Review Article

The Prevalence of Endometriosis in Adolescents with Pelvic Pain: A Systematic Review

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A B S T R A C T

Study Objective: Endometriosis is a recognized cause of pelvic pain in adolescents with menstrual symptoms that significantly affect education, activity, and social interactions. We aim to provide an updated systematic review of the prevalence of endometriosis in adolescents with pelvic pain presenting for gynecological investigation.
Data Sources: We searched Medline, Embase, and Cinahl from 2011 to July 2019.
Methods of Study Selection: We included cohort studies of adolescents with pelvic pain undergoing gynecological investigation. Two authors independently selected studies and extracted study characteristics and prevalence data. Methodological quality was assessed using the Critical Appraisal Skills Program for cohort studies.
Results: This updated systematic review evaluated a total of 19 studies including 1243 symptomatic adolescents. In all, 648 of 1011 (64%) adolescents undergoing laparoscopy were found to have endometriosis. The prevalence ranged from 25% to 100%, with a mean prevalence of 64%. Thirteen studies including 381 participants categorized disease severity using the revised American Society of Reproductive Medicine classification. Among these, 53% of participants (201/381) had stage I, 28% (105/381) had stage II, 20% (76/381) had stage III, and 13% (49/381) had stage IV disease.
Conclusions: The prevalence of endometriosis among adolescents with pelvic pain symptoms is high. Endometriosis is treatable, and prompt recognition will help to ensure that adolescents are signposted earlier to appropriate specialists. The management of adolescents with suspected endometriosis should be consistent with best practice guidance. Despite recommendations to increase the awareness and knowledge of endometriosis in adolescence, minimal research has followed.
Key Words: Adolescent, Endometriosis, Prevalence

Introduction

Endometriosis, defined as the presence of endometrial glands and stroma located outside the uterus, is characterized by pain and subfertility.[1] Estimates of disease prevalence suggest that endometriosis affects up to 75% of symptomatic women, yet its etiology is poorly understood. Pain symptoms in adolescent women are common, with between 50% and 90% reporting dysmenorrhea and or chronic pelvic pain.[2,3] Distinguishing between primary and secondary causes of dysmenorrhea is difficult, with limited recourse to pelvic examinations and transvaginal ultrasound. Endometriosis is the most common cause of secondary dysmenorrhea in adolescents.[3,4] Symptoms lead to reduced physical and mental health, with reported educational and professional disruptions averaging 19 days per year.[5]

The gold standard diagnostic test for endometriosis remains laparoscopy and biopsy; however advancements in imaging modalities have allowed for accurate noninvasive diagnoses.[6] The increasing accuracy of magnetic resonance imaging (MRI) and transvaginal ultrasound for the detection of deep endometriosis allows for more informed deision making, with 83%-91% sensitivity and 98% specificity, respectively.[7,8] For many young women. there are significant diagnostic delays with their symptoms minimized, normalized, or dismissed by physicians. These delays can be 3 times longer for women whose onset of symptoms occurred during adolescence,[9] and may result in disease progression and symptom deterioration. Health economic analyses in the United States have shown an annual societal cost of $49.6 billion due to endometriosis.[10]

Despite growing recognition that endometriosis symptoms often begin in adolescence, research within adolescent populations is scarce. In order to implement improved diagnostic pathways and management, the disease burden must first be established. A previous systematic review evaluated the disease prevalence in adolescents, but this is now more than 8 years old and was limited to studies with only surgical confirmation.[3] We conducted an updated systematic review of the prevalence of endometriosis, confirmed laparoscopically or via imaging, in the adolescent population with pelvic pain.

MH and RD-S contributed equally to this work.

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Methods

A protocol with explicitly defined objectives, criteria for study selection, approaches to assessing study quality, and statistical methods was developed in line with the previous systematic review.[3] We have reported the systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[10]

A comprehensive and systematic literature review was undertaken searching Medline, Embase, and Cinahl from June 2011 to July 2019. We searched the register using MeSH and free text combinations with Boolean logic of the following search terms: endometrio*, test*, diagnos*, accura*, marker, screen*, detect*, Adolescen*, teenage*, child*. There were no language restrictions.

