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ARTICLE

Adenomyosis diagnosis among adolescents and young women with dysmenorrhoea and heavy menstrual bleeding

BIOGRAPHY

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KEY MESSAGE

Adenomyosis may be diagnosed among teenagers and young women with heavy menstrual bleeding alone or in combination with dysmenorrhoea by a detailed ultrasound evaluation. The early identification of this condition allows appropriate treatment to be provided for the associated symptoms.

ABSTRACT

Research question: What is the prevalence of adenomyosis at ultrasonography among adolescents and young women reporting dysmenorrhoea and/or heavy menstrual bleeding (HMB)?

Design: This observational cohort study involved adolescents and young women referred for dysmenorrhoea and/or HMB to the Adolescent Medicine Unit at Careggi University Hospital, Italy. Patients with endometriosis and bleeding disorders were excluded. Transvaginal ultrasonography or transrectal sonography using a transvaginal probe was performed. The myometrium was described according to the Morphological Uterus Sonographic Assessment criteria. Details of baseline characteristics, clinical data and symptoms were collected. The presence of sonographic features of adenomyosis and the association between imaging findings and clinical symptoms were evaluated.

Results: The cohort included 95 patients aged between 13 and 25 years, referred for dysmenorrhoea (88.4%), HMB (23.2%) or both (13.7%). According to the MUSA criteria the sonographic diagnosis of adenomyosis was made in 27.4% of patients, with the diffuse type the most prevalent. Uterine wall asymmetry, hyperechoic intramyometrial islands, translesional vascularity and an interrupted junctional zone were the most common features. Patients with imaging findings of adenomyosis had significantly higher rates of HMB than those with a normal myometrial appearance (38.5% versus 17.4%, $P = 0.030$). In addition, the coexistence of dysmenorrhoea and HMB was significantly associated with adenomyosis (odds ratio 5.68, 95% confidence interval 1.65–19.5).

Conclusions: Adenomyosis may be diagnosed among teenagers and young women referred with dysmenorrhoea and/or HMB. The clinical presentation is relevant for the diagnosis, with HMB alone and HMB plus dysmenorrhoea significantly associated with the sonographic identification of adenomyosis.

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KEY WORDS
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Adolescence
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Heavy menstrual bleeding
Pelvic pain
Pelvic ultrasonography

INTRODUCTION

Adenomyosis is a uterine disorder characterized by the presence of endometrial stroma and glands in the myometrial tissue (*Vannuccini and Petraglia, 2019*; *Zhai et al., 2020*). For many years adenomyosis has been considered a disease of multiparous and peri-menopausal women, as the diagnosis has been based on hysterectomy specimens (*Parazzini et al., 2009*; *Vercellini et al., 1995*). However, thanks to the availability of advanced diagnostic imaging methods, the disease may be identified also in young and nulliparous patients (*Chapron et al., 2017*; *Naftalin et al., 2012*; *Pinzauti et al., 2015*). By using magnetic resonance imaging (MRI) or transvaginal ultrasonography (TVUS), diffuse or focal phenotypes may be identified, the most common symptoms being dysmenorrhoea, dyspareunia, heavy menstrual bleeding (HMB) and infertility (*Chapron et al., 2020*).

Based on the combination of imaging and clinical presentation, including both symptoms and history, the overall prevalence of adenomyosis ranges between 20% and 30%, increasing in prevalence with age and reaching a peak of 35% in women aged 40–49 years, even though the epidemiology of this condition is heterogeneous (*Upson and Missmer, 2020*). The morphology and symptomatology of the disease may be different over the reproductive years, resulting in pelvic pain being the main complaint among young women, given the relevant association with endometriosis (*Lazzeri et al., 2014*; *Perelló et al., 2017*), whereas HMB is more common among patients over 40 years old (*Isaacson and Loring, 2020*).

