SYSTEMATIC REVIEW

Prevalence of adenomyosis in symptomatic adolescents and young women: a systematic review and meta-analysis

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Objective: Many adolescents and young women experience dysmenorrhea, a condition that is often trivialized or overlooked but can cause a substantial deterioration in health-related quality of life. Therefore, we conducted a systematic review and meta-analysis to investigate the overall prevalence of symptomatic individuals with ultrasound/magnetic resonance imaging–diagnosed adenomyosis in the 12–25 year-age group. This could inform management and treatment decisions.

Evidence Review: The PubMed/Medline, Embase, and Scopus databases were searched for full-length, English-language reports published between 2015 and 2024. This systematic review with meta-analysis was conducted and reported following the Joanna Briggs Institute methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. We included observational studies that assessed the number of patients with adenomyosis among adolescents and young women, the majority of whom presented with dysmenorrhea. The methodological quality of the included studies and their potential risk of bias were ascertained using the Joanna Briggs Institute Critical Appraisal Tool for Prevalence Studies. The main outcome was the prevalence of adenomyosis among symptomatic adolescents (midpoint of the study age range, $<$20 years) and young women (midpoint of the study age range, $\geq$20 years). Three meta-analyses, categorized by age, were performed using Stata to pool adenomyosis prevalence data from selected studies. The risk of endometriosis in women with and without adenomyosis was ultimately assessed as an exploratory and confirmatory investigation by combining the odds ratio estimates from each study using the random-effects model.

Results: Six studies comprising 1,300 individuals met the inclusion criteria. The prevalence of adenomyosis ranged from 5.9% to 46.0%, with an overall weighted mean of 20.7% (95% confidence interval [CI], 11.5–31.6) with high heterogeneity ($I^2 = 94.8\%$). The aggregate estimates were as 16.9% (95% CI, 8.8%–27.0%) in the adolescent subgroup and 29.7% (95% CI, 17.5%–43.5%) in the young woman subgroup. The risk of endometriosis in patients with adenomyosis was significantly higher than that in patients without adenomyosis, with a pooled odds ratio of 3.39 (95% CI, 2.11–5.45), without statistically significant heterogeneity across studies.

Conclusion: The findings of the present review should assist clinicians in developing a high index of suspicion for adenomyosis when adolescents and young women present with chronic severe dysmenorrhea and menorrhagia. Limiting the diagnostic delay and considering secondary prevention medical interventions may improve the quality of life and limit the risk of disease progression. Further rigorous prospective analytic studies are required to better define the epidemiological patterns of adenomyosis in the postmenstrual decade in different population subgroups. (F S Rev® 2025;6:100083. ©2024 by American Society for Reproductive Medicine.)

Key Words: Adenomyosis, adolescents, endometriosis, dysmenorrhea, menorrhagia

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Data availability: The data included in this article were extracted from the published original articles. Additional information regarding the distribution of data according to strata of age and coexistent endometriosis was provided on request by the authors of some studies. No new data were generated to support this article.

Checklist provided for this review: Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020.

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ESSENTIAL POINTS

- On the basis of a meta-analysis of available data, the overall prevalence of adenomyosis in 1,300 symptomatic adolescents and young women with severe dysmenorrhea and heavy menstrual bleeding was estimated to be 20.7% (95% confidence interval [CI], 11.5–31.6).
- A trend toward an increase in adenomyosis prevalence with increasing age was observed because the estimates were 16.9% (95% CI, 8.8%–27.0%) in adolescents and 29.7% (95% CI, 17.5%–43.5%) in young women.
- The generalizability of the findings is limited because only six studies were selected, five of which were from a single country, recruited predominantly white participants, and reported highly heterogeneous estimates.
- The results of this study should help clinicians develop a high index of suspicion for adenomyosis when adolescents and young women present with chronic severe dysmenorrhea and heavy menstrual bleeding.

Until a few years ago, adenomyosis attracted limited interest in the scientific community, mainly because it was generally diagnosed not by imaging techniques but by histopathologic examination of uteri removed from patients with menorrhagia and dysmenorrhea. Therefore, once the diagnosis was made, the condition was no longer a clinical problem. This also influenced the definition of the epidemiological characteristics of adenomyosis, which was largely considered a disease of parous women in their forties, rare in young women, and almost nonexistent in adolescents (1, 2).

However, the last 2 decades have witnessed an increasing focus on adenomyosis as both pelvic ultrasound (US) and magnetic resonance imaging (MRI) have been shown to be highly reliable techniques for detecting adenomyosis with the uterus in situ (3–5). Moreover, standardized and consistent diagnostic criteria have been defined (6–9). The implementation of nonsurgical diagnostic modalities not only led to the introduction of medical and minimally invasive nonsurgical alternatives to hysterectomy for symptomatic patients who wished to preserve their uterus (10, 11) but also allowed a substantial redefinition of the epidemiological characteristics of adenomyosis, which began to be identified in progressively younger age groups (1). In addition, the reliable imaging detection of adenomyosis in young women led to the observation of an association between adenomyosis and endometriosis (11,12).