Two reviewers (MH and RDS) independently screened titles and abstracts. The authors critically reviewed the full texts of selective studies to assess eligibility. Any discrepancies between the reviewers were resolved by discussion. We included prospective and retrospective longitudinal studies assessing the prevalence of endometriosis in adolescents with pain symptoms. “Adolescence” was based on the World Health Organization (WHO) definition as a transitional phase of growth and development between childhood and adulthood between ages 10 and 19 years.[11]

Two reviewers (MH and RDS) extracted the data independently using a pilot-tested data extraction sheet. Information collected from each study included study design, setting, and participants. We extracted all relevant raw data from each study. Two reviewers (MH and RDS) independently assessed each study for methodological quality using the Critical Appraisal Skills Program (CASP) for cohort studies.[12] CASP is based on 3 main sections that systematically review the following questions: (1) Are the results of the study valid, and is the bias limited? (2) What are the results? (3) Will the results help me locally? The appraisal questions were graded with a “+” when the authors felt the criterion was achieved; a “+/−” when the answer was unclear; and “−” when the criterion was clearly not achieved.

The primary outcome reported will be the prevalence of endometriosis and secondary outcomes include disease severity.

Results

A previous systematic review evaluated the disease prevalence in adolescents, identifying 15 studies. In our updated review, we identified 4 new studies, resulting in a total of 19 studies when combining with the previous systematic review.[13–16] The PRISMA flowchart for included studies is shown in Figure 1. There were a total of 1243 participants across the 19 studies,[4,13–30] with the largest study by Ragab et al in 2015. A summary of the study characteristics is shown in Table 1. Seven prospective observational studies,[13,14,19,22,26,28,30] 11 retrospective observational studies,[4,15–18,20,21,23,25,27,29] and 1 comparative cohort study[24] were included for analysis. There were 3 studies identified that had data on endometriosis prevalence in adolescents; however, the data were combined with those for the adult population and could not be extracted from the published paper. The authors did not respond to the request for the raw data, and so these papers were not included in the final analysis.[31–33] All included studies were relatively small (20-140 participants undergoing laparoscopy). The participants included ranged in age from 10 years[30] to 25 years.[16] A single study evaluated adolescent dysmenorrhea longitudinally over a mean duration of 10 years.[15]

The majority of studies were conducted in high-resource settings,[4,15–30] with the exception of Ragab et al and Al-Jefout et al studies, which were conducted in Jordan and Egypt, respectively.[13,14] Seven prospective studies[13,14,19,22,26,28,30] recruited patients from clinics in advance of their surgical intervention and diagnosis. All studies included patients with pain symptoms. The pain symptoms investigated included chronic pelvic pain,[22,27–30] chronic pelvic pain unresponsive to medical therapy,[4,14,17,18,20,21] dysmenorrhea,[13,15,22,23,25,34] and abdominal mass.[16] Seven studies[4,14,17–21] offered laparoscopy only to those patients with pain refractory to medical therapy, whereas 12 studies[13,15,16,22–30] reviewed the prevalence of endometriosis among patients with pain without detailing their response to medical therapy, or preoperative imaging. Of these 12 studies, the criteria for offering laparoscopy varied, including dysmenorrhea[13,15,22–25] and chronic or mixed pelvic pain symptoms.[16,26–30]

