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Inês Tomás Jerónimo Oliveira

Non-invasive diagnosis of endometriosis in adolescents:
a systematic review

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Non-invasive diagnosis of endometriosis in adolescents:
a systematic review

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Professor Doutor João Bernardes

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TÍTULO DISSERTAÇÃO

Non-invasive diagnosis of endometriosis in adolescents: a systematic review

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ASSINALE APENAS UMA DAS OPÇÕES:

É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTES TRABALHOS APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
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Ao meu orientador, Dr. Pedro Viana Pinto, por ter aceitado este desafio e sobretudo pela disponibilidade. Aos amigos que Medicina me deu, por todos os momentos e partilhas. À família de Aveiro, pelo amor para a vida toda. À minha irmã, pela paciência no momento das indecisões. Ao Ivo, por todo o apoio, sem ele não seria possível. Ao meu namorado, por me inspirar.

Em especial, ao meu grande pilar.

As minhas conquistas são também as tuas, minha mãe.

Non-invasive diagnosis of endometriosis in adolescents: a systematic review

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ABSTRACT

Study Objectives: Our aim was to review the evidence concerning the non-invasive diagnosis of endometriosis in adolescents.

Methods: A systematic review was written following the SWiM reporting guidelines. The study research was made across three databases (MEDLINE/PubMed, Scopus, and Web of Science) to identify articles about the adolescent population and the diagnosis of endometriosis through non-invasive methods. The search included the keywords "endometriosis," "adolescents," "diagnosis," "ultrasound," and "MRI." Only English language articles were considered and those published prior to 2000 were excluded. The established outcomes focused on clinical symptoms, ultrasound (US), and magnetic resonance imaging (MRI) findings suggestive of endometriosis.

Results: We included 26 articles, mostly comprising case series and cross-sectional studies. The pooled analysis involved 2,299 female adolescents (age range 8-25 years old) with clinically suspected, imaged, and/or surgically confirmed endometriosis. The most frequently reported symptom was dysmenorrhea, followed by chronic pelvic pain. Among adolescents clinically suspected of endometriosis undergoing ultrasound (US), 32.8% exhibited at least one sign of endometriosis. Of the 167 patients with ultrasound-diagnosed endometriosis, 48.5% had deep infiltrating endometriosis (DIE), and 45.5% had an endometrioma detected. Three studies assessed MRI findings, revealing that 49.8% presented with signs of endometriosis.

Conclusions: Dysmenorrhea and chronic pelvic pain stand out as key symptoms of adolescent endometriosis. Although their diagnostic accuracy varies, both US and MRI have emerged as valuable tools for diagnosing the disease. While the US may have limitations, especially in detecting subtle lesions, MRI shows promise, even in cases with normal previous ultrasounds. Early recognition and proactive diagnosis are crucial for improving the management of endometriosis in adolescents.

KEYWORDS: Endometriosis, adolescent, diagnosis, ultrasound, US, magnetic resonance imaging, MRI.

1. INTRODUCTION

Endometriosis is a common gynaecological disorder thought to affect around 64% of adolescents with pelvic pain undergoing gynaecological investigation¹. It was first described in adolescents as early as the 1940s². Although more than 4 million reproductive-age women have been diagnosed with the disease, population-based studies show that an estimated 6 of 10 cases are undiagnosed³.

This chronic inflammatory disease is defined by endometrium-like tissue outside the uterus, most commonly on the ovary, peritoneum, and adjacent organs like the bladder or rectum⁴. Even though a benign disease, ectopic endometrial tissue may implant and develop an inflammatory reaction responsive to estrogens, leading to dysmenorrhea, dyspareunia, chronic pain, and infertility⁵. Although several theories have been developed over the years, the exact cause behind this disease remains unknown⁶. The natural course of the disease is unclear, and questions persist about the potential progression of superficial endometriosis to other subtypes, spontaneous regression, or implications for infertility, especially in the absence of treatment. The American Society for Reproductive Medicine (ASRM) categorises endometriosis into four stages (minimal, mild, moderate, and severe), determined by the location, depth, and site of lesions and adhesions⁷. Despite being the most widely used system, multiple revisions of the ASRM classification have not notably enhanced its predictive accuracy for pain, dyspareunia, or infertility^{8,9}.

Endometriosis is remarkably responsible for a decrease in women's quality of life (QOL), not only due to the physical discomfort it causes but also because of the mental and emotional burden involved¹⁰, both in adults and adolescents. It has been shown that dysmenorrhea occurs in 16% to possibly as high as 93% of teen girls and is the leading cause of recurrent short-term school absence in this age group¹¹. A survey analysis demonstrated that women with endometriosis

often begin to report symptoms in their adolescence, with 70% of the patients reporting before age 20 and nearly 40% before 15¹².

Diagnosis of endometriosis remains a challenge worldwide, especially in women who first experience symptoms at a young age. Recent evidence points out that it takes around 8 years to diagnose this disorder¹³ and the median delay in diagnosis increases if the symptoms are present in adolescence^{13, 14}. The lack of pathognomonic features or biomarkers¹⁵, the absence of an accurate and sufficient non-invasive diagnostic test^{16, 17}, and the variability in symptom patterns over time¹⁸ illustrate the difficulty imposed on clinicians, especially general practitioners, in the diagnosis of this disease. Furthermore, the disease in its earlier stages may be associated with different imaging and laparoscopic signals. To worsen the scenario, it is also known that the awareness of endometriosis in adolescents among medical professionals is low¹⁹.

Since symptoms of endometriosis usually begin in adolescence^{20, 21} and the huge future medical and social consequences associated, an approach in this age group becomes even more important. Furthermore, it is recognized that early lesions, although smaller and subtler may be associated with more severe symptoms than bigger and more fibrotic lesions, that are less metabolically active and inflammatory⁶. Treating the disease before central sensitization occurs may be key to guaranteeing a better quality of life for these patients. Furthermore, the need for a laparoscopy to make a diagnosis of this disease is, nowadays, not adequate for adult women and maybe even less for adolescents.

This systematic review aims to gather evidence concerning the accuracy of non-invasive diagnosis of endometriosis in adolescent patients. This contribution seeks to enhance our understanding of the appropriate approach in this specific population.

2. METHODS

This systematic review was conducted according to Synthesis without meta-analysis (SWiM) reporting guideline,²² used as an extension to PRISMA²³. The systematic review protocol is registered in the international PROSPERO database as No. CRD42023457516. Considering that this study was a systematic review, an Institutional Review Board was not required.

2.1 Search strategy

We aimed to assess how is endometriosis diagnosed in adolescent females, more specifically which non-invasive diagnostic procedures are being applied in adolescents with suspected endometriosis to achieve an early diagnosis. We took into consideration a variety of studies from 2000 onward in this analysis. Randomized controlled trials (RCTs), prospective cohort studies, case–control studies, retrospective cohort studies, and case series were screened.

We searched three databases: MEDLINE/Pubmed, Scopus, and Web of Science. The search strategy used was the query ("adolescent" OR "adolescence" OR "adolescents" OR "pediatric" AND "endometriosis" AND ("diagnosis" OR "ultrasound" OR "MRI")), on 24 August 2023. The search was limited to publications in the English language and articles published earlier than 2000 were excluded. The reference list of the included studies and relevant reviews on the matter were analysed to identify other studies for potential inclusion in this article.

2.2 Inclusion and exclusion criteria and study selection

All records identified using our search strategy were independently screened by two authors based on the titles and abstracts, applying predetermined inclusion and exclusion criteria. Any discrepancies were resolved by consensus, and different interpretations were resolved by a third author. The second selection stage was based on reviewing the full text of potentially relevant articles. The same independent reviewers read relevant full-text articles for inclusion.

Articles were included if the following inclusion criteria were met: a) adolescent population defined as patients between 10 and 24 years old, as defined by Sawyer et al.²⁴, or patients that

were referred as “adolescent” or “teenager”; b) patients who either have clinically suspected endometriosis or have received a diagnosis of endometriosis; c) the outcome refers to the diagnosis of endometriosis using non-invasive methods (clinical symptoms and/or imaging) or where the invasive diagnosis is compared with the non-invasive methods; and d) observational studies or interventional studies.

We excluded non-original studies classified as guidelines, reviews, conference abstracts, editorials, opinion articles, or protocols, as well as case reports and articles where the full-text manuscript was not available, after efforts contacting authors. Articles were excluded if they focused solely on adult women aged 18 or older and did not conduct a cluster analysis based on age, making it impossible to extract data specifically for the desired adolescent population.

For the process of study selection, EndNote was used to exclude duplicated studies, and online Rayyan software was used to help in the organization and selection of eligible studies.

2.3 Quality assessment

Quality assessment of cohort and cross-sectional studies was conducted using the Newcastle-Ottawa Scale (NOS) ²⁵. For the cross-sectional studies, an adapted NOS was used²⁶ and to evaluate the methodological quality of the case series and address potential biases in their conduct we used the JBI (Joanna Briggs Institute) Critical Appraisal tool ²⁷.

2.4 Data extraction

The following data was independently extracted from each of the studies to a spreadsheet: authors, publication year, country, study design, study period, studied population, number of participants either with clinically suspected and/or with the confirmed diagnosis of endometriosis by imaging and/or laparoscopically. Other items included were the non-invasive diagnosis imaging modality mentioned/used, outcomes of interest, and the aim of the study. Study outcomes on the clinical presentation of endometriosis, ultrasound (US), and Magnetic

resonance imaging (MRI) findings of endometriosis, and rASRM classification data from patients that have undergone laparoscopy/laparotomy were extracted too. A standardized table was created for each outcome after the data from the included studies were extracted. The studies were categorized based on the outcomes that were classified by the non-diagnostic tools used, such as clinical diagnosis, US findings, and MRI findings. This was thought to be the most transparent method of reporting the results.