Recently, features of adenomyosis have been identified on TVUS in adolescents aged 12–20 years reporting dysmenorrhoea and other painful symptoms, even though it was associated with endometriosis in 44% of cases (*Exacoustos et al., 2022*). Similarly, a 46% prevalence of adenomyosis was found among young women between 14 and 24 years of age, with a relevant link with endometriosis, and dysmenorrhoea and dyspareunia as a clinical presentation (*Zannoni et al., 2020*). However, limited evidence is currently available on adenomyosis among adolescents in the absence of endometriosis. In addition, dysmenorrhoea is a common symptom among adolescents (*Smorgick and As-Sanie, 2018*); similarly, HMB is reported by one-third of teenagers aged between 16 and 18 years, interviewed using a questionnaire on bleeding symptoms (*Friberg et al., 2006*). A number of investigations may be requested to identify possible secondary causes of these symptoms, even though a proportion represent a primary condition or developmental disorder (*Ferries-Rowe et al., 2020*). Thus, the aim of the study was to evaluate the prevalence and imaging findings of adenomyosis among teenagers and young women aged less than 25 years and with dysmenorrhoea and/or HMB.

MATERIAL AND METHODS

An observational cohort study was conducted in a group of teenagers and young women (n = 103) aged 13–25 years consecutively referred to the Adolescent Medicine Unit between January 2021 and July 2022 with complaints of dysmenorrhoea and/or HMB. Only those in whom at least 2 years had elapsed since menarche were included. Patients already taking combined oral contraceptives or progestins at the time of the first consultation were not recruited for the study. Similarly, those with bleeding disorders, endometriosis, uterine/ovarian tumours or uterine anomalies were not included in the cohort.

The family and clinical history were collected, focusing also on the characteristics of the menstrual cycle (regularity, amount and duration of bleeding and whether HMB or iron deficiency anaemia [IDA] was present). The presence of dysmenorrhoea, dyspareunia, dyschezia and dysuria was also evaluated. Severity of gynaecological pain was defined according to visual analogue scale (VAS) scores: no pain (VAS ≤4), mild pain (VAS 5–6), moderate pain (VAS 6–7) and severe pain (VAS ≥8). The patients evaluated at the Adolescent Medicine Unit included those with at least moderate dysmenorrhoea who had been referred from primary care gynaecology services. Absenteeism from school and social activities, and non-responsiveness to non-steroidal anti-inflammatory drugs (NSAID) was considered a further criterion for severe dysmenorrhoea. HMB was defined as excessive menstrual blood loss that interferes with a woman's physical, social, emotional and/or material quality of life (*2021 exceptional surveillance of heavy menstrual bleeding*, *2021*). Excessive menstrual blood loss was defined as persistent heavy bleeding for longer than 7 days, flooding sensations, shedding of clots or a change of sanitary protection every 1–2 h. The Pictorial Bleeding Assessment Chart, after 3 months' observation, was used to objectively identify HMB when the score was above 100 (*Sanchez et al., 2012*).

TVUS was performed in sexually active patients, whereas a transrectal approach (transrectal sonography [TRS]) was proposed in those who were not sexually active, after appropriate counselling and a description of the procedure. If accepted, TRS was undertaken using a vaginal probe, which was lubricated and slowly advanced into the rectum, preferably empty on the day of the examination. The examination was normally well tolerated by the patients. If TRS was declined, transabdominal pelvic ultrasonography was performed, but the individual was excluded from the cohort study (n = 8). The ultrasound examination was made by a single operator, a gynaecologist with expertise in gynaecology imaging (S.V.) and a specific competence in endometriosis and adenomyosis. The operator was not blinded to the clinical information as this represented the indication for the exam. Ultrasonography was performed using ultrasonography machines (Voluson E8, GE HealthCare, Zipf, Austria) with a transvaginal probe (5–7.5 MHz) with two-dimensional and three-dimensional evaluation, and colour and power Doppler evaluation.

The uterus, including the endometrium and myometrium, and the adnexa were accurately described in terms of their dimensions and ultrasound appearance. In the three-dimensional evaluation, the coronal view of the uterus was reconstructed to assess the morphology of the uterine cavity and the appearance of the junctional zone. The myometrium was evaluated for adenomyosis according to the Morphological Uterus Sonographic Assessment (MUSA) criteria (*Van den Bosch et al., 2015*): an enlarged globular uterus, asymmetrical thickening of the myometrium, myometrial cysts, echogenic subendometrial lines and buds, hyperechogenic islands, fan-shaped shadowing, an irregular or interrupted junctional zone and translesional vascularity on colour Doppler scanning (FIGURE 1).