Prevalence Using Diagnostic Imaging

The previous systematic review did not include any studies in which imaging was used to confirm endometriosis.[3] In this review, 3 studies included the use of imaging to aid in the diagnosis or as an alternative to laparoscopy.[13,14,16] In the Ragab et al study, of the 220 adolescents with severe dysmenorrhea, 56 were offered laparoscopy: 34 participants underwent laparoscopy, whereas 22 declined surgery and opted for magnetic resonance imaging (MRI).[13] The prevalence of highly suspected endometriosis based on MRI was 17 of 22 (77%) with imaging features of endometrioma, including a cystic mass with high signal intensity on T1-weighted images and loss of signal intensity on T2-weighted images. This was comparable to the 27 of 34 (79%) diagnosed cases in participants who underwent laparoscopy. In the study by Fong et al, 42 of the 45 participants underwent a preoperative ultrasound scan (USS), and only 1 participant was found to have a normal USS.[16] The 41 participants with positive ultrasound findings suggestive of endometriosis had ovarian pathology with ultrasound characteristics of cysts including uniloculated (10%), low-level echos (69%), and complex features (12%). The scan findings were consistent with the findings at laparoscopy. The study by Al-Jefout et al also performed preoperative USS on all participants.[14] Eight patients were found to have positive ultrasound findings of ovarian cysts (28%); of these, 5 patients were described as having unilateral cysts with low-level echogenicity, and 3 patients complex ovarian cysts with features suggestive of ovarian endometrioma. A further 12 participants with a negative ultrasound findings

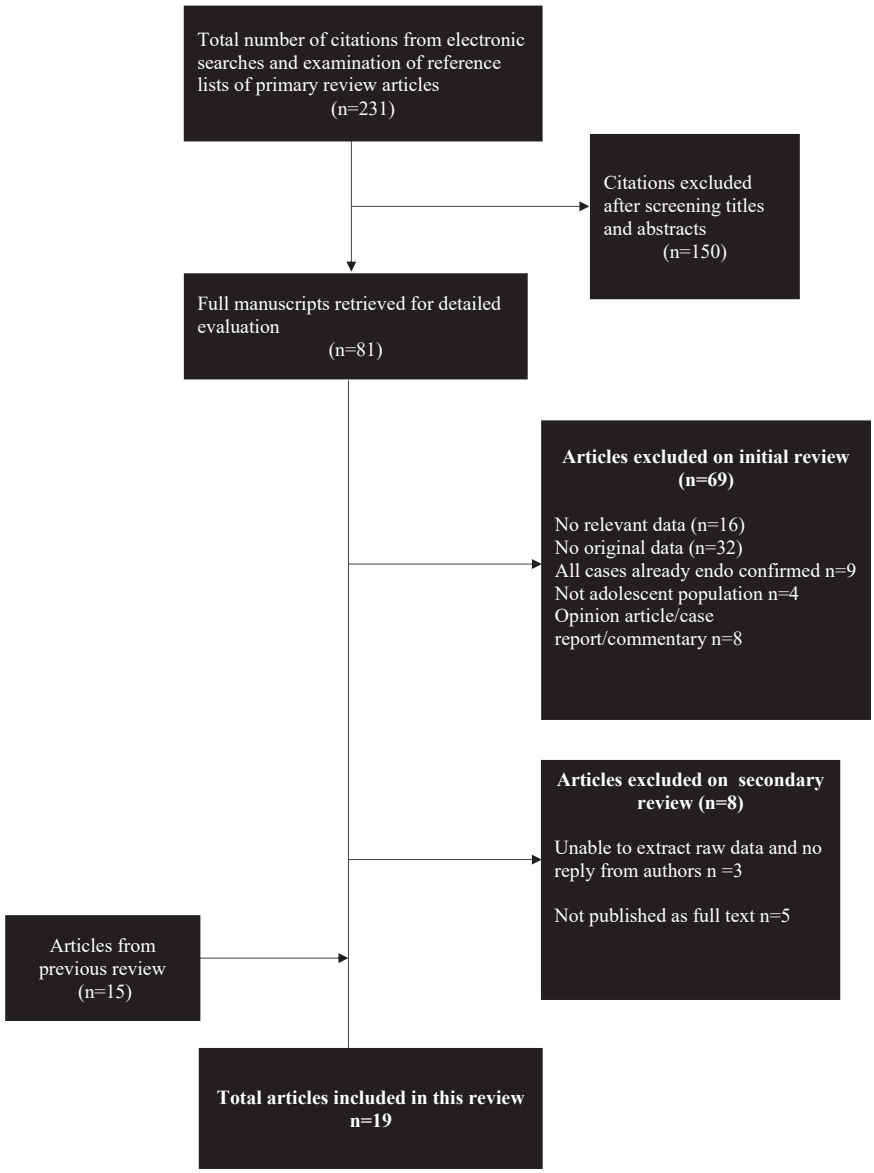

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of included studies.

were observed to have evidence of endometriosis at laparoscopy.