Every study's results were combined, and since this condition significantly affects quality of life and none of the studies indicated a high risk of bias, none of the results were chosen for prioritization.

3. RESULTS

Our search identified a total of 1197 articles and 281 duplicates were excluded. After a review of 916 titles and abstracts, we retained 84 full-text articles for eligibility. Among them, 26 articles were included: 2 cohort, 1 case-control, 4 cross-sectional, and 19 case series studies. A flow diagram was created, using a PRISMA flowchart to describe this search method (*Figure 1*) and the main study characteristics are displayed in *Table I*.

Overall, the analysis included a total of 2 167 female adolescents with clinical and/or imagiological suspected diagnosis of endometriosis and 1124 (51.9%) female adolescents who underwent laparoscopy for a definitive diagnosis of endometriosis. The term 'adolescents' was defined differently in each study, with some authors sticking to the World Health Organization definition (up to 19 years old), while others defined it until 25 years old. The age range of the population studied was from 8 to 25 years old and the weighted mean of ages was 18,2 years old, calculated with the findings presented in 21 articles; 5 articles were excluded for this calculation due to lack of reports of individual patient ages. This systematic review covered cases from several continents.

Among 19 case series studies assessed using the JBI Critical Appraisal Checklist, 16 were deemed to have a "low" risk of bias, while 3 were categorized as having a "moderate" risk. Cross-sectional studies, evaluated through the NOS, scored between 5 and 7 points out of 10, with notable weaknesses in the selection process. The case-control study, with a NOS score of 5 out of 9 points, demonstrated bias in the representativeness of cases, selection of controls, and comparability. Cohort studies, despite the highest risk of selection bias, were considered of high quality. Bias assessment evaluation is demonstrated in **Supplementary Table S1**.

1. Clinical characteristics of endometriosis in adolescents

The clinical symptoms and physical examination findings of endometriosis in adolescent patients were assessed in 23 articles (**Supplementary Table S2**).

The typically reported symptoms of endometriosis such as dysmenorrhea and chronic pelvic pain were encompassed by less typical symptoms, such as vague abdominal pain, and gastrointestinal and genitourinary symptoms. Of the total of 1426 endometriosis patients included in this analysis, dysmenorrhea was the predominant symptom, reported by 82.9% of adolescent girls (1182 patients). Furthermore, 43% reported having chronic, acute, or acyclic pelvic discomfort, 18% abnormal uterine bleeding and 19% gastrointestinal symptoms. Dyspareunia was reported by 13.7% and urinary complaints were scarcely reported (6.6% of patients). Infertility was also a rare complaint (2.1%) since a great proportion of women were not sexually active or actually looking to conceive.

*Khashchenko et al.*²⁸ revealed moderate-severe dysmenorrhea in 97.8% (95.6% persistent to NSAIDs) of adolescents with laparoscopically confirmed peritoneal endometriosis (PE). High-intensity pain (7.5 ± 2.1 vs. 2.5 ± 2.3 in the control group, VAS points, $p < 0.001$) that most often began 1 day before menses and lasted 3 days into menses was reported; the majority (63.3%, 57/90) referred the symptoms since menarche and approximately 15.6% experienced pain daily.

DiVasta et al.¹⁸, reported endometriosis symptoms starting at 13 years old on average; Martire et al.²⁹ found more painful symptoms in adolescents with US signs of endometriosis.

Al-Jefout's study³⁰ found a significant association ($p=0.039$) between endometriosis and cold intolerance, particularly in those with generalized anxiety disorder.

The majority of cases described (74.2%) had mild to moderate disease according to the ASRM (**Table II**), with studies, such as Marsh et al.³¹ and Unger et al.³² with no cases of severe endometriosis (stage III and IV).

2. US Findings

Overall, only 7 studies reported US findings in patients with endometriosis (**Table IIIA**).

Among the 509 adolescents who underwent US testing and were clinically suspected of having endometriosis, 32.8% exhibited at least one ultrasound marker indicative of the disease. Out of the 167 patients with ultrasound-confirmed endometriosis, 45.5% presented with endometrioma, 48.5% had deep infiltrative endometriosis (DIE), 40.1% showed signs of adenomyosis, and 13.7% displayed adhesions.

Martire et al.²⁹, included in their study adolescents with ultrasound for different clinical indications; from this population, 36 women had at least one sign of endometriosis; DIE was detected in 10 adolescents. The symptom that exhibited the strongest correlation with ultrasound findings of endometriosis was dysmenorrhea, reported in 86.1% of the patients. In their study in 2023¹⁶, there was a statistically significant difference in the number of cases between early adolescents (12-16 years – 27/39 with normal ultrasound) and young women (21–25 years – 90/211 with normal ultrasound); the majority of patients with US signs had posterior DIE (53.4%, the majority in the uterosacral ligaments) and an endometrioma (41.2%). Only one case of anterior DIE was identified in both studies.

In the articles with a laparoscopic diagnosis of endometriosis, the majority described a pelvic

mass in the US, but not specifically endometrioma. Interestingly, in the study by Yang et al.³³, adolescents with genital tract malformations had mainly ovarian endometriosis (14/15), while adolescents with a normal genital tract had both, DIE (26/48) and ovarian endometriosis (41/48).

Table IIIB summarizes the results of the data analysis, for the detection of endometriotic lesions in the ultrasound, compared with the gold standard, laparoscopy. In the study by Yang et al.³³, of 63 patients with endometriosis, a pelvic mass was found in 87.3%. In the Audebert et al. study³⁴, 36.4% of the findings in the US correspond to an endometrioma and DIE after histological confirmation. Ragab et al.³⁵, from the 56 patients who had severe dysmenorrhea refractory to medical therapy and positive ultrasound picture of endometriosis, only 34 accepted laparoscopy, with a confirmed diagnosis in 79.4% of the cases. In the Khashchenko et al. study²⁸, ecografic signs of PE were found in only 3,3% of the patients.

3. Pelvic MRI Findings

Table IV represents the 3 studies that included MRI findings of adolescent patients with suspected or confirmed endometriosis.

Among 22 patients in the study by Ragab et al. with severe dysmenorrhea and positive ultrasound for endometriosis who declined laparoscopy, an MRI had findings consistent with endometriosis in 77.3% (n=17)³⁵.

Of the 308 adolescent girls included in Millischer et al.³⁶, 39.3% presented with endometriosis signs at MRI, the majority (88.9%) with DIE; 11,4% had also signs of adenomyosis. The majority of ovarian endometriomas occurred in those aged ≥ 18 years, while retrocervical lesions were observed from a young age (< 15 years). Rectosigmoid lesions were rare (3.3%), with all the intestinal lesions diagnosed after the age of 17 years. Ureteral or bladder involvement was absent. Interestingly, 107 adolescents with endometriosis suspected in the MRI had a previous

ultrasound without suspicion of the disease.

In *Khashchenko et al.*²⁸ study, 78.9% of pediatric patients showed MRI signs of PE, mainly in uterosacral ligaments (39.4%), parametrium (38.0%), pouch of Douglas (25.4%), and peritoneum of the ovarian fossae (29.6%).

4. DISCUSSION

Despite being widely researched in adult women, endometriosis presents a variety of difficulties for clinicians particularly when it comes to adolescents. Given the limited literature surrounding diagnostic characteristics in this population, the management approach often relies on extrapolated data gathered in adults. This study collected data to enhance our understanding of this disease in adolescents and the efficacy of the non-invasive tools at our disposal to achieve an early diagnosis, showing that dysmenorrhea and chronic pelvic pain are the most common symptoms of the disease in adolescents and that ultrasound and MRI may have an important role for its diagnosis. All the subtypes of endometriosis were diagnosed, going through peritoneal lesions, ovarian endometriosis and DIE.

1. Clinical characteristics of endometriosis in adolescents

Overall, adolescents with endometriosis commonly experience severe dysmenorrhea resistant to conventional treatments such as contraceptive pills, NSAIDs, or antispasmodics. The second most frequently reported symptom was pelvic pain, which, when coupled with persistent dysmenorrhea despite pharmacological treatments, strongly correlates with the presence of endometriosis. Nongynecologic symptoms may also occur frequently in adolescents with endometriosis, such as gastrointestinal manifestations and other vague abdominal symptoms. Attention should be given to the potential bias that may be implicit when addressing dyspareunia. In early adolescence, a higher number of pre-sexually active girls results in a lower percentage of dyspareunia being reported, as shown in *Martire et al.*²⁹, however, sexually active teenagers appear to have more severe dyspareunia than do older women³⁷.

Martire's 2020 and 2023 results^{16, 29} reveal that although dysmenorrhea was considered an indication for US examination in 10.4% of cases, the symptom was self-reported by 54.4% of patients when interviewed, making it the most common symptom. The 2023 study further found that patients reported severe dysmenorrhea only when specifically questioned about pelvic pain and asked to score their symptoms using the Visual Analogue Scale (VAS). These findings suggest not only an underestimation of endometriosis symptoms by adolescents, who may perceive dysmenorrhea as a natural aspect of menstruation but also by general practitioners. Both articles underscore dysmenorrhea as a reliable indicator of endometriosis, emphasizing the need to recognize it in adolescents as a warning sign. The studies highlight the crucial need for actively inquiring about this symptom to ensure accurate diagnosis and appropriate management.

