments in medical records and physician questionnaires. Soriano found a positive predictive value of 94% for the endometriosis READ codes included in their study, with 70% of women undergoing a diagnostic procedure in the year before their endometriosis diagnosis. In the current study, the same list of READ codes was used to identify patients in the CPRD GOLD with the exclusion of 3 codes that were felt by the study team physician to reflect adenomyosis rather than endometriosis; adolescents with a READ code for adenomyosis (and no READ codes for endometriosis) were excluded from the primary analyses and included in a sensitivity analysis to examine the potential effects of this exclusion.

Surgically confirmed endometriosis

Linkage of CPRD GOLD data with other datasets is available for English and UK practices that have consented to participate. CPRD linkage data, referred to as CPRD GOLD, includes patients from 416 of the 601 practices contributing data to CPRD ^[18]. In the current study, for the primary objective, for women with a READ code for endometriosis in CPRD GOLD, who also have linkage information for HES, the presence of codes for surgical procedures during which endometriosis could be visualized, within ± 1 year of the recording of their endometriosis READ code in their medical record, in HES and in CPRD GOLD was determined. A sensitivity analysis was conducted to estimate the percentage of adolescents with a surgical procedure during which endometriosis could be visualized that also had a diagnosis for endometriosis associated with the procedure. Additionally, women without an endometriosis READ code in CPRD GOLD and with a code within HES for a procedure during which endometriosis could be visualized and a corresponding discharge diagnosis of endometriosis were included as cases of surgically confirmed endometriosis. Histological evidence was not required for cases to be considered surgically confirmed.

Clinically diagnosed endometriosis

For the secondary objective of estimating the incidence of clinically diagnosed endometriosis (including cases with and without surgical confirmation) the same list of READ codes for the primary objective was used to identify endometriosis cases. Women with a READ code for endometriosis in CPRD GOLD without additional evidence of surgical confirmation were added to the cases already identified for the primary objective.

Statistical analyses

Selected characteristics of female adolescents 15-17 years of age enrolled in CPRD were described in 2011 (the mid-point

of the study period). For the calculation of incidence rates, participants were required to have no recorded diagnoses of endometriosis in their medical record before the start of the study period. Incidence was defined as all participants with a first endometriosis diagnostic code in each calendar year from January 1st, 2006 to December 31st, 2016.

The yearly incidence rate was calculated by dividing the number of individuals with endometriosis newly diagnosed in a calendar year, by the number of person-years of follow-up of all eligible female adolescent patients 10-17 years contributing to the CPRD GOLD for each calendar year. The overall incidence rate was calculated as the total number of new cases per age group over the study period divided by the total person-time at risk in each age group. Age at the time of diagnosis was used to classify incident endometriosis cases by age group. Follow-up for each study participant began on January 1st, 2006 and ended when the participant received an endometriosis diagnosis, was censored due to death or disenrollment, or the end of the study period, whichever event occurred first. Confidence intervals (95%) were calculated for all incidence and percentages using the exact method.

Results

On average, there were 52,644 and 94,981 female adolescents age 15-17 annually in the linked CPRD GOLD+HES data and the CPRD GOLD data, respectively, with ≥ 1 year of up-to-research-standard data before the start of the study period. The majority of females 15-17 years of age enrolled in CPRD GOLD attended general practice offices located in England (75.7%). The most commonly reported symptoms, recorded in adolescents' medical records, in the sample of 15-17-year-old female adolescents were abdominal pain (3.7%) and dysmenorrhea (2.3%) (Table 1).

Endometriosis incidence was limited to the 15-17 year age group given the small number of cases identified in the 10-14 year age group and CPRD GOLD's privacy reporting guidelines (cells with < 5 observations must be suppressed), regardless of whether the cases were surgically confirmed or