Given this background, we thought it important to review the available evidence on the prevalence of adenomyosis diagnosed by US or MRI in adolescents and young women in the period from menarche to 25 years of age to provide a rough estimate of the likely magnitude of the issue. Indeed, assessing the frequency of adenomyosis in adolescents and young women with dysmenorrhea and menorrhagia seems extremely important because symptom normalization, dismissal, and misdiagnosis are particularly common in this specific subgroup, possibly leading to diagnostic delay (13–22).

The upper age limit was chosen considering also the sudden and sharp rise in the incidence curve of diagnosed endometriosis around this age (23–25). Therefore, if there is a common pathogenesis or a causal relationship between adenomyosis and endometriosis, it seems crucial to focus on the young population from menarche to 25 years of age.

MATERIALS AND METHODS

This systematic review and meta-analysis was conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 recommendations (26) and the Joanna Briggs Institute methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data (27).

Our primary objective was to answer the following condition, context, and population research question (27): what is the prevalence of individuals with adenomyosis (condition) diagnosed by US and/or MRI in studies published in the last decade (context), in adolescents or young women presenting primarily with dysmenorrhea (population)? The hypothesis was that, contrary to previous beliefs (2, 28, 29), adenomyosis is common in symptomatic individuals aged 12–25 years. We considered studies published before 2015 to be less relevant due to insufficient awareness of the condition in this age stratum among healthcare providers (28–32), limited focus on detection of early lesions on imaging (3–5, 30–32), and inconsistent standardized diagnostic criteria (6, 9).

The secondary objective was to assess whether the prevalence of individuals with adenomyosis is lower in "adolescents" (midpoint of the study age range, <20 years) than in "young women" (midpoint of the study age range, ≥20 years). The hypothesis was that the prevalence of patients with adenomyosis is higher in the older age group than in the younger age group due to a time-related increased risk of disease onset/progression.

The study protocol has been preregistered on PROSPERO (Registration ID Number CRD42024544720; accepted on May 20, 2024). Because only published, deidentified data were used, institutional review board ethical approval was not required.

Search strategy

Two reviewers (C.B. and V.B.) searched the PubMed/Medline, Embase, and Scopus databases for eligible studies published between January 1, 2015, and July 1, 2024. The search terms ("adenomyosis") and ("prevalence") were used as Medical Subject Heading (MeSH PubMed) or Embase subject heading (EMTREE EMBASE) terms or as a combination of free text. The search terms and algorithm used are described in detail in Supplemental File 1 (available online). To identify further relevant publications, the reference list of the retrieved articles was searched manually, and PubMed's "Similar articles" and "Cited by" functions were used.

Eligibility criteria

This review was restricted to full-length, English-language articles published in peer-reviewed journals. We included observational studies, cross-sectional or cohort studies, that assessed and defined the number of patients with a diagnosis of adenomyosis (numerator) in a study population of adolescents and young women undergoing pelvic evaluation by US or MRI primarily for dysmenorrhea (denominator). Studies were excluded if they did not provide age-categorized data, investigated the presence of multiple potential causes of various pelvic symptoms without a specific focus on adenomyosis, diagnosed adenomyosis exclusively in a selected population of patients with endometriosis, and included cases detected by surgical techniques. Articles without original data (reviews, abstracts presented at meetings, case reports, editorials, opinions, book chapters, letters, practice guidelines, study protocols, and commentaries) were not considered.

Study selection and data extraction

Two reviewers (C.B. and V.B.) independently screened the publications by reviewing titles, abstracts, and keywords. The selected relevant articles were then retrieved to assess their eligibility. Any disagreements were resolved through discussion and, if necessary, consultation with a third adjudicating reviewer (F.C.).

The following data were abstracted from each report and tabulated using a standardized extraction form: first investigator's last name; year of publication; country; study design; selection criteria; number and characteristics of participants including age; definition of symptoms; imaging modality; and adenomyosis diagnostic criteria. Moreover, the prevalence of adenomyosis in the study population was categorized according to the two predefined age strata. Finally, the prevalence of adenomyosis was calculated in women with and without endometriosis. In some cases, additional original information was requested from the investigators (20, 33–36).

Assessment of methodological quality

We appraised the methodological quality of the included studies and their potential risk of bias using the Joanna Briggs Institute Critical Appraisal Tool for Prevalence Studies (27). Nine items are included in this checklist for studies reporting prevalence data: "Was the sample frame appropriate to address the target population?"; "Were the study participants sampled in an appropriate way?"; "Was the sample size adequate?"; "Were the study subjects and the setting described in detail?"; "Was the data analysis conducted with sufficient coverage of the identified sample?"; "Were valid methods used for the identification of the condition?"; "Was the condition measured in a standard, reliable way for all participants?"; "Was there appropriate statistical analysis?"; and "Was the response rate adequate, and if not, was the low response rate managed appropriately?" Four alternative options, "yes," "no," "unclear," and "not applicable," are possible for each question. One point was assigned for each "yes," and 0 point was assigned for each "no" or "unclear." Because question 9 was not pertinent to the studies considered for this review, thus "not applicable," the possible summary score ranged from 0 to 8. The methodological quality of the included study was classified as "good" if the score was 7 or 8, "moderate" if the score was 4–6, and "low" if the score was ≤ 3 (37).