Prevalence at Laparoscopy

For each study, the overall prevalence of endometriosis found at laparoscopy, the data for histological confirmation and classification of the disease is presented in Table 2. Endometriosis was confirmed by visual confirmation only in 6 studies[4,15,20,21,23,28] Biopsies were performed in the remaining 13 studies.[13,14,16–19,22,24–27,29,30] No study exclusively used histological confirmation. Of the 13 studies in which biopsies were performed, it was reassuring to note that 9 had 100% correlation between histological diagnosis and visual diagnosis.[13,14,16,17,19,24,26,29,30] One study had poor correlation, with only 43% (6 of 14) of biopsy samples showing histological confirmation of endometriosis.[27] The staging of endometriosis was classified using the revised American Fertility Society classification 1985,[4,17,23,25] the revised American Fertility Society classification 1997,[19,21,24,29,30] the Acosta classification 1973,[18,22–24] the Semm classification,[35] and the Kistner classification system.[26] Fifteen studies (320 participants) included participants with minimal to mild endometriosis,[4,13–19,21–25,29,30] and 11 studies (145 participants) included participants with moderate to severe endometriosis[13,14,16–19,22–24,29,30] as defined by their respective classification. Among those patients classified using the American Fertility Society Classification, 53% (201 of 381) had stage I, 28% (105 of 381) had stage II, 20% (76 of 381) had stage III, and 13% (49 of 381) had stage IV disease.

The prevalence of visually confirmed endometriosis varied widely among included studies from 25%[28] to 100%.[16,20,21,23,24,29,30] Studies varied in their methods for surgical diagnosis. The recommended approach of a single experienced surgeon conducting all operations occurred in

Table 1
Study Characteristics of Included Papers

Authors and Year	Sample Size	Country	Study Design	Age Range and/or Mean Age, yr	Study Objective
Goldstein et al 1980	140	USA	Prospective	10-19.25	To describe the experience in adolescents who have endometriosis
Chatman and Ward 1982	43	USA	Prospective	12-19	To outline the magnitude of the problem of endometriosis
Vercellini et al 1989	47	Italy	Retrospective	11-19 (18.7)	To determine the value of laparoscopy in the differential diagnosis of CPP
Davis et al 1993	36	USA	Retrospective	13-20 (16.6)	To describe the appearance, stage and treatment of endometriosis in adolescents
Reese et al 1996	67	USA	Retrospective	11-19	To determine the incidence, clinical stage and lesion type of endometriosis in adolescents
Emmert et al 1998	105	Germany	Retrospective	11-19 (17.3)	To determine the incidence, type and clinical stage of endometriotic lesions
Laufer et al 1997	46	USA	Retrospective	13-21 (16.1)	To evaluate adolescent girls with CPP not responding to medical therapy
Kontoravdis et al 1999	98	Greece	Prospective	16-19	To evaluate the role of laparoscopy in the diagnosis and treatment of CPP in adolescents
Bai et al 2002	39	Korea	Retrospective	14-21 (20.1)	To evaluate the age distribution, diagnosis, clinical stage and treatment of endometriosis in adolescents
Stavroulis et al 2006	31	UK	Retrospective	13-20 (16.5)	To determine the frequency and severity of endometriosis in adolescents with CPP unresponsive to medical treatment
Ventolini et al 2005	52	USA	Prospective	12-18	To compare mild-and-severe forms of endometriosis and to follow up their fecundability on long term
Kalu et al 2008	28	UK	Retrospective	15-21	To describe the clinical features and treatment outcome following the laparoscopic treatment of endometriosis
Doyle et al 2009	90	USA	Retrospective	12-24	To evaluate the effect of combined surgical-medical treatment on endometriosis progression in adolescents
Roman 2010	20	New Zealand	Comparative cohort	17.4	To describe the experience with laparoscopic excision in adolescents and to compare it with a nonadolescent population
Vicino et al 2010	38	Italy	Prospective	10-21	To analyze the clinical manifestations of endometriosis in adolescents
Ragab et al 2015	220	Egypt	Prospective	15.2	To investigate the prevalence of adolescence endometriosis among school-aged girls with severe dysmenorrhea
Fong et al 2017	45	Singapore	Retrospective	14-25	To describe the prevalence and disease pattern of endometriosis in young women
Al-Jefout et al 2018	28	Jordan	Prospective	15-21 (18.4)	To explore the prevalence and clinical manifestations of endometriosis in young Jordanian women with CPP refractory to conventional medical therapy.
Knox et al 2019	70	Australia	Retrospective	15.7	To ascertain predictors of prognosis and the likelihood of endometriosis being diagnosed