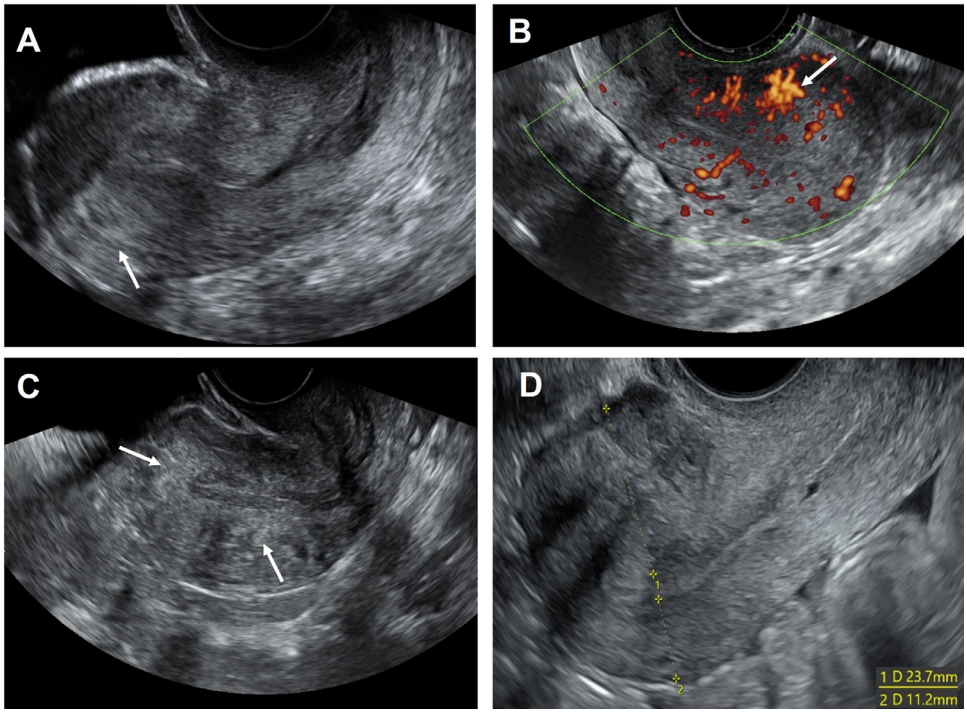

FIGURE 1 Transvaginal ultrasound images of adenomyosis. (A) Hyperechoic myometrial islands (arrow) (direct feature). (B) Translesional myometrial vascularization (arrow) demonstrated on colour Doppler scanning (indirect feature). (C) Diffuse hyperechoic myometrial islands (arrows) (direct feature). (D) Asymmetrical myometrial thickening, with the anterior and posterior myometrial wall thickness indicated by dotted yellow lines (indirect feature).

According to the definition of direct and indirect features of adenomyosis, following the revised MUSA criteria (*Harmsen et al., 2022*), a diagnosis of adenomyosis was made if at least one of the direct features (myometrial cysts, hyperechogenic islands or subendometrial lines or buds) was identified on ultrasonography. Adenomyosis was classified as focal or diffuse if either more or less, respectively, than 25% of the circumference of the lesion was surrounded by normal myometrium. An adenomyoma was defined as a well-defined lesion completely surrounded by normal myometrium (*Van Den Bosch et al., 2019*). The severity of adenomyosis was classified according to the extent of the disease in terms of the percentage of overall affected myometrium (mild <25%, moderate 25–50%, severe >50%) (*Chapron et al., 2020*; *Van Den Bosch et al., 2019*).

The presence on ultrasonography of adnexal/ovarian cysts and myometrial or endometrial pathologies was also noted. The presence of endometriosis was ruled out by a systematic ultrasound assessment of the pelvis, according to the International Deep Endometriosis Analysis consensus (*Guerriero et al., 2016*). The adnexa were examined in order to exclude the presence of ovarian or tubal endometriosis. Sonographic 'soft markers', i.e. site-specific tenderness and ovarian mobility, were searched for to suggest superficial endometriosis and adhesions. The anatomical structures in the anterior compartment (bladder and ureter) and posterior compartment (bowel, utero-sacral ligaments, recto-vaginal septum and pouch of Douglas), along with the sliding sign (*Hudelist et al., 2013*; *Menakaya et al., 2016*), were explored to rule out deep endometriosis.