The assessment was performed independently by two reviewers (C.B. and V.B.). Any disagreement in the ascertainment of the quality of evidence was discussed with a third adjudicating reviewer (F.C.).

Data synthesis

Three meta-analyses were preplanned to pool the adenomyosis prevalence data across the selected studies: the overall weighted mean proportion of patients with adenomyosis in the total population of individuals aged ≤ 25 years; the overall weighted mean proportion in the subgroup of individuals aged <20 years; and the overall weighted mean proportion in the subgroup of individuals aged ≥ 20 years. For the comparison of adenomyosis prevalence in the two prespecified age strata, only studies with ≥ 10 participants per age stratum were included. Moreover, to evaluate the risk of endometriosis in women with adenomyosis compared with those without, we combined the odds ratio (OR) estimates from each study using the inverse variance method according to the random-effects model.

All analyses were performed using Metaprop, a command implemented in Stata to compute meta-analysis of proportions (38). The Freeman-Tukey arcsine square root transformation was applied to the data before pooling for meta-analysis (39). Estimates of overall proportions and corresponding 95% confidence intervals (CIs) were calculated using a random-effects model (40). The probability value of the difference in adenomyosis prevalence between adolescents and young women was indicated. The χ^2 P values of I^2 statistic were also reported to evaluate the heterogeneity of the estimates across studies. Two sensitivity analyses were conducted by excluding the studies with outlier data (19, 36).

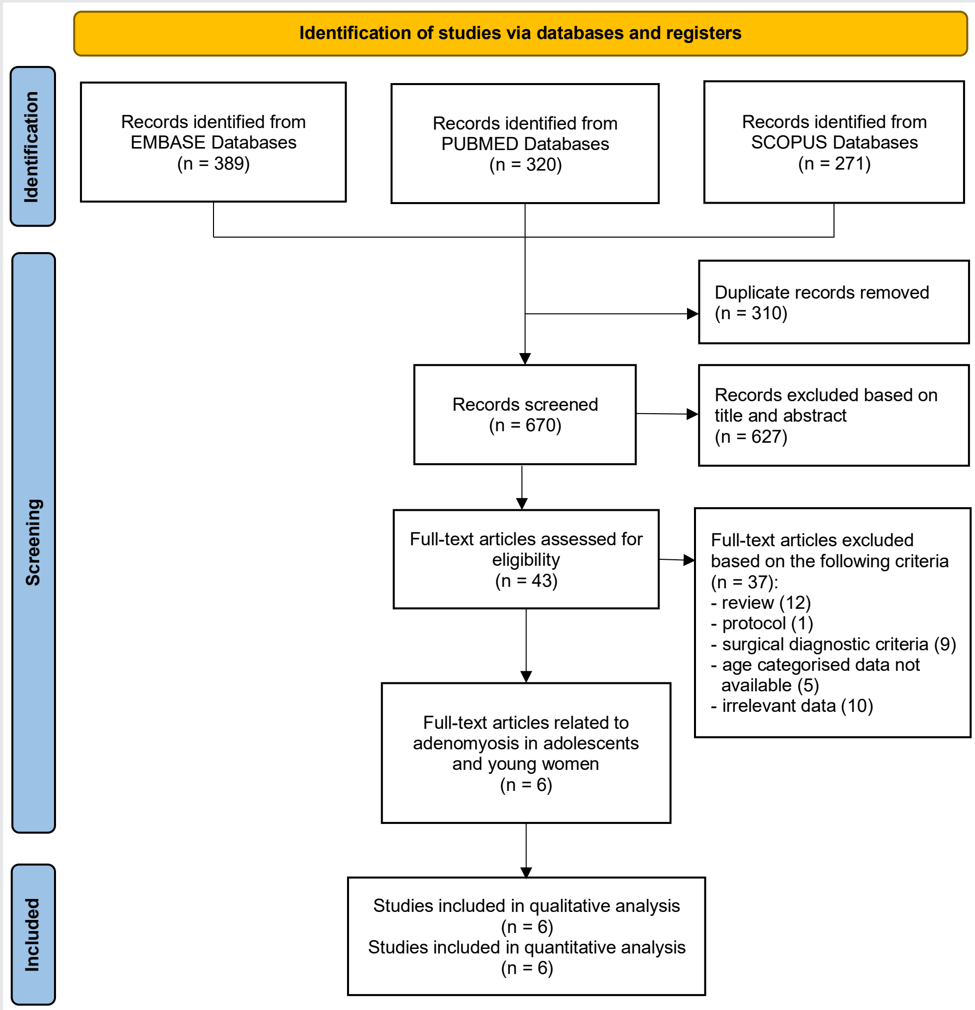
RESULTS

The database search identified 980 records, of which 310 were duplicates and 627 were removed during the title and abstract screening. Of the 43 full-text articles assessed for eligibility, 37 were excluded for various reasons. Eventually, six studies comprising 1,300 individuals met the original inclusion criteria (19, 20, 33–36). The PRISMA 2020 flow diagram of the literature search results and selection process is shown in Figure 1 (27).