The results demonstrated by *Al-Jefout et al.*³⁰ suggest a potential link between chronic pain conditions, such as endometriosis, and a higher likelihood of anxiety-related symptoms, including cold intolerance.

While symptoms may align closely with the existence of endometriosis, they do not necessarily correspond to the stage or severity of the disease. The proposition that has been put forward suggests that endometriosis may be characterized as a "progressive" condition, as proposed by *Brosens et al.*^{21, 38}. Prior studies addressing non-invasive endometriosis diagnosis in adolescents³⁹ revealed that the majority of adolescents are diagnosed with Stage I endometriosis. Our study reinforces these observations, with most laparoscopically confirmed cases in the lower ASRM stages.

Stochino's findings⁴⁰ suggest an age-related increase in endometriosis severity, with adolescents (<20 years) having a mean disease stage of II. Furthermore, in the studies by *DiVasta* and *Martire et al.*^{16, 18, 29}, no cases of advanced disease were diagnosed by laparoscopy or ultrasound, respectively, corroborating previous results mentioned. This is consistent with published data in regards to staging of endometriosis^{41, 42, 43, 44, 45}.

An exception is observed in 5 studies^{33, 46, 47, 48, 49}, which report a large proportion of patients with endometriosis Stage III and IV. This advanced-stage prevalence may be attributed to complex cases treated in tertiary centres, delayed healthcare seeking, traditional medicine use, and the acceptance of surgery only when pelvic masses are evident. Fong's findings⁴⁹ suggest that older age (82.3% of women aged 21-25 years), higher prevalence of ovarian endometriomas (a marker of extensive disease), and selection bias (retrospective nature of the study) contributed to advanced-stage overrepresentation. Importantly, the majority of cases with higher ASRM stages in adolescents are due to ovarian endometriomas (compared with extensive peritoneal or adhesive disease). Lee et al.⁴⁸ reported only cases of Stage III and IV since the population included were adolescent females who underwent surgery for endometrioma, a lesion frequently associated with advanced endometriosis, a condition that often requires surgical intervention.

Endometriosis in its early stages may be associated with more metabolically active lesions, possibly associated with more painful symptoms, as opposed to larger more fibrotic lesions. *Wuest et al.*³⁷ observed in their study that women younger than 24 years old with endometriosis had higher visual analogue scale scores for dysmenorrhea and non-cyclic pelvic pain than women older than 24. *Tandoi et al.*⁴⁷ pointed out that young age represents a determinant for the recurrence of the disease, speculating that the younger the age of onset, the more aggressive form of endometriosis. Also, *Smorgick et al.*⁵⁰ demonstrated that the occurrence of daily pelvic pain was found to be more common among women with early-stage endometriosis.

2. US findings

Girls undergoing US had an average age of 17.3 years, reflecting late adolescence. This aligns with increased sexual activity, contraception-seeking behaviour, and gynaecological consultations. Notably, only 7 of 26 articles provided detailed US findings, even though the majority of articles mentioned its use.

Only 32.8% of the adolescents evaluated by ultrasound without laparoscopy showed signs of endometriosis, possibly due to challenges in detecting small lesions in young patients. Some examinations were performed with a transrectal probe, which may have a lower sensibility for this disease. However, it should be reinforced that even with normal US findings in adolescents, the disease should be taken into consideration. Experienced sonographers in accurately diagnosing endometriosis in this age group should be involved in the diagnosis.

Dysmenorrhea (86.1%) and dyspareunia (22.2%) were the most frequently reported symptoms by Martire et al. (16) that were linked to ultrasound findings for endometriosis. In the younger age group (12 to 16 years old), there was a lower prevalence of posterior DIE, endometrioma, and adenomyosis compared with the oldest group (17 to 20 years old). Martire's studies highlight the prevalence of posterior compartment involvement in adolescent patients with endometriosis, contrasting with minimal reports in the anterior compartment, where only one lesion was reported. These results are consistent with the ones found by *Ozyer*⁵¹ and *Millischer*³⁶. This anatomical distribution supports the retrograde menstruation theory in this population, explaining the preference for lesions in Douglas's pouch⁵².

Genital tract malformations were identified as a feature associated with endometriosis, with adolescents with genital malformations³³ having an earlier diagnosis and mainly endometriomas⁵³. This can be attributed to the correlation between obstructive tract anomalies and increased retrograde menstruation, both risk factors for severe pelvic pain and endometriosis⁵⁴. Studies vary greatly in how sensitive the US is for diagnosing endometriosis. The study design and the population recruitment strategy (adolescents with a laparoscopic diagnosis of endometriosis) limited the calculation of the true negative and false positive rates, and consequently the specificity of the US.

Our results suggest a complex landscape regarding the accuracy of ultrasound in diagnosing endometriosis in young females. The heterogeneity in methodologies, such as the requirement

for laparoscopic confirmation and retrospective data collection, contributes to varying true positive rates across studies.

3. MRI findings

In the studies included, MRI seems to be a promising diagnostic tool even in patients who previously had normal ultrasounds. Results should be interpreted carefully, as we are not aware of how the previous US was performed (transvaginal/transabdominal approach, experienced sonographers...) and one study focused on PE. MRI provides accurate insights into various forms of endometriosis and proves informative in assessing the extent of organ involvement, the presence of lesions away from the transvaginal ultrasound field, and the severity of adhesive processes. *Khashckenko et al.*²⁸ corroborate the superior diagnostic accuracy of MRI over ultrasound (US) for detecting PE in adolescents.

*Millischer et al.*³⁶ revealed an age-dependent increase in the prevalence of MRI-visible endometriosis, particularly among adolescents with severe dysmenorrhea, confirming that endometrioma and/or DIE can be observed in a large number of adolescents. Caution is warranted due to the potential overestimation of DIE lesions, given the recognized rate of false positives in MRI, even when administered by trained radiologists.

Limitations

This systematic review notes some limitations: English-only searches, a small sample size (n=26), and varied 'adolescent' definitions, leading to population heterogeneity. Scarce publications on ultrasound and MRI limit understanding of their role in diagnosing endometriosis. Also, the literature mainly comprises case series, offering low-grade evidence. Laparoscopic challenges in diagnosing subtle atypical lesions such as those that are clear, white, or red being more common are more prone to being missed during surgery even by experienced surgeons adding complexities. This means that even in reports with laparoscopically confirmed endometriosis, the population might be truly underrepresented. Selection bias comes from predominantly

including adolescents with prior diagnoses. The suitability of ASRM classification is uncertain in this population and data heterogeneity prevents the performance of a meta-analysis.

Strengths

While an increasing number of papers have addressed endometriosis in adolescence in recent years, this systematic review represents the first comprehensive systematic review focused on non-invasive diagnostic methods for endometriosis in this specific population, with a high number of adolescents included from many different countries. The study's strength lies in its meticulous methodological design, with a registered a priori protocol, guarding against selective reporting and substantial deviations from the original plan. Despite variations in age groups, outcome measures, and follow-up moments in the published literature, the study provides the most precise overview of the current knowledge on diagnosing endometriosis in the adolescent population. Promisingly, the majority of studies in this review were classified as low risk of bias, contributing to the robustness of the findings.

Future research

Future research should not only concentrate on identifying disease markers and expanding the role of MRI but also on enhancing endometriosis awareness by patients, general practitioners, and paediatricians for further diagnosis, emphasizing predictive algorithms for the disease stage such as questionnaires assessing women's medical, obstetric and family history, along with the pattern of symptoms. Continued validation and wider implementation of these algorithms may help cut down on pointless surgeries, particularly in cases where patients with severe symptoms and advanced disease who are not responding to current treatments might benefit more from surgery. Research on imaging methods for diagnosing endometriosis in adolescents is vital for improving diagnostic accuracy. Advances in transvaginal ultrasound criteria and additional techniques show promise.

5. CONCLUSION

This systematic review has successfully identified patterns that can offer valuable insights for clinicians when assessing adolescent patients with pelvic pain. Dysmenorrhea and persistent pelvic pain were the most frequently reported symptoms while US and MRI appear to offer valuable information for the disease's diagnosis when performed by qualified radiologists and sonographers. Posterior DIE is also identified in this population and anterior compartment DIE seems rare. Furthermore, adolescents seem to experience severe pain more frequently than older women. The great number of different pain symptoms and low-stage lesions, based on the ASRM classification, reported in adolescents aligns with the hypothesis that endometriosis is a progressive disease. The review underscores the importance of non-invasive endometriosis diagnosis in adolescents, advocating for careful consideration of surgical interventions when imaging is normal. This represents an important step forward in understanding and managing endometriosis in adolescents.

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Author Contributions

All authors contributed to the design of this review. IO and PP developed the search strategy with the help of JB. After the final search, IO was the first reviewer for article screening. PP and JB were the independent second and third reviewers for article screening. IO and PP contributed to data analysis, interpretation and writing. JB contributed to data interpretation, reviewing the article and approving the final version.

Disclosure/Conflict of Interest Statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Figure Legend

Figure 1. PRISMA flowchart ²³ showcasing the search method.

N – Number

Table Legends

Table I. Characteristics of included studies in our systematic review.

N.Par - number of participants with clinically and/or imagistically suspected and/or confirmed diagnosis of endometriosis; NID - Non-invasive diagnosis method used; US - ultrasound imaging; MRI - magnetic resonance imaging; rASRM - revised American Society of Reproductive Medicine classification; CPP= chronic pelvic pain

*weighted mean age

TABLE II. Studies where endometriosis adolescent patients underwent laparoscopy/laparotomy and the Revised American Society for Reproductive Medicine classification of endometriosis was utilized (rASRM).