The institutional review board (n.14558_oss approved on 28 May 2019) approved the study protocol, and all the participants gave informed written consent.

Statistical analysis

Clinical and imaging data were entered into an electronic database and analysed using the software SPSS (Statistical Package for Social Sciences; IBM SPSS Statistics 23, IBM Corporation, USA). Continuous data were checked for normality using normal probability plots. A descriptive analysis was conducted with an evaluation of position measures (mean and median) and dispersion indices (standard deviation and range) for the quantitative variables. The binomial variables were described by calculating the absolute and percentage frequencies.

A chi-squared test or Fisher's exact test was used to compare binomial variables between adolescent and young women with and without adenomyosis on ultrasonography. The Mann–Whitney *U*-test or independent-samples t-test was carried out to compare continuous variables. Logistic regression, with a stepwise entry of covariates, was used to calculate the odds ratios (OR), presented with 95% confidence intervals (CI), to evaluate the association between a diagnosis of adenomyosis and the presence of symptoms. A *P*-value <0.05 was considered statistically significant.

RESULTS

The study cohort included 95 patients (mean age of 17.6 ± 3.2 years), 68.4% of whom were teenagers (≤19 years). The baseline characteristics of the cohort are shown in **TABLE 1**. The mean body mass index was 21.7 ± 4.2 kg/m^2 and only 3.2% of participants (n = 3) were obese. A positive family history of gynaecological disease was found in 11.6% of patients, and one-third of the cohort reported at least

TABLE 1 BASELINE CHARACTERISTICS OF THE STUDY COHORT

Baseline characteristics	Study population (*n* = 95)
Age (years)	17.6 ± 3.2
Body mass index (kg/m^2)	21.7 ± 4.2
Family history	
Gynaecological diseases	11 (11.6%)
Breast cancer	5 (5.3%)
Cardiovascular diseases	28 (29.5%)
Diabetes	26 (27.4%)
Born prematurely	7 (7.4%)
Smokers	15 (15.8%)
Regular physical activity	33 (34.7%)
Systemic comorbidities	
None	63 (66.3%)
Migraine	4 (4.2%)
Allergies	7 (7.4%)
Asthma	3 (3.2%)
Coeliac disease	1 (1.1%)
Thyroid diseases	3 (3.2%)
Immune disorders	7 (7.4%)
Psychiatric disorders	5 (5.3%)
Epilepsy	2 (2.1%)
Menstrual history	
Age at menarche (years)	11.8 ± 1.2
Cycle regularity	83 (87.4%)
Dysmenorrhoea	84 (88.4%)
Severe dysmenorrhoea	17 (17.9%)
Dyspareunia	2 (2.1%)
Dyschezia	2 (2.1%%)
Dysuria	1 (1.1 %)
HMB	22 (23.2%)
Dysmenorrhoea + HMB	13 (13.7%)
Sexually active	49 (51.6%)

Data are presented as mean ± SD or n (%).

HMB, heavy menstrual bleeding.

one medical condition (TABLE 1). The cohort comprised only nulliparous patients, except for a single individual with one previous elective abortion. Regarding the menstrual symptoms, 87.4% had a regular-frequency menstrual cycle and dysmenorrhoea was reported by a large number of patients (88.4%), whereas severe menstrual pain was reported by only 17.9%. A small percentage also referred dyspareunia (*n* = 2, 4.1% among those who were sexually active), dyschezia and dysuria (TABLE 1). HMB was identified in 23.2% of participants and in 13.7% was associated with dysmenorrhoea.

The study population underwent TVUS (*n* = 49; 51.6%) or TRS (*n* = 46; 48.4%). Ultrasound features of adenomyosis according to the MUSA criteria were found in 27.4% of participants, and there was no significant difference between adolescents and young women (20/65 versus 6/30; 30.8% versus 20%; *P* = 0.329). FIGURE 2 represents the frequency of direct and indirect features of the disease on ultrasonography. Uterine wall asymmetry, hyperechoic intramyometrial islands, increased myometrial vascularization and an interrupted junctional zone were the most common features. In most patients a diffuse pattern of adenomyosis was diagnosed (*n* = 24; 92.3%), although the severity of the disease was mild (*n* = 18; 69.2%) to moderate (*n* = 8; 30.8%). Focal adenomyosis was found in only one case, whereas an adenomyoma was diagnosed in another.