Study overview

Of the six included studies, three were retrospective cohort studies (19, 20, 33), two were prospective cohort studies (34, 35), and one was a cross-sectional study (36). Five studies were conducted in Italy (19, 20, 34–36), and one was conducted in France (33). Sample sizes ranged from 95 (35) to 371 (20) individuals. For one study (34), only data

FIGURE 1



Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (27) flow diagram of the literature search and study selection process.

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on women aged 18–25 years of age (n = 130), which were provided by the investigators on request, were considered for the present review. Therefore, the final study population for this review consisted of 1,274 individuals.

The mean age of the subjects ranged from 17 (33, 35) to 23 (34) years. All (20, 33, 35, 36) or most (19, 34) participants had dysmenorrhea, which was always measured using a visual analogue scale. A current or past history of endometriosis was an exclusion criterion in two studies (34, 35). Thus, only four studies (19, 20, 33, 36) assessed the association between adenomyosis and endometriosis. Adenomyosis was diagnosed by US in five studies (19, 20, 34–36), according to the original (9) or revised (8) Morphological Uterus Sonographic Assessment criteria in four studies (19, 20, 35, 36), and by MRI in one study (33) on the basis of the recommendations of Bazot and Daraï (6).

The baseline characteristics of the included studies are summarized in Table 1 (6–9, 19, 20, 33–36). The overall methodological quality was considered "good" for four studies (19, 20, 33, 34) and "moderate" for 2 (35, 36). Data on the risk of bias assessment are reported in detail in Supplemental Table 1, available online.

Primary outcome: prevalence of adenomyosis in symptomatic adolescents and young women

Overall, adenomyosis was diagnosed in 224 (crude percentage, 17.6%) of 1,274 participants. The prevalence of adenomyosis ranged from 5.9% (19) to 46.0% (36), and the overall weighted mean prevalence estimate of adenomyosis was 20.7% (95% CI, 11.5–31.6) with high heterogeneity (I^2 = 94.8%, $P<.00001$; Fig. 2).

When two sensitivity analyses were performed by first excluding the study by Martire et al. (19) and then the study by Zannoni et al. (36), the prevalence rates of adenomyosis were 24.5% (95% CI, 14.8%–35.7%) with high heterogeneity

TABLE 1

Main characteristics of the selected studies assessing adenomyosis prevalence in symptomatic adolescents (midpoint of the study age range, < 20 years) and young women (midpoint of the study age range, ≥20 years): literature data, 2015–2024.

Investigator	Year	Country	Study design	No. of patients	Participants	Mean age, y (range)	Definition of symptoms (measurement methods)	Exclusion criteria	Diagnostic modality	Diagnostic criteria
Martire et al. (19)	2020	Italy	Retrospective cohort study	270	Patients who underwent US evaluation for different indications;[a] approximately 55% with dysmenorrhea	18.0 (12–20)	Painful symptoms defined as a VAS score of >4	Pregnancy Previous pelvic surgery Current use of hormonal treatments	TVUS or TRUS	Van den Bosch et al. (9)
Martire et al. (20)	2023	Italy	Retrospective cohort study	371	Patients with severe dysmenorrhea	20.8 ± 3 (12–25)	Severe dysmenorrhea defined as a VAS score of ≥7	Pregnancy Previous pelvic surgery	TVUS or TRUS	Harmsen et al. (8) and Van den Bosch et al. (9)
Millischer et al. (33)	2023	France	Prospective cohort study	308	Patients with severe dysmenorrhea	17.4 ± 1.9 (12–20)	Severe dysmenorrhea defined as menstrual pelvic pain resistant to NSAIDs; mean VAS score of >7	Pregnancy Contraindications to MRI Obstructive müllerian anomalies Patients with only suspected superficial endometriosis	MRI	Bazot and Daraï (6)
Pinzauti et al. (34)	2015	Italy	Prospective cohort study	130[b]	Patients seeking contraceptive counseling and US evaluation; approximately 80% with dysmenorrhea	22.7[c] (18–25)	Severity of pain symptoms evaluated by VAS. Dysmenorrhea VAS score of >7	Past or current history of endometriosis Uterine fibroids/benign ovarian cysts/ endometrial pathology Current use of hormonal treatments or medications that affecting menstrual cycle Previous uterine surgery History of infertility	TVUS	Exacoustos et al. (7)
Vannuccini et al. (35)	2024	Italy	Prospective cohort study	95	Patients with dysmenorrhea and/or HMB	17.6 ± 3.2 (13–25)	Dysmenorrhea defined as a VAS score of ≥6. HMB defined as a PBAC score of ≥100	History of endometriosis Current use of hormonal treatments Bleeding disorders Uterine/ovarian tumors Congenital uterine anomalies	TVUS or TRUS	Harmsen et al. (8)

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TABLE 1

Continued.