TABLE III. A - US findings in patients with clinically suspected endometriosis and US findings in patients laparoscopically diagnosed with endometriosis. **B** - Diagnostic accuracy of US findings in adolescent patients with clinically suspected endometriosis who underwent US and laparoscopic surgery to confirm the diagnosis of endometriosis.

NR - not reported; DIE - deep infiltrating endometriosis; US - ultrasound; PE - peritoneal endometriosis; NR – not reported

*24.1% of the adolescent population were referred to the US unit for a routine scan in the absence of any symptoms or clinical suspicions ($270 \times 24.1\% = 65$; $270 - 65 = 205$). Since no asymptomatic teenager had endometrial signs in ultrasound, 65 adolescents were excluded from the analyses.

**18.1% of the teenagers had routine examination referrals for the US, meaning that endometriosis was not suspected by the clinician in these cases. 67 teenagers were excluded from our analyses since all endometriotic abnormalities had been identified in symptomatic patients.

***60.7% accepted laparoscopic surgery.

TABLE IV. Pelvic MRI findings in patients with clinically and/or imagological suspected signs of endometriosis

NR - not reported; OMA - ovarian endometrioma; DIE - deep infiltrating endometriosis; PE - peritoneal endometriosis

Supplementary Table S1. A. Bias appraisal in case-series studies included in the systematic review. **B.** Bias appraisal in the cross-sectional studies included in the systematic review. **C.** Bias appraisal in the case-control study included in the systematic review. **D.** Risk of bias from the NOS tool for the cohort studies included in our systematic review.

NA – not applicable; UN – unclear.

Supplementary Table S2. Studies evaluating the clinical symptoms and physical examination findings of endometriosis in adolescent patients with suspected or confirmed diagnosis of endometriosis by laparoscopy.

GI - gastrointestinal; GU - genitourinary; VAS - visual analogue scale; MRI - magnetic resonance imaging; NSAIDs - non-steroidal anti-inflammatory drugs.

Identification of studies via databases and registers

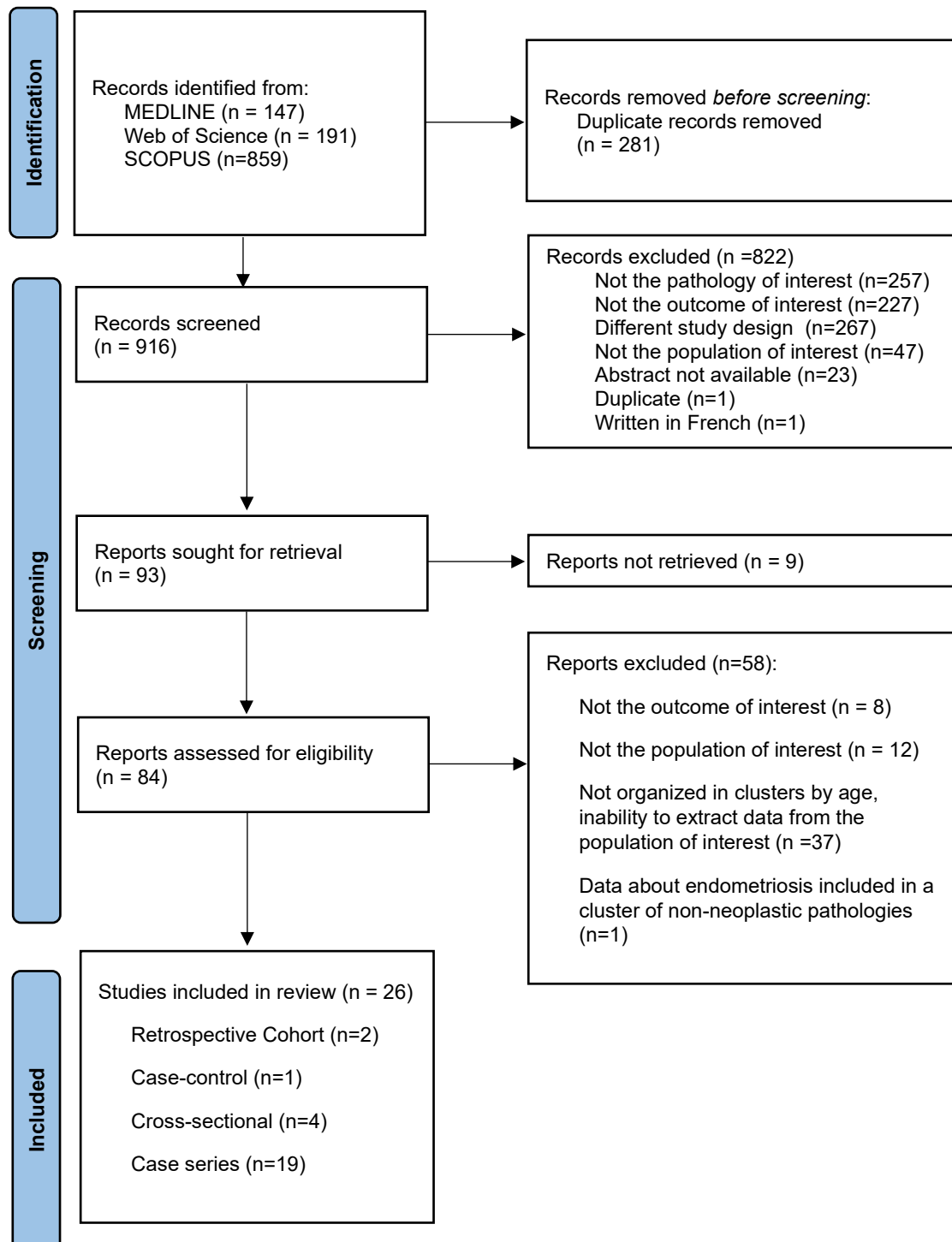


Table I. Characteristics of included studies in our systematic review.

<i>Author, year</i>	<i>Country</i>	<i>Study design</i>	<i>Study period</i>	<i>Population of the study*</i>	<i>N. Par.</i>	<i>Mean age</i>	<i>NID image</i>	<i>Outcomes of interest</i>	<i>Aim of the study</i>
Bai, S et al 2002 ⁵⁵	Korea	Retrospective analysis; Case series	1990-1999	Adolescent girls aged 14 to 21 years old, who had undergone a laparotomy or laparoscopy and were diagnosed with endometriosis.	39	20,1	-	Chief symptoms leading to the diagnosis, clinical stage, age distribution, and treatment modality.	Evaluate the age distribution, diagnosis, clinical stage, and treatment for endometriosis in adolescents in Korea.
Marsh, E et al, 2005 ³¹	USA	Case-series	-	Premenarcheal girls, aged 8 to 13 years old, with chronic pelvic pain of unclear origin who underwent US and laparoscopic excision of endometriotic lesions.	5	-	US	Visual presence of endometriosis and decrease in pelvic pain after destruction of lesions.	Identify endometriosis as a cause of chronic pelvic pain in premenarcheal girls without an obstructive anomaly of the reproductive tract.
Roman, J et al, 2010 ⁵⁶	New Zealand	Comparative Cohort	2003-2009	Female patients aged 14 to 19 years old, who underwent operative laparoscopy at Braemar Hospital with the presumptive diagnosis of endometriosis.	20	17.4	US; MRI	Chief complaint at the initial consultation; gynaecological examination findings; VAS for endometriosis-related symptoms; surgical findings.	Describe their experience with laparoscopic excision of endometriosis in an adolescent population and to compare it with a non-adolescent population treated during the same period.
Vicino, M et al, 2010 ⁴⁶	Italy	Prospective analysis; Case-series	2005-2006	Females aged ≤21 years who had a first surgically confirmed diagnosis of endometriosis.	38	18.6	-	Age at diagnosis, symptoms at presentation, and stage of disease according to rASRM classification.	Analyze the clinical manifestations of endometriosis in adolescents.
Tandoi, I. et al, 2011 ⁴⁷	Italy	Retrospective analysis; case series	2000 - 2005	Female aged 16 to 21 years old with a surgically and histologically confirmed first diagnosis of endometriosis by laparoscopy or lapa-rotomy.	57	19	US	Recurrence of endometriosis after conservative surgery for endometriosis based on clinical symptoms, physical examination, and US findings.	Determine a profile of women with a consistently higher risk of recurrence who may benefit from specific management strategies.
Unger, C et al, 2011 ³²	USA	Case-series	-	Patients aged 13 to 16 years old, with complaints of severe pelvic pain, and diagnosed with stage 1 endometriosis at the time of laparoscopy.	3	14	-	Clinical presentation.	Describe 3 cases of endometriosis progression in adolescents who did not maintain medical regimen postoperatively.
Yeung, P et al, 2011 ⁵⁷	USA	Prospective analysis;	1999-2007	Teenagers aged 12 to 19 years old, with symptoms suspicious for	17	-	-		Determine long-term outcomes after complete laparoscopic excision in a teenage population.