The comparison between participants with features of adenomyosis on ultrasonography and those with normal findings showed that the presence of adenomyosis was significantly associated with HMB (38.5% versus 17.4%; *P* = 0.030), and with HMB associated with coexistent dysmenorrhoea (30.8% versus 7.2%; *P* = 0.003) (TABLE 2). The two groups did not significantly differ in terms of severe dysmenorrhoea (TABLE 2). The multivariate analysis, including clinical symptoms and baseline characteristics, retained only the coexistence of HMB and dysmenorrhoea in the model as a statistically significant association with the presence of adenomyosis on ultrasonography in this sample of adolescents and young women (OR 5.68, 95% CI 1.65–19.5).

DISCUSSION

The present study showed that 27.4% of adolescent and young women referred with dysmenorrhoea and/or HMB showed ultrasound features of adenomyosis. On this background, a clinical diagnosis of adenomyosis may be made by combining symptoms and imaging findings through an integrated approach (*Chapron et al., 2020*).

The use of non-invasive diagnostic imaging techniques in the last decade has allowed an improvement in the detection of gynaecological conditions such as endometriosis and adenomyosis (*Donnez et al., 2022*; *Vannuccini and Petraglia, 2019*), given also the introduction of shared terminology and diagnostic criteria to follow (*Harmsen et al., 2022*; *Van den Bosch et al., 2015*; *Van Den Bosch et al., 2019*). In sexually active patients, the identification of adenomyosis by TVUS is accurate, and, in those who are not sexually active TRS is an acceptable option for use among adolescents girls (*Güdücü et al., 2013*; *Sun and Fu, 2007*; *Timor-Tritsch et al., 2003*).

The most common ultrasound MUSA criteria found in the present cohort were

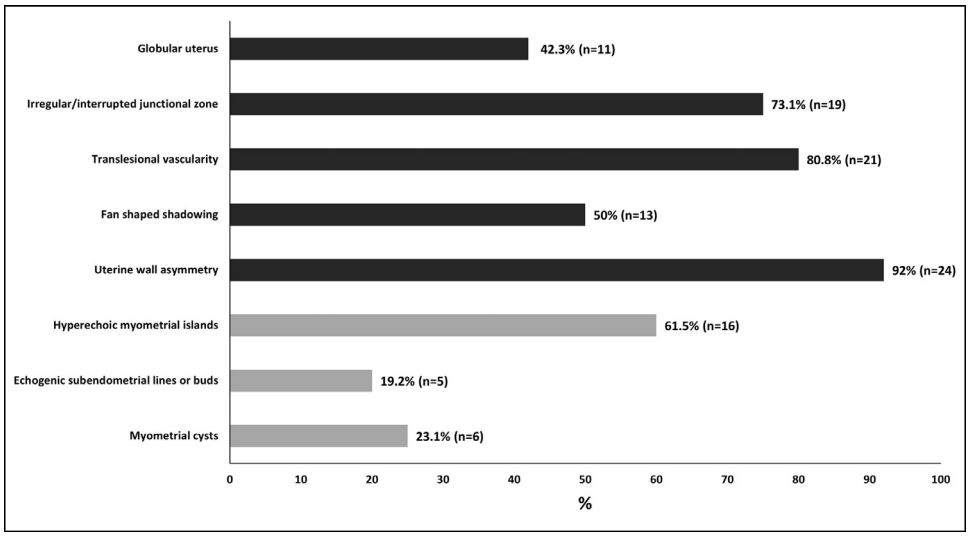

FIGURE 2 Frequency of direct (grey bars) and indirect (black bars) sonographic features of adenomyosis ($n = 26$) according to the Morphological Uterus Sonographic Assessment criteria.

uterine wall asymmetry, hyperechoic intramyometrial islands, translesional vascularity and an interrupted junctional zone, which is consistent with a previous report on a population of a similar age, despite the coexistence of endometriosis in 44% of participants (*Exacoustos et al., 2022*). In the present cohort, the majority of cases showed a diffuse phenotype, an observation that differs from the findings of Exacoustos and colleagues (*Exacoustos et al., 2022*), where focal adenomyosis was also well represented, probably because of the association with endometriosis (*Chapron et al., 2017*). In the present cohort only one participant showed a focal phenotype and another an adenomyoma. Although rare, adenomyoma should be considered as a differential diagnosis when there is severe menstrual and non-menstrual pain in adolescents. A number of case reports have been published on juvenile cystic adenomyomas, which are typically characterized by a progressive worsening of dysmenorrhoea and pelvic pain after menarche (*Brosens et al., 2015*; *Deblaere et al., 2019*).