CPP, chronic pelvic pain.

a minority of studies.[4,14,21,27,30] As previously reported, the heterogenous appearance of endometriosis resulted in a variable false-positive rate associated visual confirmed endometriosis ranging from 0%[13,16,17,24–26,29,30] to 57%.[27] The characterization of adolescent endometriotic lesions was described in 7 studies,[4,17,20,23–26] including the following features for diagnosis: red vascular lesions[4,17,20,23–26]; white opaque lesions[4,17,25]; blue-black lesions[4,17,20,23]; peritoneal pockets[17,23,25]; yellowish brown lesions[25]; and bleb-like vesicular lesions.[4,17,20,26]

Critical Appraisal of Methodology

All selected studies were assessed for methodological quality using the CASP criteria. The overall appraisal of the studies showed good methodological quality, and, in particular, the newly added 4 studies met the criteria across all questions. The weakest paper was that of Kontoravdis et al (1999), in which the lack of detail meant that it was difficult to appraise their methodology. A summary of the critical appraisal of the 19 included articles can be found in Table 3.

Discussion

Main Findings

The prevalence of endometriosis in adolescents who present for investigation of pelvic pain is high. The disease distribution from minimal to severe is comparable to that in adults. Diagnosis via imaging modalities such as USS or MRI were shown to be useful in some studies and may be more appropriate for younger patients. Doctors managing adolescents with pelvic pain must adhere to similar guidance as outlined for the adult population. The sequalae of chronic pain during educational study warrants greater vigilance, including prompt referral of patients from primary to secondary care where empirical treatments fail.

Strengths and Limitations

This systematic review was conducted with a comprehensive search strategy and robust methodology and analysis. All studies included in this review reported the primary endpoint, diagnosis of endometriosis, either visually or histologically.