		case series		endometriosis who underwent laparoscopic excision.				Rate of recurrent (or persistent) endometriosis.	
Yang, Y et al, 2012 ³³	China	Retrospective analysis; case series	1992-2010	Patients aged 12 to 20 years of age who underwent surgery and had a pathologically confirmed diagnosis of endometriosis	63	18,4	US	Clinical symptoms, preoperative ultrasound findings, surgical procedures, and findings, and post-operation management (recurrence).	Present the experience in diagnosis, management, and follow-up of endometriosis in a Chinese adolescent population.
Lee, D. et al, 2013 ⁴⁸	Korea	Cross-sectional	2003-2010	Adolescent females ≤ 20 years old who underwent laparoscopic surgery for the treatment of endometrioma	35	19.2	-	Clinical characteristics include demographic factors, menstrual patterns, and characteristics of endometriosis.	Evaluate the clinical characteristics of endometrioma in adolescent women compared to women of other age groups.
Özyer et al, 2013 ⁵¹	Turkey	Retrospective analysis; case series	2007-2011	Adolescent females and young women, aged 17 to 24 years old who underwent laparoscopic surgery for ovarian endometrioma	63	22	US	Symptoms on admission; endometriosis characteristics during surgery; Adnexal adhesions according to rASRM classification.	Evaluate clinical aspects of endometriomas encountered in late adolescent females and young women and to review the issues specifically related to the disease in this age group.
Andres, M et al, 2014 ⁵⁸	Brazil	Retrospective analysis; case series	2008-2013	Patients, aged 13 to 20 years old, undergoing surgery with a histological diagnosis of endometriosis	21	17,9	US; MRI	The clinical condition of adolescents with Endometriosis.	Report the clinical characteristics of adolescent patients with endometriosis.
Smorgick, N et al, 2014 ⁵⁰	USA	Retrospective analysis; case series	2000-2011	Adolescents and young women who underwent surgery for suspected/confirmed endometriosis and were ≤22 years old at the time of surgery	86	19,9	-	Pain symptoms; indication for surgery; endometriosis stage reported according to the revised AFS classification.	Describe the prevalence and characteristics of advanced-stage endometriosis in adolescents and young women.
Timur, E et al, 2015 ⁵⁹	Turkey	Retrospective analysis; case series	2008-2012	Patients < 18 years who underwent an operation for an adnexal mass	41	14,5	US; MRI	Complaints during admission, images of the masses that were detected with different modalities, laboratory findings, applied surgical procedures, and pathology findings.	Evaluate preoperative findings, surgical procedures, and histopathologic findings of the adolescent patients who had surgery for adnexal mass.
Dun, E et al, 2015 ¹¹	USA	Retrospective analysis; case series	2001-2009	Adolescent females, aged 10 to 21 years old with endometriosis diagnosed during laparoscopy for pelvic pain	25	17,2	-	Symptoms, time from onset of symptoms to correct diagnosis, number, and type of medical professionals seen, diagnosis, treatment, and postoperative outcomes.	Describe the experience of adolescents who underwent laparoscopy for pelvic pain and were diagnosed with endometriosis.

Ragab, A. et al 2015 ³⁵	Egypt	Cross-sectional	2012-2014	Adolescent school girls from 3 different schools covering rural and urban areas in Egypt, with symptoms and signs suggestive of endometriosis	56	15.2	US; MRI	Symptoms of endometriosis, the accuracy of abdominal US, MRI, and laparoscopic findings.	Determine the prevalence of endometriosis among adolescent school girls with severe dysmenorrhea.
Audebert, A et al, 2015 ³⁴	France	Retrospective analysis; case series	1998-2013	Adolescents, aged 12 to 19 years old who underwent surgical treatment for endometriosis.	55	17,8	US; MRI	The main indications for surgery, are preoperatively ultrasound findings, medical history, family history of endometriosis, operative findings, clinical symptoms, and MRI findings at follow-up.	Illustrate the different clinical presentations of these cases while providing accurate follow-up data, with a focus on the recurrence of symptoms, disease, and fertility outcomes.
Fong, Y et al, 2017 ⁴⁹	Singapore	Retrospective analysis; case series	2000-2007	Patients aged 14 to 25 years old who had laparoscopy for suspected endometriosis, with histological.	45	-	US	Presenting symptoms, Investigation findings (preoperative US).	Describe the disease pattern in a group of young Asian women with a histological diagnosis of endometriosis.
Matalliotakis, 2017 ⁶⁰	Greece	Retrospective analysis; case series	1996-2016	Patients aged 13 to 21 years old who underwent surgical treatment for endometriosis using laparoscopy or laparotomy	55	18,3	-	Presenting symptoms, age at menarche, history of asthma, obstetric outcome, family history, and congenital malformations.	Evaluate endometriosis in adolescents and young girls; review the menstrual, reproductive characteristics, and risk factors.
Al-Jefout, M et al, 2018 ³⁰	Canada	Prospective analysis, case series	2010-2014	Female patients, aged 15 to 21 years old, who had CPP refractory to conventional medical therapy	28	18.4	US	Presence and stage of endometriosis at laparoscopy, the presence of cold intolerance, and the severity and duration of pain symptoms.	Explore the prevalence and clinical manifestations of endometriosis in young women with CPP refractory to conventional medical therapy.
DiVasta, A et al, 2018 ¹⁸	USA	Cross-sectional	2012-2016	Adolescents (diagnosed at ≤18 years old) with surgically confirmed endometriosis.	295	16	-	Clinical presentation - self-reported pain, dysmenorrhea, urinary or bowel movement habit changes, infertility.	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.
Stochino-Loi, E et al, 2020 ⁴⁰	France, Switzerland, Denmark	Retrospective analysis; case series	2009-2014	Adolescent patients, aged < 20 years old, who underwent surgical management of symptomatic endometriosis.	32	-	-	Main baseline painful symptoms compared between groups of age.	Assess the relationship between age, location of the disease, and surgical procedures performed in patients undergoing surgical management of endometriosis.

Martire, F et al, 2020 ²⁹	Italy	Retrospective analysis; case series	2014-2019	Adolescent patients aged 12 to 20 years, who received a pelvic US examination with a transvaginal (TVS) or transrectal (TRS) probe.	205	18	US	Locations of endometriosis were recorded using a dedicated ultrasound mapping sheet and the severity of painful symptoms.	Evaluate the ultrasonographic presence of different forms of endometriosis and the associated clinical symptoms in adolescent women.
Khashchenko, E. P et al, 2023 ²⁸	Russia	Case-control study	2020-2022	Cases: Girls from menarche to 17 years old with a laparoscopically confirmed diagnosis of peritoneal endometriosis (PE); Controls: healthy adolescent girls of the same age with regular periods and no gynaecological and endocrine pathologies.	90 (cases)	16	US; MRI.	Clinical symptoms, diagnostic accuracy of VAS score; US for the pelvic organs; MRI findings - frequency of suspected PE, location of endometriotic foci, and accuracy of signs in the prediction of laparoscopic confirmation of PE.	Compare the clinical features, instrumental diagnostics, and surgical and histological peculiarities in adolescent patients with peritoneal endometriosis.
Martire, F et al, 2023 ¹⁶	Italy	Retrospective analysis; case series	2016-2021	Women aged 12–25 years were referred to a gynaecological ultrasound (US) Unit with severe dysmenorrhea.	304	20,8	US	Locations of endometriosis using the US; Painful symptoms correlated to the different endometriosis forms.	Diagnose endometriosis in young patients ≤ 25 with severe dysmenorrhea through US findings and correlate the symptoms to its different forms.
Millischer, A et al, 2023 ³⁶	France	Prospective analysis; cross-sectional	2019-2020	Adolescents aged 12-20 years who underwent MRI for severe dysmenorrhea	345	17,4	MRI	Data on the endometriosis phenotypes (OMA and/or DIE) and distribution of anatomical lesions; The severity of painful symptoms.	Evaluate the prevalence of MRI of ovarian endometrioma (OMA) and deep infiltrating endometriosis (DIE) in adolescents presenting with severe dysmenorrhea.
Wüest, 2023 ³⁷	Switzerland	Retrospective cohort study	2017-2020	Patients, aged 15 to 24 years old, with a diagnosis of endometriosis (either clinically suspected, diagnosed by examination and imaging, or confirmed by surgery).	144	-	US; MRI	The difference in the severity of the symptoms between 2 age groups, with and without hormonal treatment.	Analyze the clinical characteristics and severity of symptoms in adolescent patients with endometriosis compared with older patients.
Total					2167	18,2*			

N.Par - number of participants with clinically and/or imagistically suspected and/or confirmed diagnosis of endometriosis; NID - Non-invasive diagnosis method used; US - ultrasound imaging; MRI - magnetic resonance imaging; rASRM - revised American Society of Reproductive Medicine classification; CPP= chronic pelvic pain

*weighted mean

TABLE II. Studies where endometriosis adolescent patients underwent laparoscopy/laparotomy and the **Revised American Society for Reproductive Medicine classification of endometriosis** was utilized (rASRM).