The present study highlighted that HMB alone and HMB coexisting with dysmenorrhoea are significantly associated with an ultrasound diagnosis of adenomyosis among adolescents and young women. HMB is often a neglected symptom in gynaecological evaluation, on one hand because it is difficult to objectively assess, and on the other hand because of "normalization", meaning it is underestimated and underreported (*Vannuccini et al., 2022*). Among young patients, the prevalence of HMB varied widely, from 15% to 37%, but data are scarce and mixed (*Friberg et al., 2006*; *Oleka and Dietrich, 2020*). A questionnaire on menstrual bleeding administered to young girls at secondary school identified 37% as having HMB (*Friberg et al., 2006*). The most common cause of HMB among adolescents and young women is ovulatory dysfunction, followed by bleeding disorders (*Borzutzky and Jaffray, 2020*; *Munro et al., 2018*). The present study showed that the presence of HMB is significantly related to the diagnosis of adenomyosis in this group of young patients, as has already been observed in adults (*Donnez et al., 2022*).

Furthermore, a significantly higher prevalence of IDA was reported among adolescents and young women with adenomyosis in the present cohort. HMB is a relevant cause of IDA, impairing the quality of life of adolescents (*Wang et al., 2013*) and being more frequently underestimated and underreported, especially iron deficiency before the development of anaemia proper (*Johnson et al., 2016*). The association of adenomyosis with HMB and IDA supports the need for a combined treatment, including not only hormonal drugs (*Vannuccini et al., 2018*), but also iron replacement therapy.

The data from the present study agree with previous cohort and case series studies conducted in young patients showing an incidence of adenomyosis ranging between 25% and 35%, even though, in most cases, the study populations in the literature included participants with endometriosis, and the symptoms were mainly related to menstrual pain (*Chapron et al., 2017*; *Exacoustos et al., 2022*; *Zannoni et al., 2020*). Dysmenorrhoea is a common finding among adolescents, ranging from 30% to 90%; however, if only severe pain is considered, the figure drops to 15–40% (*Smorgick and As-Sanie, 2018*). The prevalence of dysmenorrhoea in the present cohort – nearly 90% – is consistent with previous reports (*Söderman et al., 2019*), and that of severe dysmenorrhoea (17.9%) is slightly lower than that reported in the literature. Nevertheless, adenomyosis is one of the causes to consider if secondary dysmenorrhoea is suspected (*Hewitt, 2020*). In the present cohort, dysmenorrhoea was not significantly associated with a diagnosis of adenomyosis unless menstrual pain was associated with HMB. Presumably, the exclusion of cases of endometriosis, despite the limitations of entirely ruling out the presence of endometriosis lesions in such a unique population of young women, may reveal the clinical profile of adenomyosis alone, which seems to be mainly characterized by a combination of dysmenorrhoea and HMB, rather than only severe dysmenorrhoea.

A number of limitations of this study should be acknowledged, such as the small sample of cases and the lack of further confirmation of adenomyosis by MRI. However, recent systematic reviews suggest that MRI and TVUS are accurate

TABLE 2 BASELINE CHARACTERISTICS, MEDICAL HISTORY AND MENSTRUAL SYMPTOMS AMONG PATIENTS WITH ADENOMYOSIS ON ULTRASONOGRAPHY AND THOSE WITH NORMAL MYOMETRIAL FINDINGS