Investigator	Year	Country	Study design	No. of patients	Participants	Mean age, y (range)	Definition of symptoms (measurement methods)	Exclusion criteria	Diagnostic modality	Diagnostic criteria
Zannoni et al. (36)	2024	Italy	Cross-sectional study	100	Patients with CPP	20.0 (14–24)	Dysmenorrhea assessed by VAS; median score, 9	Estroprogestin combinations, progestins, or GnRH-a in the 3 months before enrolment	TAUS and TVUS or TRUS	Harmsen et al. (8) and Van den Bosch et al. (9)

Note: CPP = chronic pelvic pain; GnRH-a = gonadotropin-releasing hormone analogue; HBM = heavy menstrual bleeding; MRI = magnetic resonance imaging; NSAID = nonsteroidal anti-inflammatory drug; PBAC = pictorial blood loss assessment chart; TAUS = transabdominal ultrasound; TRUS = transrectal ultrasound; TVUS = transvaginal ultrasound; US = ultrasound; VAS = visual analogue scale.

[a] Irregular menstrual cycles, dysmenorrhea, heavy menstrual bleeding, CPP, congenital uterine anomalies, ovarian cysts, well-woman visits, and others.

[b] The original study population included 156 patients between the ages of 18 and 30 years. As this review focuses on women up to 25 years of age, 26 patients aged >26 years were excluded.

[c] Calculated after excluding patients aged >25 years.

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(I^2 = 93.0%, P<.00001) and 16.5% (95% CI, 9.5%–24.9%) with high heterogeneity (I^2 = 91.9%, P<.00001), respectively (data not shown).

Secondary outcomes: age-related prevalence and association with endometriosis

The prevalence of adenomyosis was assessed in the two separate and preplanned age strata. The study by Pinzauti et al. (34) was excluded from the analysis of the adolescent subgroup because it included <10 participants aged <20 years. The prevalence rates of individuals with adenomyosis were 110 (crude percentage, 12.9%) of 855 in the adolescent subgroup (range, 5.9%–36.5%) and 110 (crude percentage, 26.8%) of 411 in the young woman subgroup (range, 20.0%–56.2%). The overall weighted mean estimates of adenomyosis prevalence were 16.9% (95% CI, 8.8%–27.0%; I^2 = 91.2%; P<.00001) in the adolescent subgroup and 29.7% (95% CI, 17.5%–43.5%; I^2 = 85.6%; P=.0001) in the young woman subgroup (Figs. 3 and 4). The difference between adolescents and young women in the overall weighted mean prevalence of adenomyosis was not statistically significant (P=.1090).

To further characterize our populations for the potential association with endometriosis as a concomitant morbidity, the frequency of endometriosis in individuals with or without adenomyosis was assessed as an exploratory analysis. This association was reported in four studies (19, 20, 33, 36). The risk of endometriosis in patients with adenomyosis was significantly higher than that in patients without adenomyosis, with a pooled OR of 3.39 (95% CI, 2.11–5.45; Supplemental Fig. 1, available online). The heterogeneity between studies was not statistically significant (P=.059), with ORs ranging from 2.35 (19) to 5.63 (36).

DISCUSSION

Main findings

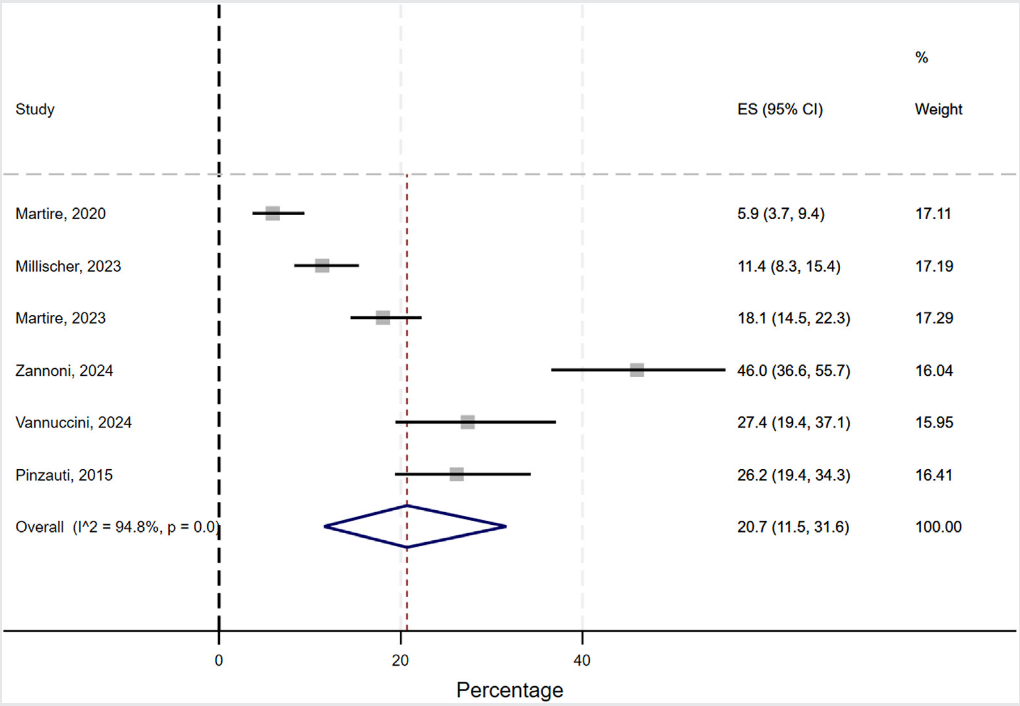
On the basis of the results of the available prevalence studies, approximately 1 in 5 adolescents and young women complaining of severe dysmenorrhea had a US or MRI diagnosis of adenomyosis. This estimate is higher than previously thought (2, 28, 29) and represents a novel epidemiological scenario (32, 41). However, this overall prevalence was observed in a subset of symptomatic individuals who most likely do not represent the general population from which they were selected.