Author	No pat.	<i>rASRM classification of endometriosis</i>			
		I	II	III	IV
<i>Bai, et al.</i> ⁵⁵	39	4 (10%)	17 (44%)	11 (28%)	7 (18%)
<i>Marsh, et al.</i> ³¹	5	5 (100%)			
<i>Roman, et al.</i> ⁵⁶	20	8 (40%)	9 (45%)	1 (5%)	2 (10%)
<i>Vicino, et al.</i> ⁴⁶	38	7 (18.4%)	5 (13.2%)	13 (34.2%)	13 (34.2%)
<i>Tandoi, et al.</i> ⁴⁷	57	14 (24.6%)		43 (75.4%)	
<i>Unger, et al.</i> ³²	3	3 (100%)	0	0	0
<i>Yeung, et al.</i> ⁵⁷	17	5 (29.4%)	11 (64.7%)	1 (5.9%)	0
<i>Yang, et al.</i> ³³	63	5 (7.9%)	2 (3.2%)	33 (52.4%)	23 (36.5%)
<i>Lee, et al.</i> ⁴⁸	35			17(49)	18(51)
<i>Özyer, et al.</i> ⁵¹	63	55 (87%)		8 (13%)	
<i>Smorgick, et al.</i> ⁵⁰	86	58 (67%)	8(9%)	7(8%)	13(15%)
<i>Dun, et al.</i> ¹¹	25	17 (68%)	5 (20%)	3 (12%)	0
<i>Ragab, et al.</i> ³⁵	27	12 (44.4%)	7 (26%)	8 (29.6%)	0
<i>Audebert, et al.</i> ³⁴	55	33 (60%)		22 (40%)	
<i>Fong, et al.</i> ⁴⁹	45	5 (11.1%)	8 (17.8%)	19 (42.2%)	13 (28.9%)
<i>Matalliotakis, et al.</i> ⁶⁰	55	25 (45.4%)	20 (36.4%)	8 (14.5%)	2 (3.7%)
<i>Al-Jefout, et al.</i> ³⁰	20	9 (45%)	8 (40%)	2 (10%)	1 (5%)
<i>DiVasta, et al.</i> ¹⁸	295	295			
<i>Khashchenko, et al.</i> ²⁸	90	58 (64.4%)	25 (27.8%)	7 (7.8%)	0
<i>Wüest, et al.</i> ³⁷	34	21 (61.8%)	5 (14.7%)	6 (17.6%)	2 (5.9%)
Total	744	552 (74.2%)		192 (25.8%)	

TABLE III. A - US findings in patients with clinically suspected endometriosis and US findings in patients laparoscopically diagnosed with endometriosis. **B** - Diagnostic accuracy of US findings in adolescent patients with clinically suspected endometriosis who underwent US and laparoscopic surgery to confirm the diagnosis of endometriosis

US findings in patients with clinically suspected endometriosis				
Author, year	No. patient	Age range	US method/device	US findings (no patients, %)
Ragab, 2015 ³⁵	220	NR	Transabdominal probe	Positive US findings (56, 25.4%)
Martire, 2020 ²⁹	205*	12-20	Voluson E6 or E8 device with transvaginal/transrectal probe	≥ 1 US sign of endometriosis (36, 17.6%): Negative posterior sliding sign (18, 6.7%) Adnexal adhesions (18, 6.7%) DIE (10, 3.7%) Endometrioma (22, 8.1%)
Martire, 2023 ¹⁶	304**	12-25	Voluson E6 or E8 or E10 device with transvaginal/transrectal probe	≥ 1 typical US sign of pelvic endometriosis or adenomyosis (131, 43.1%) Posterior DIE (70, 18.9%) Anterior DIE (1, 0.3%) Endometrioma (54, 14.5%) Adenomyosis (67, 18.1%) Adhesions (15, 13.7%)
Total of patients with clinically suspected endometriosis	729	12-25	-	167 (32.8%) ≥ 1 sign of endometriosis in US DIE (81/167, 48.5%) Endometrioma (76/167, 45.5%) Adenomyosis (67/167, 40.1%) Adhesions (33, 19.8%)
US findings in patients laparoscopically diagnosed with endometriosis				
Yang, 2012 ³³	63	12-20	NR	Pelvic mass (55, 87.30%) Genital tract malformations (15, 23.8%)
Audebert, 2015 ³⁴	55	12-19	NR	Pelvic mass (23, 41.8%) Mullerian abnormality (4, 7.3%)
Fong, 2017 ⁴⁹	42	14-25	NR	Bilateral ovarian cysts (18, 42.9%) Unilateral ovarian cyst (23, 54.8%)
Al-Jefout, 2018 ³⁰	20	15-21	NR	Ovarian mass (8, 40%) Endometrioma (3, 15%)
Khashchenko, 2023 ²⁸	90	15-17	Vivid-q, GE HEALTHCARE, with transabdominal probe	Signs of peritoneal endometriosis (3, 3.3%): thicker uterine walls, thicker endometrium, similar ovarian morphologies.
Total of patients with laparoscopically diagnosis of endometriosis	270	12-25	-	Pelvic mass/cyst: 127 (47%) Endometrioma: 3 (1.1%)

B.

Author	US FINDING	NO PATIENTS	TP (%)	FP (%)	FN (%)	TN (%)
<i>Yang, et al.</i> ³³	Pelvic mass	63	87.3	-	12.7	-
<i>Audebert, et al.</i> ³⁴	Pelvic mass	55	36.4	-	63.6	-
<i>Ragab, et al.</i> ³⁵	NR	34***	79.4	20.6	0	100
<i>Fong, et al.</i> ⁴⁹	Ovarian cyst	42	97.6	-	2.4	-
<i>Khashchenko, et al.</i> ²⁸	PE	90	3,3	-	96.7	-

NR - not reported; DIE - deep infiltrating endometriosis; US - ultrasound; PE - peritoneal endometriosis; NR – not reported

*24.1% of the adolescent population were referred to the US unit for a routine scan in the absence of any symptoms or clinical suspicions ($270 \times 24.1\% = 65$; $270 - 65 = 205$). Since no asymptomatic teenager had endometrial signs in ultrasound, 65 adolescents were excluded from the analyses.

**18.1% of the teenagers had routine examination referrals for the US, meaning that endometriosis was not suspected by the clinician in these cases. 67 teenagers were excluded from our analyses since all endometriotic abnormalities had been identified in symptomatic patients.

***60.7% accepted laparoscopic surgery.

TABLE IV. Pelvic MRI findings in patients with clinically and/or imagological suspected signs of endometriosis.

Author, year	No. Pat.	Age (years)	Protocol	MRI machine	MRI findings (no patients, %)
Ragab, 2015 ³⁵	22	15.2 (mean age)	Clinical and sonographic suspicion of endometriosis. After refusing laparoscopy.	-	Findings of endometriosis (17, 77.3%)
Millischer, 2023 ³⁶	308	12-20	After a recorded clinical history where severe dysmenorrhea was reported	1.5T MRI machine (Sonata; Siemens, Erlangen, Germany)	Findings of endometriosis (121, 39.3%): Isolated OMA (14, 11.6%) Isolated DIE (96, 79.3%) DIE and OMA (11, 9.1%) No visible lesion (187, 60.7%) Type of endometriosis among 121 patients: OMA (25, 20.7%) Retrocervical lesions (106, 87.6%) Rectosigmoid lesions (4, 3.3%) Associated adenomyosis (21, 17.4%) Uterine contractions (39, 32.2%)
Khashchenko, 2023 ²⁸	90	15-17	After clinical history and US imaging recorded in patients with laparoscopically diagnosis of PE	GE Signa Excite 1.5T and GE Signa Architect 3.0T MRI systems	Peritoneal endometriosis (71, 78.9%): Uterosacral ligament (39.4%) Parametrial tissue (38%) Along the ovarian capsule (35.2%) Paraovarian tissue (29.6%) Peritoneum and tissue of the Douglas pouch (25,4%) Posterior leaf of broad ligament (18.3%) Paracervical tissue (5.6%)
Total	420	12-20			209 (49.8%)

NR - not reported; OMA - ovarian endometrioma; DIE - deep infiltrating endometriosis; PE - peritoneal endometriosis

Supplementary Table S1. A. Bias appraisal in case-series studies included in the systematic review. **B.** Bias appraisal in the cross-sectional studies included in the systematic review. **C.** Bias appraisal in the case-control study included in the systematic review. **D.** Risk of bias from the NOS tool for the cohort studies included in our systematic review

A. Case series studies											
JB1 checklist questions/ Author, year	1	2	3	4	5	6	7	8	9	10	%
Bai, 2002 ⁵⁵	no	yes	yes	no	no	yes	no	yes	yes	NA	50
Marsh, 2005 ³¹	no	yes	yes	no	no	yes	yes	yes	yes	NA	60
Vicino, 2010 ⁴⁶	yes	yes	yes	no	no	yes	yes	yes	yes	NA	70
Tandoi, 2011 ⁴⁷	yes	yes	yes	no	no	yes	yes	yes	yes	yes	80
Unger, 2011 ³²	no	yes	yes	no	no	yes	yes	yes	no	NA	50
Yeung, 2011 ⁵⁷	no	yes	yes	yes	no	yes	yes	yes	yes	yes	80
Yang, 2012 ³³	no	yes	yes	no	no	yes	yes	yes	yes	yes	70
Özyer, 2013 ⁵¹	yes	yes	yes	no	no	yes	yes	yes	yes	yes	80
Andres, 2014 ⁵⁸	yes	yes	yes	yes	yes	yes	yes	yes	yes	NA	90
Smorgick, 2014 ⁵⁰	yes	yes	yes	yes	no	yes	yes	yes	yes	yes	90
Timur, 2015 ⁵⁹	yes	yes	yes	no	no	yes	no	yes	yes	yes	70
Dun, 2015 ¹¹	yes	yes	yes	yes	no	yes	yes	yes	yes	yes	90
Audebert, 2015 ³⁴	no	yes	yes	yes	yes	yes	yes	yes	yes	NA	80
Fong, 2017 ⁴⁹	yes	yes	yes	yes	yes	yes	yes	yes	yes	UN	90
Matalliotakis, 2017 ⁶⁰	yes	yes	yes	no	yes	yes	yes	yes	yes	yes	90
Al-Jefout, 2018 ³⁰	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	100
Stochino, 2020 ⁴⁰	yes	yes	yes	no	UN	yes	yes	yes	yes	yes	80
Martire, 2020 ²⁹	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	100
Martire, 2023 ¹⁶	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	100

B. Cross-sectional studies									
Author, year	Selection				Comparability	Outcome			Total
	1	2	3	4	1	1	2		
Lee, 2013 ⁴⁸	*			*		**	*		5
Ragab, 2015 ³⁵	*	*		*		*	*		5
DiVasta, 2018 ¹⁸	*	*			*	**	*		6
Millischer, 2023 ³⁶	*	*		*	*	**	*		7
C. Case-control study									
Study	Selection				Comparability	Outcome			Total
	1	2	3	4	1	1	2	3	
Khashchenko, 2023 ²⁸	*			*	*	*	*		5
D. Cohort study									
	1	2	3	4	1	1	2	3	Total
Roman, 2010 ⁵⁶	*	*	*	-	**	*	*	-	7 (Good quality)
Wüest, 2023 ³⁷	*	*	*	-	*	*	*	*	7 (Good quality)

NA – not applicable; UN – unclear.