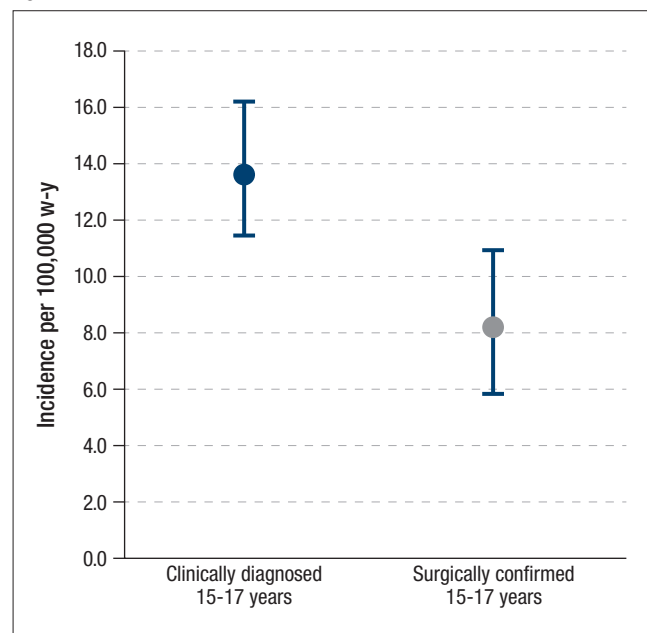
Table 1 Selected characteristics of female adolescents 15-17 years of age enrolled in CPRD GOLD in 2011.

N		89932
Age, n (%)	15	30234 (33.6)
	16	30010 (33.4)
	17	29688 (33.0)
Geographic location, n (%)	England	68092 (75.7)
	Scotland	9951 (11.1)
	Wales	8224 (9.1)
	Northern Ireland	3665 (4.1)
Symptoms and comorbidities, n (%)	Pelvic pain	168 (0.2)
	Abdominal pain	3367 (3.7)
	Dyspareunia	125 (0.1)
	Dysmenorrhoea (including primary dysmenorrhoea)	2084 (2.3)
	Premenstrual syndrome	130 (0.1)
	Irritable bowel syndrome	346 (0.4)

clinically diagnosed.

The incidence of surgically confirmed endometriosis per 100,000 women-years in UK adolescents 15-17 years was 8.09 (95% CI: 5.86-10.90) from 2006-2016 (Figure 1). Incidence of surgically confirmed endometriosis ranged from 10.03 (95% CI: 3.26-23.42) to 16.59 (95% CI: 7.16-32.68) over the study period for the years during which there were enough incident cases (> 5 cases) to calculate the incidence rate. Thirty-one of the incident surgically diagnosed cases (72%) had a code for endometriosis associated with their surgical procedure. The incidence of clinically diagnosed endometriosis per 100,000 women-years in UK adolescents 15-17 years of age was 13.65 (95% CI: 11.42-16.19) (Figure 1).

Figure 1 Incidence of Clinically Diagnosed and Surgically Confirmed Endometriosis per 100,000 Women-Years in Adolescents 15-17 years of Age, in the UK Based CPRD GOLD+HES, 2006-2016.



Incidence of clinically diagnosed endometriosis ranged from 5.23 (95% CI: 1.70-12.21) to 23.21 (95% CI: 13.97-36.24) over the study period for the years during which there were enough incident cases (> 5 cases) to calculate the incidence rate.

The inclusion of READ codes for adenomyosis increased the number of cases of clinically diagnosed endometriosis in the study population 15-17 years of age from 172 to 181 and did not identify any additional potential cases of surgically confirmed endometriosis.

Discussion

The incidence of endometriosis in the adolescent population has been reported in 7 studies^[3-7,10,13] identified in the published literature, however, the adolescent age group within these studies included young adults > 18 years as well as adolescents. Incidence estimates from these studies ranged from 13.0 - 210.0 per 100,000 women-years (Table 2). The current study specifically focused on adolescents < 18 years of age to fur-

Table 2 Comparison of adolescent and young adult endometriosis incidence rates across population-based studies in the published literature.

Author, year	Country in which study was conducted	Age range for adolescent age group	Incidence per 100,000 women-years
DiBello, 2020	UK	15 to 17	8.09 (95% CI: 5.86-10.90)**
Eisenberg, 2018	Israel	15 to 19	39.0
Soriano, 2017	UK	12 to 19	19.0
Morassuto, 2016	Italy	15 to 20	13.0**
Abbas, 2012	Germany	15 to 24	210.0
Glyfason, 2010	Iceland	15-19	20.0**
Leibson, 2004	US	15-24	113.0
Houston, 1987	US	15-19	69.7

**limited to surgically confirmed cases

ther understand the use of surgery in the diagnostic process for younger adolescents. Incidence estimates likely varied across these studies due to differing age ranges for the adolescent age group, varying case definitions (some studies required surgical confirmation of endometriosis while others did not), quality of the data sources used, varying medical practice across countries, and differences in study time periods.