Interestingly, according to a recent meta-analysis, among 21 longitudinal studies evaluating 25,600 subfertile women, the overall pooled prevalence of adenomyosis was 10%, a finding that provides further relevance to the present results (42).

In the subgroup analysis, the overall weighted mean proportion of participants with adenomyosis was not significantly higher in young women than in adolescents, although the crude percentage estimate in the former subgroup (26.8%) was twice that in the latter (13.2%).

The pooled OR for endometriosis in participants with adenomyosis compared with those without adenomyosis was

FIGURE 2



Overall weighted mean prevalence of adenomyosis in adolescents and young women. Studies were ordered by central point of age range and year of publication. Literature data, 2015–2024.

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>3. The strength and consistency of the association across different studies from independent research groups suggest that the relationship between adenomyosis and endometriosis may not be explained merely by selection bias and confounding (40).

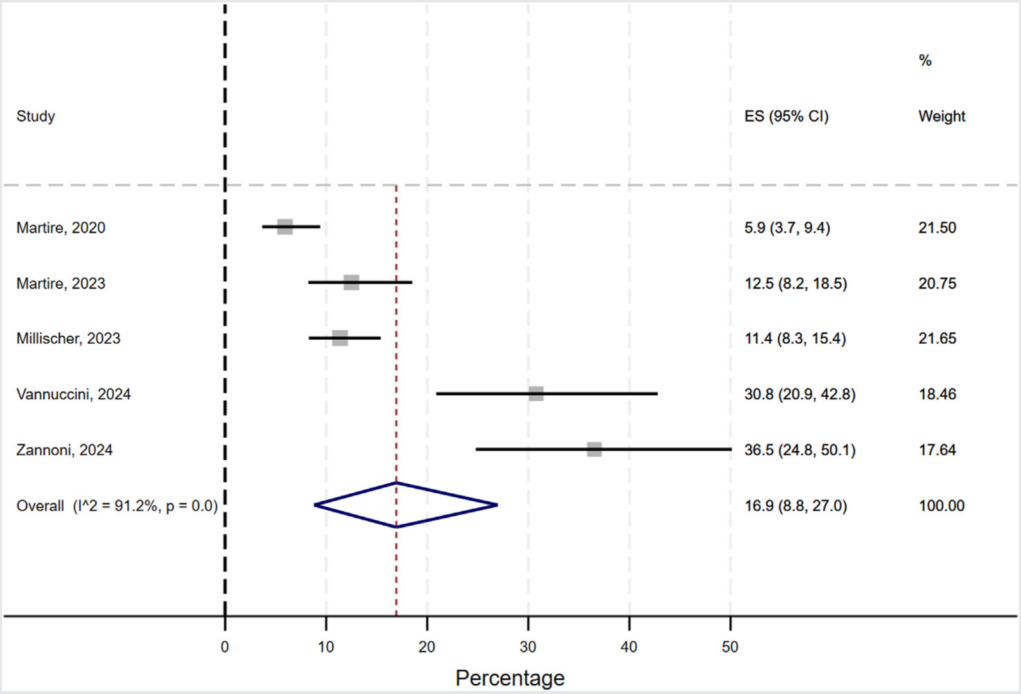
Interpretation

Understanding the origin of dysmenorrhea is of paramount importance, especially in adolescents and young women, whose complaints are generally normalized and dismissed by both relatives and healthcare providers (14, 15, 21). Such attitudes can have potential emotional, academic, employment, and social downstream consequences although at the same time discouraging the initiation of appropriate specialized investigations and effective treatments aimed at improving health-related quality of life (13, 14, 16–22, 41).

It has been reported that approximately two thirds of adolescents with chronic pelvic pain harbor early-onset endometriosis (13, 43). In this case, however, the symptoms may be aspecific and affect the correct diagnosis (16, 17). Moreover, superficial peritoneal endometriotic implants may escape detection on US and MRI (44). Conversely, adenomyosis is associated with two specific symptoms, dysmenorrhea and menorrhagia, and can be detected even in its early stages when US and MRI are performed by expert observers using updated equipment (3–5, 7).The main finding of the present review should now mandate a systematic in-depth evaluation of all adolescents and young women with otherwise defined "primary dysmenorrhea" (13), with the precise aim of excluding the presence of adenomyosis in addition to other potential causes. Diagnostic and therapeutic measures for secondary prevention of the disease have been proposed recently (41). In particular, long-term, endocrinologic intervention should aim at interrupting the estrogen-based inflammatory and fibrogenic mechanisms, limit pelvic exposure to refluxing endometrial glands, stop repeated inflammatory events both at the endometrial-myometrial junction and on the peritoneal surface of pelvic structures, relieve dysmenorrhea, and improve health-related quality of life (41).