Supplementary Table S2. Studies evaluating the clinical symptoms and physical examination findings of endometriosis in adolescent patients with suspected or confirmed diagnosis of endometriosis by laparoscopy.

Author, year	No. pat.	Age (years)	Method of final diagnosis	Clinical presentation (no, % of patients)
Case series				
Bai, 2002 ⁵⁵	39	14-21	Laparoscopy/ laparotomy	Chronic pelvic pain (11, 27%) Acute pelvic pain (8, 21%) Palpable pelvic mass (8, 21%) Dysmenorrhea (7, 18%) Infertility (1, 3%)
Vicino, 2010 ⁴⁶	38	≤ 21	Laparoscopy	Pelvic pain (38, 100%)
Tandoi, 2011 ⁴⁷	57	16-21	Laparoscopy/ laparotomy	Dysmenorrhea (43, 75%) Chronic pelvic pain (21, 37%) Dyspareunia (13, 23%) Dyschezia (3, 5.3%) Menometrorrhagia (1, 1.7%)
Unger, 2011 ³²	3	13-16	Laparoscopy	Severe pelvic pain (3, 100%)
Yeung, 2011 ⁵⁷	17	12-19	Laparoscopy	Dysmenorrhea (14, 82.4%) Dyschezia (13, 76.5%) Chronic Pelvic pain (13, 76.5%) Painful exercise (12, 70.6%) Intestinal cramping (10, 58.8%) Bladder pain and tender exam (9, 52.9%) Constipation (7, 41.2%) Dyspareunia (3, 17.6%)
Yang, 2012 ³³	63	12-20	Laparoscopy/ laparotomy	Cyclic pelvic pain (45, 71.4%) Acute abdominal pain (19, 30.1%) Gastrointestinal dysfunction (19, 30.1%) Chronic pelvic pain (13, 20.6%) Irregular menses (5, 7.9%) Dyspareunia (1, 1.6%)
Lee, 2013 ⁴⁸	35	≤ 20	Laparoscopy	Pelvic pain (27, 77%) Incidentally (8, 23%)
Ozyer, 2013 ⁵¹	63	17-24	Laparoscopy	Chronic pelvic pain (28, 44%) Infertility (15, 24%) Incidentally (8, 13%) Dysmenorrhea (11, 8%)
Andres, 2014 ⁵⁸	21	13-20	Laparoscopy	Dysmenorrhea (17, 80.9%) Incapacitating dysmenorrhea (7, 33.3%) Chronic pelvic pain (7, 33.3%) Deep dyspareunia (7, 33.3%) Cyclic bowel symptoms (3, 14.2%) Infertility (1, 4.7%)
Smorgick, 2014 ⁵⁰	86	≤ 22	Laparoscopy/ laparotomy	Pelvic pain (70, 81.4%) Dyspareunia (46, 53.5%) GI symptoms (15, 17.4%) GU symptoms (10, 11.6%) Infertility (2, 2.3%)
Dun, 2015 ¹¹	25	10-21	Laparoscopy	Dysmenorrhea (16, 64%) Abnormal/irregular uterine bleeding (15, 60%) GI symptoms (14, 56%) GU symptoms (13, 52%)

				Menorrhagia (11, 44%)
Audebert, 2015 ³⁴	55	12-19	Laparoscopy	Dysmenorrhea (53, 96.4%) Chronic pelvic pain, dyspareunia, acute pain, and/or dyschezia (47, 85.4%) Infertility (5, 9%)
Fong, 2017 ⁴⁹	45	14-25	Laparoscopy	Mild dysmenorrhea (20, 44.5%) Severe dysmenorrhea (18, 40%) Noncyclical pain (2, 4.4%) Menorrhagia (2, 4.4%)
Matalliotakis, 2017 ⁶⁰	55	13-21	Laparoscopy	Dysmenorrhea (45, 81%) Pelvic pain (40, 72%) Infertility (6, 11%)
Al-Jefout, 2018 ³⁰	20	15-21	Laparoscopy	Chronic pelvic pain (CPP) refractory to NSAIDs and hormonal therapy (20, 100%) Cold intolerance (14, 75%) Severe CPP with VAS ≥ 7 (14, 70%) Abnormal uterine bleeding (7, 35%)
Stochino, 2020 ⁴⁰	32	< 20	Laparoscopy	Dysmenorrhea (30, 93.7%) Deep dyspareunia (19, 76%) Chronic pelvic pain (23, 71.9%) Defecation pain (10, 31.2%) Constipation (9, 28.1%) Diarrhea (8, 25%)
Martire, 2020 ²⁹	36	12-20	US	Dysmenorrhea (31, 86.1%) Heavy menstrual bleeding (20, 55.5%) Dyspareunia (8, 22.2%) Chronic pelvic pain (5, 13.9%) Dyschezia (5, 13.9%) Functional bowel symptoms (4, 11.1%) Dysuria (3, 8.3%)
Martire, 2023 ¹⁶	131	12-25	US	Dysmenorrhea (131, 100%) Heavy menstrual bleeding (80, 61.1%) Dyspareunia (71, 54.2%) Dischezia and/or bowel functional symptoms (58, 44.3%) Dysuria (13, 9.9%)
Cross-sectional study				
Ragab, 2015 ³⁵	56	15.2 (mean age)	US, MRI	Severe dysmenorrhea refractory to NSAIDs and hormonal therapy (56, 100%) GI symptoms (27, 48.2%) GU symptoms (15, 26.8%)
DiVasta, 2018 ¹⁸	295	8-18	Laparoscopy	Nausea associated with pain (130, 69.5%) General acyclic pelvic pain (194, 65.8%) Severe dysmenorrhea (186, 63.1%) Moderate dysmenorrhea (86, 29.2%) Vomiting associated with pain (45, 24.6%) Mild dysmenorrhea (20, 6.8%)
Case-control study				
Khashchenko, 2023 ²⁸	90	15-17	Laparoscopy	Dysmenorrhea moderate-severe (88, 97.8%) Dysmenorrhea persistent to NSAIDs (86, 95.6%) Dysmenorrhea at menarche (57, 63.3%) GI symptoms (35, 38.9%) Heavy menstrual bleeding (31, 34.4%)

				GU symptoms (22, 22.4%)
Cohort study				
Roman, 2010 ⁵⁶	20	14-19	Laparoscopy	Dysmenorrhea (16, 80%) Non-menstrual pelvic pain (4, 20%)
Wuest, 2023 ³⁷	144	15-24	Clinically confirmed diagnosis	Dysmenorrhea (133, 92.4%) Dyspareunia Non-cyclic pain Dysuria, dyschezia
Total	1426	8-25	-	Dysmenorrhea (1182, 82.9%) Pelvic pain (527/1227, 43%) Gastrointestinal symptoms (233/1227, 19%) Abnormal menstrual bleeding (257, 18%) Dyspareunia (168/1227, 13.7%) Genito-urinary symptoms (85/1282, 6.6%)

GI - gastrointestinal; GU - genitourinary; VAS - visual analogue scale; MRI - magnetic resonance imaging; NSAIDs - non-steroidal anti-inflammatory drugs.



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page and paragraph/ table #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1: "Non-invasive diagnosis of endometriosis in adolescents: a systematic review".
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 2 and 3 (Abstract): "Study Objectives: Our aim was to review (...) management of endometriosis in adolescents."
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 4 (paragraph 3): "Endometriosis is remarkably responsible for a decrease in women's quality of life (QOL)..." Page 5: "Diagnosis of endometriosis remains a challenge worldwide (...) not adequate for adult women and maybe even less for adolescents."
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 5 (paragraph 3): "This systematic review aims (...) specific population".
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Page 6 (paragraph 1): "The systematic review protocol is registered in the international PROSPERO database as No. CRD42023457516".
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 6 (paragraph 2): "We aimed to assess how is endometriosis diagnosed in adolescent females, more specifically which non-invasive diagnostic procedures are being applied in adolescents with suspected endometriosis to achieve an early diagnosis. We took into consideration a variety of studies from 2000 onward in this analysis. Randomized controlled trials (RCTs), prospective cohort studies, case-control studies, retrospective cohort studies, and case series were screened."
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 6 (paragraph 3): "We searched three databases: MEDLINE/Pubmed, Scopus, and Web of Science (...) on 24 August 2023 (...) The reference list of the included studies and relevant reviews on the matter were analysed to identify other studies for potential inclusion in this article."
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 6: "The search strategy used was the query ("adolescent" OR "adolescence" OR "adolescents" OR "pediatric" AND "endometriosis" AND ("diagnosis" OR "ultrasound" OR "MRI") (...)) The search was limited to publications in the English language and articles published earlier than 2000 were excluded."