Eisenberg *et al.*, Glyfason *et al.*, Abbas *et al.* and Morassutto *et al.*, utilized medical codes within electronic medical records, registries, and administrative databases to identify endometriosis cases. This methodology may not detect cases that have been diagnosed, but for which a corresponding medical code has not been entered into a patients' medical record. Leibson *et al.*, Houston *et al.*, and Soriano *et al.* utilized more comprehensive case definitions including review of the information within the notes section of patients' medical records, an assessment of false positive and false negative cases, and physician survey. The current study utilized the validated set of endometriosis medical codes for endometriosis from the study by Soriano *et al.*, demonstrated to have a positive predictive value of 94%. Soriano *et al.* estimated the incidence of clinically confirmed endometriosis using UK based THIN data and reported rates similar to those found in the current study utilizing CPRD GOLD+HES^[4]; the incidence rate of clinically confirmed endometriosis in adolescents 12-19 years reported by Soriano *et al.* was 0.19 per 1,000 women years, versus 0.18 (95% CI: 0.16-0.19) per 1,000 women-years, in the current study.

The incidence of endometriosis in adolescents 15-17 years, was found to be very low in this study in comparison with reported rates in adults. The incidence of endometriosis in adults reported from population-based studies ranges from 65.0 to 350.0 per 100,000^[3-13]. Based on the published literature, the incidence of endometriosis tends to peak between 30-44 years of age^[3-7,13]. These patterns of age-related disease incidence can be partially explained by an observed delay between symptom development and endometriosis diagnosis.

Additionally, as a definitive diagnosis of endometriosis requires surgery, which many physicians are reluctant to undertake in younger women, adolescents may be misdiagnosed and

under treated for years. In accordance with the low incidence of diagnosed endometriosis in our study, only 2.3% of adolescents had evidence of a primary dysmenorrhea diagnosis; the prevalence of primary dysmenorrhea has been reported in the literature to range between 16-93% in the adolescent population depending upon the population sampled with only 6% of adolescents reporting receipt of medical advice to help in managing their condition^[20]. There is evidence to suggest that endometriosis in adolescents may progress if left untreated^[14]. Furthermore, based on the clinical recommendations from the National Institute for Health and Care Excellence (NICE), physicians should consider referring young women (≤ 17 years) with suspected endometriosis to a pediatric and adolescent gynecology service or specialist endometriosis service^[21]. Increased diagnosis of suspected endometriosis in adolescents, even if the diagnosis is not definitively supported by surgical evidence, can lead to treatment and potentially better outcomes for young women experiencing this disease. Strengths of this study include the use of a population-based sample from a well-established epidemiological data source as well as a validated code list to identify endometriosis cases. Furthermore, this study adds important information to the published literature concerning the use of surgery in the endometriosis diagnostic process in the adolescent population. However, this study has some limitations that should be considered when interpreting the results. The primary objective is limited in its generalizability to English/UK practices that participate in CPRD GOLD/HES linkage. Therefore, the results from the primary objective may not be generalizable to the overall UK population.

Another potential limitation is that the CPRD GOLD is based on medical records from the practices of participating GP physicians. There is the possibility that adolescents are diagnosed with endometriosis by a specialist and this diagnosis would not be recorded within their GP record leading to an underestimate of prevalence and incidence of clinically diagnosed endometriosis. However, the expectation in the UK is that chronic conditions should be recorded in GP records. Finally, histological confirmation of endometriosis was not required in our study.

Conclusion

Endometriosis was infrequently diagnosed in this population-based sample of adolescents age 10-17 years in the UK and diagnosis mostly occurred in those ≥ 15 years. In accordance with clinical guidelines, there was limited surgical confirmation of endometriosis in this adolescent population. Increased diagnosis of suspected endometriosis in adolescents can lead to treatment and potentially better outcomes for young women experiencing this disease.

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