The prevalence of adenomyosis was not significantly different in the subgroup aged <20 years compared with that in the subgroup aged >20 years. This may be partly explained by the high qualitative and quantitative heterogeneity of the included studies. Although most enrollees reported dysmenorrhea, the baseline criteria for participant selection were different in two studies (19, 34), and the mean degree of severity of dysmenorrhea was inconsistent across studies. Moreover, the number of cases was generally limited. For these reasons, the point estimates of individual studies were highly heterogeneous, and the CIs were substantially wide. In fact, a type II error cannot be excluded. If this is the case and if, similar to endometriosis (45–47), adenomyosis is also a progressive disease (48), early detection may allow timely

FIGURE 3



Prevalence of adenomyosis in adolescents (midpoint of the study age range, <20 years). Literature data, 2020–2024.

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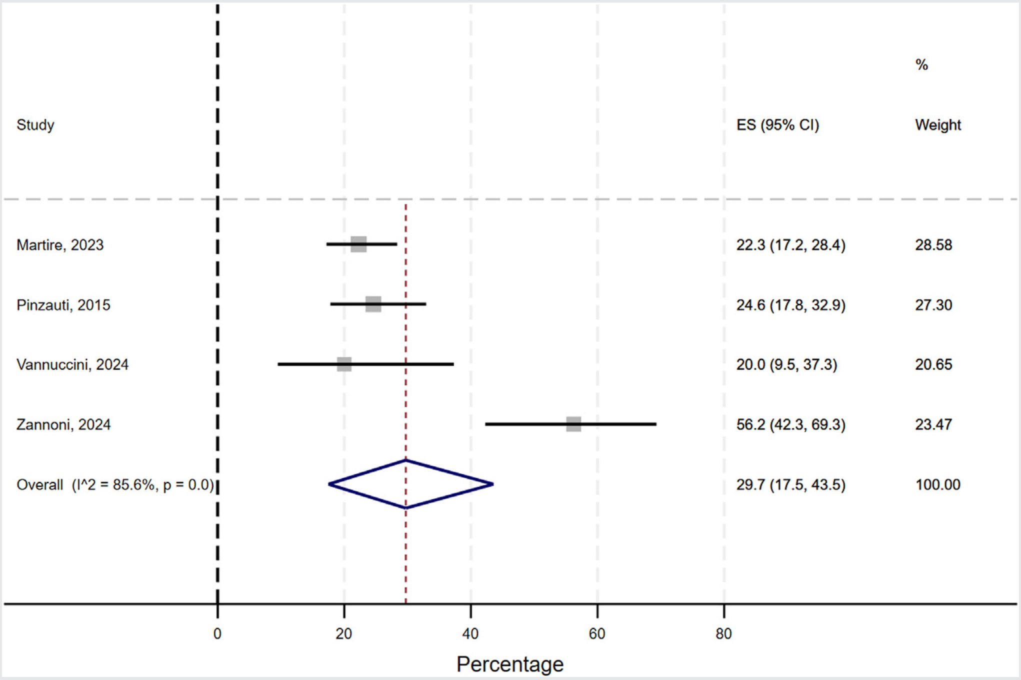
FIGURE 4



Prevalence of adenomyosis in young women (midpoint of the study age range, ≥20 years). Literature data, 2015–2024.

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secondary prevention with hormonal medications (41). Theoretically, this could limit the risk of reduced fertility and major obstetric complications later in life (49).

Finally, adenomyosis and endometriosis are both menstruation-related disorders (50). Therefore, a strong association between adenomyosis and endometriosis whether on the basis of shared risk factors or common pathogenic links was expected (51–57). The pathogenic mechanisms that may underlie the development and progression of endometriosis and adenomyosis and their connection have been extensively described in a previous review from our group (39). Although this association is well known, our confirmatory results should be considered robust because they are based on consistent within-study comparisons, which may limit selection and information bias, as well as confounding. Moreover, the quantitative heterogeneity between studies was limited. This should support the validity of the overall result.

Some investigators hypothesize that adenomyosis precedes the onset of endometriosis, suggesting a causal relationship between the two conditions (58, 59). Indeed, data from recent studies (60, 61) and the results of a systematic review of the available evidence (62) have shown that the pattern of myometrial contractility is abnormal in patients with adenomyosis and endometriosis. This dysperistalsis, characterized by an increased frequency, duration, and intensity of myometrial contractions, as well as a loss of physiological directionality during the menstrual phase, with a predominantly aberrant cervicofundal peristaltic wave pattern (60–62), may favor transtubal reflux and ultimately the development of endometriosis (39, 59, 63).