PRISMA 2009 Checklist

Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 6 and 7 (Inclusion and exclusion criteria and study selection): "All records identified using our search strategy were independently screened by two authors based on the titles and abstracts, applying predetermined inclusion and exclusion criteria. Any discrepancies were resolved by consensus, and different interpretations were resolved by a third author. The second selection stage was based on reviewing the full text of potentially relevant articles. The same independent reviewers read relevant full-text articles for inclusion."
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 7 and 8 (Data extraction): "The following data was independently extracted from each of the studies to a spreadsheet"
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 7 and 8: "(...) extracted from each of the studies to a spreadsheet: authors, publication year, country, study design, study period, studied population, number of participants either with clinically suspected and/or with the confirmed diagnosis of endometriosis by imaging and/or laparoscopically. Other items included were the non-invasive diagnosis imaging modality mentioned/used, outcomes of interest, and the aim of the study. Study outcomes on the clinical presentation of endometriosis, ultrasound (US), and Magnetic resonance imaging (MRI) findings of endometriosis, and rASRM classification data from patients that have undergone laparoscopy/laparotomy were extracted too."
Risk of bias in individual studies / Risk of bias across studies	12/ 15	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 7 (Quality assessment): "(...) of cohort and cross-sectional studies was conducted using the Newcastle-Ottawa Scale (NOS). For the cross-sectional studies, an adapted NOS was used and to evaluate the methodological quality of the case series and address potential biases in their conduct we used the JBI"
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure I
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table I
Risk of bias within and across studies	19/ 22	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 9 (paragraph 1): "Among 19 case series studies assessed using the JBI Critical Appraisal Checklist (...) Bias assessment evaluation is demonstrated in Supplementary Table S1"



PRISMA 2009 Checklist

Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 12, 13, 14, 15, 16: "adolescents with endometriosis commonly experience severe dysmenorrhea resistant to conventional treatments (...) Caution is warranted due to the potential overestimation of DIE lesions, given the recognized rate of false positives in MRI, even when administered by trained radiologists." Page 17 (strengths): "first comprehensive systematic review focused on non-invasive diagnostic methods for endometriosis in this specific population, with a high number of adolescents included from many different countries. The study's strength lies in its meticulous methodological design, with a registered a priori protocol."
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 16 and 17 (Limitations): "This systematic review notes some limitations"
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 18: "This systematic review has successfully identified patterns that can offer valuable insights for clinicians"; "Future research should not only concentrate on identifying disease markers".
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 18: "The authors declared no financial support."

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Authorship

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Article Types published in JPAG

1. Original Studies
2. Case Reports
3. Brief Report
4. Reviews
5. Letters to the Editor
6. Editorials
7. Commentary
8. NASPAG Documents

Original Studies

The study should have a clear research question and the structure follows the items of the applicable transparent reporting guideline (www.equator-network.org) based on the study design, see Table 1. The headings should include structured abstract, keywords, Introduction, Methods, Results, and Discussion. Case series are considered as small cohorts and these manuscripts should follow the format of an original study.

Case Reports

A case report is a brief description of a specific finding and management that is unusual and instructive and not previously reported. The case report should have a clear purpose and teaching point; simply being the first case reported does not usually justify publication. The structure of the case report follows the CARE

transparent reporting guideline (www.equator-network.org) including assent of the patient and consent of parent(s)/guardian(s). Case series are considered as small cohorts and these manuscripts should follow the format of an original study.

Brief Report

A brief report may describe studies of any type of design. Brief reports describe preliminary or confirmatory work, or studies that are limited by their design or methodology. The headings should include Introduction, Methods, Results, and Discussion.

Reviews

Reviews address a specific topic and represent literature review and author opinions and recommendations and follow the PRISMA transparent reporting guideline. Reviews must have a narrative abstract that introduces the topic being reviewed and summarizes the article. Reviews are typically commissioned by the Editor-in-Chief.

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Systematic reviews are defined as a literature review with a systematic search with and without meta-analysis. Systematic reviews should follow the PRISMA transparent reporting guideline or the SWiM transparent reporting guideline.

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Letters containing pertinent observations on an article previously published in the journal or on research in general will be considered. Letters should provide constructive criticism and information that is of interest to the reader. When a specific article published in the journal is the topic of the letter, the senior author of the article will be given the opportunity to respond. The Editorial Board reserves the right to shorten letters when necessary to comply with journal style. All Letters to the Editor should be submitted through the journal's online submission system {HYPERLINK" <http://www.editorialmanager.com/jpag>"}

Editorials

A guest editorial may be requested by the Editor-in-Chief related to a specific topic in the field of pediatric and adolescent gynecology, or specifically related to an article published in the journal.

Commentary

Commentaries papers are typically by invitation only and address topics including clinical perspectives, practice-related issues, ethical dilemmas, or experiences of clinical relevance to pediatric and adolescent gynecology. These may be topics about which evidence is insufficient for a systematic or expert review.

NASPAG Documents

Position Statements and Clinical Opinions from NASPAG Committees that have been endorsed by the NASPAG Board are published in the Journal.

The following table shows the abstract word count, manuscript word count, maximum number of references, and maximum number of tables and figures per type of manuscript.

Table 1. Overview of manuscript type and maximum wordcount for abstract and manuscript body as well as maximum number of references tables and figures.

Article type	Abstract word count	Manuscript word count*	Max number of references	Max number of tables & figures
Original Studies	250	3000	30-35	5
Case report	125	1500	5-7	2
Brief report	250	1500	5-7	2
Review	250	3500	30-35	5
Systematic review	300	6250	50-60	5
Letter to the Editor	NA	350	4	0
Commentary	250	1500	5-7	2

NA, not applicable.

*Manuscript word count does not include the title page, abstract, references or tables/figures.

Manuscript structure

All manuscripts must follow the transparent reporting guidelines (available on equator-network.org) applicable to the appropriate study design, see Table 2.

The manuscript must include the following, arranged in this order: Title Page, Structured Abstract and Keywords, Introduction, Methods, Results, Discussion, and References. Manuscripts must be typed double-spaced with at least 1-inch margins. In addition, the manuscript should have running line numbers and page numbers, beginning with the Title page.

As of February 14, 2022, JPAG is instituting a double-blind peer review system. As a result, all submissions will need to include a separate title page that must include the authors' first and middle initials and last name, academic degree; city and state in which the study was undertaken; departments and institutional affiliation at the time the study was undertaken; and the name, telephone number, email address, and address of author responsible for correspondence concerning the manuscript. If the findings were presented at a meeting, please include the name of the meeting, the organization presenting the meeting, the location, and the date of the meeting. If any acknowledgments of collaboration or preparation of the manuscript need to be reported, they should be appearing in the Acknowledgements section on the title page. The title page should also include the word count of the abstract and the main text (not including title page, references, figure legends, and figures).

Authors should make every effort to avoid including personally identifying text from the manuscript file.

Table 2. Overview of transparent reporting guidelines for the main study types, available on equator-network.org.

Study type	Transparent reporting guideline
Randomized controlled trial	CONSORT
Observational studies	STROBE
Systematic review with meta-analysis	PRISMA
Systematic review without meta-analysis	SWiM*
Study protocol	SPIRIT
Diagnostic studies	STARD
Prognostic studies	REMARK or TRIPOD
Case reports	CARE
Clinical practice guideline	AGREE
Qualitative research	SRQR
Quality improvement	SQUIRE

* Campbell M, McKenzie JE, Sowden A, Katikireddi SV, Brennan SE, Ellis S, Hartmann-Boyce J, Ryan R, Shepperd S, Thomas J, Welch V, Thomson H. Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline BMJ 2020;368:l6890 <http://dx.doi.org/10.1136/bmj.l6890>

Required Elements

1. *Title Page.* The title page should include author's first name and middle initials and last name, academic degree; city and state in which the study was undertaken; departments and institutional affiliation at the time the study was undertaken; acknowledgment of any source of funding; disclaimers, and name, telephone number, email address, and address of the corresponding author. If the findings were presented at a meeting, include the name of the meeting, the organization sponsoring the meeting, the location, and the date of the meeting. The title page should also include the word count of the abstract, the word count of main text (not including title page, abstract, acknowledgements, references, figure legends, and figures), and the total number of figures and tables.
2. *Authorship.* See above criteria for authorship from the ICMJE
3. *Structured Abstract and Keywords.* For the maximum abstract word count see table 1. The following headings should be used in the abstract: Study Objective; Methods; Results; and Conclusion. Follow the applicable transparent reporting guideline.
4. *Keywords.* Below the abstract, provide 3 to 10 keywords or short phrases to assist in cross-indexing the article. Use terms from the medical subject heading (MeSH) [list of Index Medicus](#).

5. *Introduction.* The introduction should contain brief background information that acquaints the reader with the current state of knowledge in the area under investigation and the knowledge gap resulting in the objective of the study. Do not include data or conclusions from the work being reported. Follow the corresponding transparent reporting guideline.
6. *Methods.* This section should contain a brief description of the Study design that would allow others to replicate the study, participants of the study and/or animal models and controls and methods and procedures. Institutional Review Board (IRB) statement of approval should be included here. Follow all the method items of the applicable transparent reporting guideline.
All the statistical methods used in the study should be appropriately referenced. Specify any general use computer programs used. Avoid nontechnical uses of technical terms in statistics, such as "random," "normal," "significant," "correlation," "association" and "sample." Define statistical terms, abbreviation, and most symbols.
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A visual abstract may be submitted at the authors' discretions. If the authors choose to provide a visual abstract, authors must provide an original image that clearly represents the work described in the paper. Graphical abstracts should be submitted as a separate file in the submission system by selecting "graphical abstracts" from the drop-down list when uploading files. Please note that just as each paper should be unique, so each graphical abstract should also be unique.

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