Patient characteristics	Adenomyosis (*n* = 26)	No adenomyosis (*n* = 69)	*P*-value
Age (years)	17.7 ± 2.8	17.6 ± 3.3	0.833
Adolescents versus young women	20 (76.9%) versus 6 (23.1%)	45(65.2%) versus 2.4 (34.8%)	0.274
Sexually active versus not sexually active	15 (57.7%) versus 11 (42.3%)	34 (49.3%) versus 35 (50.7%)	0.464
Body mass index (kg/m^2)	22.4 ± 6.1	21.4 ± 3.5	0.387
Smoking	6 (23.1%)	9 (13.0%)	0.265
Systemic comorbidities	12 (46.2%)	20 (29.0%)	0.145
Menstrual history			
Age at menarche (years)	11.6 ± 1.4	11.8 ± 1.2	0.622
Cycle regularity	24 (92.3%)	59 (85.5%)	0.374
Dysmenorrhoea	23 (88.5%)	61 (88.4%)	0.861
Severe dysmenorrhoea	4 (15.4%)	13 (18.8%)	0.695
Dyspareunia	0	2 (2.9%)	0.380
Dyschezia	0	2 (2.9%)	0.380
HMB	10 (38.5%)	12 (17.4%)	0.030
Dysmenorrhoea + HMB	8 (30.8%)	5 (7.2%)	0.003
Iron deficiency anaemia	4 (15.4%)	2 (2.9%)	0.045

Data are presented as mean ± SD or n (%).

An unpaired t-test and chi-squared test were used for continuous and binomial variables, respectively.

HMB, heavy menstrual bleeding.

and comparable non-invasive imaging methods for diagnosing adenomyosis (*Alcázar et al., 2023*; *Liu et al., 2021*). Thus, TVUS should be considered the first-line diagnostic imaging method, given also the costs of and lower accessibility to MRI (*Liu et al., 2021*; *Tellum et al., 2020*).

In addition, this is one of the few studies exploring the diagnosis of adenomyosis using ultrasonography among only symptomatic adolescents and young women reporting menstrual pain or HMB. This represents one of the novel aspects of this study, which highlights the importance of combining menstrual symptoms with ultrasound findings (*Chapron et al., 2020*). The inclusion of symptomatic patients aims to evaluate the presence of adenomyosis starting from the clinical presentation, rather than just the imaging appearance in an unselected group of patients undergoing a TUVS (*Naftalin et al., 2012*; *Pinzauti et al., 2015*). Another point to emphasize is the exclusion of patients with bleeding disorders, in order to reduce the bias of coexistent conditions. Patients affected by endometriosis were also excluded, even though the diagnostic accuracy may be limited in patients who are not sexually active, in whom bimanual pelvic and speculum examination were not feasible, representing both a limitation of the study and a real-life criticism in clinical practice. In addition, minimal endometriosis cannot be entirely excluded, even though also participants with soft markers for peritoneal disease, such as pelvic adhesions, site-specific tenderness and reduced ovarian mobility (*Guerriero et al., 2016*), were not included in the cohort.

Furthermore, only patients undergoing TVUS or TRS were included in order to achieve a similar accuracy and reliable results on adenomyosis criteria. The transrectal approach may be proposed when TVUS is not possible or unacceptable, such as in adolescents, patients who are not sexually active, women with vaginal malformations or those with severe vulvo-vaginal atrophy (*Timor-Tritsch et al., 2003*; *Wong et al., 2022*). However, the lack of previous studies exploring the diagnostic accuracy of TRS for adenomyosis should be acknowledged. Nevertheless, a number of studies have shown the accuracy of using a transrectal approach by using the same transvaginal probe as an alternative to TVUS for other purposes as well, with good reliability and similar results (*Akbari Sene et al., 2022*; *Alcázar et al., 2016*; *Lee et al., 2015*; *Tellum et al., 2023*; *Wong et al., 2022*). Furthermore, if performed by an expert, TRS can achieve an diagnostic performance equivalent to that of TVUS for diagnosing endometriosis (*Gerges et al., 2021*; *Guerriero et al., 2016*; *Pascoal et al., 2022*).

In conclusion, adenomyosis is a common uterine disorder among women during reproductive life and the present data suggest that adenomyosis may also be diagnosed among teenagers and young women with dysmenorrhoea and/or HMB in combination with a detailed ultrasound evaluation. Thus, the diagnosis of adenomyosis should be considered among adolescents as well, as a result of the clinical presentation and imaging features.

AUTHOR CONTRIBUTIONS

S.V.: first draft and analysis of data; C.M., F.T., P.M. and F.P.: collection of data; M.F. and V.B.: critical revision of the manuscript for important intellectual content; F.P.: design of the study and interpretation of the results. All authors approved the final version of article to be submitted.

DATA AVAILABILITY

Data will be made available on request.

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