According to several investigators, the aforementioned findings should be contextualized in a broader evolutionary-biologic scenario, linked to the striking changes in reproductive patterns that have occurred in the postindustrial era and the consequent impressive increase in the number of ovulatory menses (39, 64–68). If this is true, the intramyometrial infiltration of basal endometrial cells would be favored by the iterative uterine wounds at the endomyometrial interface caused by monthly menstruation (50, 69, 70).

Alternatively, or in addition to the aforementioned mechanisms, Bulun et al. (50) suggest that the endometrium from patients with adenomyosis presents anomalies that may favor the disease. In fact, somatic epithelial mutations and epigenetic abnormalities in stromal cells would confer increased survival and growth capabilities to the endometrial cells of these individuals (50). In particular, identical KRAS mutations were identified in adenomyotic and endometriotic lesions in the same patients (71).

Strengths and limitations

This review was conducted and reported following the PRISMA 2020 guidelines (26) as well as the specific recommendations of the Joanna Briggs Institute for systematic reviews and meta-analyses of prevalence studies (27). The methodological quality of the included reports was appreciable, and specific biometric techniques were used to generate aggregated weighted estimates of proportions (27, 72).

A major strength of the review is that the diagnostic evaluation was always performed by highly expert and authoritative examiners, according to standardized and internationally adopted guidelines. When adenomyosis was diagnosed by MRI, the images were evaluated independently and blindly by two experienced radiologists according to strict published criteria. This should greatly reduce the risk of misclassification bias and raise the validity of the overall results. On the other hand, because the studies were conducted at tertiary referral centers, it cannot be excluded that the sample population had an increased likelihood of adenomyosis also as a result of self-referral for second opinions.

Only six studies recruiting a few hundred individuals were included in the review. On the one hand, this is a limitation; on the other hand, we consider that the awareness of adenomyosis in adolescents has only recently increased, and we believe that studies published more than a decade ago are likely to be at high risk of information bias (1, 28, 29).

Another major limitation of the present review is that five of the six included studies (19, 20, 34–36) are from a single country, that is, Italy. Therefore, the external validity of the findings may be limited, also considering that the ethnicity of the participants, although not described in detail, was presumably mainly of white Caucasian origin (42). Despite these considerations, a very high quantitative heterogeneity was observed across studies. This may be explained by qualitative heterogeneity, including the different mean ages of the participants in the selected studies. Another issue may be related by the different degrees of reported dysmenorrhea among studies and among patients in the various studies. Menstruation pain was generally measured with a visual analogue scale, an objective and validated patient-reported outcome that should ensure comparability across studies. Nonetheless, the data included in our quantitative synthesis represent the only available evidence on which to base pathogenic understanding and clinical decision-making.

CONCLUSION

The potentially progressive nature of adenomyosis and endometriosis is now recognized (45–48). These “sister entities” (50) can cause disabling pain, diminish health-related quality of life, cause absenteeism and presenteeism from school and work, and interfere with intimate and social relationships and conception (13–22, 41). In fact, gynecologists are all too often confronted with advanced and complicated disease forms, likely as a consequence of delayed diagnosis (15).

According to Munn et al. (27), systematic reviews of prevalence data can raise healthcare providers’ awareness of the actual clinical impact of diseases, including symptoms, conditions, and factors, and can inform research priorities. Grimes and Schulz (73) emphasize that descriptive studies, including cross-sectional prevalence studies, are useful for trend analysis, healthcare planning, and hypothesis generation. In this regard, the findings of the present review should induce a high index of suspicion for adenomyosis in clinicians whenever an adolescent presents with chronic severe dysmenorrhea and heavy menstrual bleeding and should prompt a timely, thorough, and focused evaluation. Moreover, if early-onset adenomyosis is identified by US or MRI, secondary prevention of disease progression and, possibly, endometriosis development could be considered by suppressing menses until conception is sought, thereby relieving disabling symptoms and preserving future reproductive potential (41).

Further rigorous prospective analytic studies are now needed to better define the epidemiological patterns of adenomyosis in the postmenstrual decade in different population subgroups. This may have both clinical and pathogenic implications (10). In particular, given the robust association with endometriosis, whether a temporal relationship exists between the two disorders should be disentangled. In addition, it would be valuable to investigate whether the strength of the association with endometriosis varies according to the type and severity of symptoms reported by patients with adenomyosis.

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CRediT Authorship Contribution Statement

Paolo Vercellini: Conceptualization, Writing – original draft, Writing – review & editing. Camilla Buffo: Investigation, Writing – original draft, Writing – review & editing. Veronica Bandini: Investigation, Writing – original draft, Writing – review & editing. Sonia Cipriani: Data curation, Formal analysis, Writing – review & editing. Francesca Chiaffarino: Data curation, Formal analysis, Writing – review & editing. Paola Viganò: Conceptualization, Writing – original draft, Writing – review & editing. Edgardo Somigliana: Conceptualization, Writing – original draft, Writing – review & editing.

Declaration of Interests

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