Table 2
Prevalence Data and Classification of Endometriosis

Authors and Year	Patients Who Underwent Laparoscopy (n)	Patients With Visually Confirmed Endometriosis n (%)	No. of Patients Who Underwent Biopsy/No. With Visually Confirmed Endometriosis (%)	No. of Patients With Histologically Proven Endometriosis/No. of Patients Who Underwent Biopsy	Classification (No. of Patients/Total No. With Endometriosis)						
					rAFS (%)				Acosta (%)		
					I	II	III	IV	Mild	Moderate	Severe
Goldstein et al 1980	140	66/140 (47%)	66/66 (100%)	66/66 (100%)	Staging system with Kistner				14/28 (50%)	11/28 (39%)	3/28 (11%)
Chatman and Ward 1982	43	28/43 (65%)	18/28 (64%)	13/18 (72%)							
Vercellini et al 1989	47	18/47 (38%)	11/18 (61%)	8/11 (72%)	12/18 (67%)	6/18 (33%)	0/18 (0%)	0/18 (0%)			
Davis et al 1993	36	36/36 (100%)	NR	NR	10/36 (28%)	8/36 (22%)	7/36 (19%)	11/36 (31%)			
Reese et al 1996	67	49/67 (73%)	3/67 (5%)	3/3 (100%)	39/49 (80%)	6/49 (12%)	3/49 (6%)	1/49 (2%)			
Emmert et al 1998	105	37/105 (35%)	14/37 (38%)	6/14 (43%)	Endoscopic endometriosis classification						
Laufer et al 1997	46	31/46 (67%)	NR	NR	24/31 (77%)	7/31 (23%)	0/31 (0%)	0/31 (0%)			
Kontoravdis et al 1999	98	24/98 (25%)	NR	NR	NR						
Bai et al 2002	39	39/39 (100%)	39/39 (100%)	39/39 (100%)	4/39 (10%)	17/39 (44%)	11/39 (28%)	7/39 (18%)			
Stavroulis et al 2006	31	11/31 (36%)	10/11 (91%)	8/10 (80%)					5/11 (45%)*		6/11 (55%)
Ventolini et al 2005	52	28/52 (54%)	28/28 (100%)	28/28 (100%)	4/28 (14%)	11/28 (39%)	12/28 (43%)	1/28 (4%)			
Kalu et al 2008	28	28/28 (100%)	NR	NR	NR						
Doyle et al 2009	90	90/90 (100%)	Not performed		67/90 (74%)	NR	NR	NR			
Roman 2010	20	20/20 (100%)	20/20 (100%)	20/20 (100%)	8/20 (40%)	9/20 (45%)	1/20 (5%)	2/20 (10%)			
Vicino et al 2010	38	38/38 (100%)	30/38 (79%)	30/30 (100%)	7/38 (19%)	5/38 (13%)	13/38 (34%)	13/38 (34%)			
Ragab et al 2015	34	27/34 (79%)	27/20 (100%)	27/27 (100%)	12/27 (44%)	7/27 (26%)	8/27 (30%)	0/27 (0%)			
Fong et al 2017	45	45/45 (100%)	45/45 (100%)	45/45 (100%)	5/45 (11%)	8/45 (18%)	19/45 (42%)	13/45 (29%)			
Al-Jefout et al 2018	28	20/28 (71%)	20/20 (100%)	20/20 (100%)	9/20 (45%)	8/20 (40%)	2/20 (10%)	1/20 (5%)			
Knox et al 2019	24	13/24 (54%)	NR	NR	NR						

NR, no result; rAFS, revised American Fertility Society score.
* Mild and moderate endometriosis were included together.

Reviews of prevalence data are not without their limitations. There was wide variation observed in the prevalence of the disease among adolescents with pelvic pain. This may reflect varying degrees of specialization of the unit offering surgery from small centers[13] to high-volume national referral PAG centers.[16] The criteria for offering laparoscopy varied between studies, including those participants with pain refractory to medical therapy, adolescents with dysmenorrhea, and those with chronic or mixed pelvic pain symptoms. This clinical heterogeneity is likely to account for variable pretest prevalence rates between cohorts.

Interpretation

The findings are consistent with the previous review demonstrating a high prevalence of endometriosis among adolescents with pelvic pain. Menstrual disorders in adolescents are common.[36] A survey of 2240 adolescents found that 63% experience discomforting menstrual symptoms and that 27% sometimes or always miss school due to menstrual symptoms.[36] The provision of secondary care adolescent gynecological services is limited in comparison to adult services, yet the disease prevalence appears similar. Referral pathways, including guidance on referral from primary to secondary care, need clarity promotion and coordinated implementation.

There are greater diagnostic challenges associated with adolescents, as transvaginal ultrasound and vaginal examination may be contraindicated. Alternative methods such as transabdominal ultrasound, transrectal ultrasound, or MRI may be useful tools prior to considering surgical investigation.[37] Imaging modalities have not been validated in an adolescent population, and we anticipate that they provide similar accuracy to exclude ovarian and deep endometriosis, not peritoneal disease, in adolescents as they do in adults.[7,38–40] Surgical investigation of adolescents with normal imaging needs careful consideration. There is little evidence to demonstrate that surgical removal of peritoneal endometriosis improves overall symptoms, quality of life,[41] and alteration of the natural course of the disease in later life.[42]

Despite international recommendations in 2013 to increase research among the adolescent population, there remains a paucity of high-quality research.[42] This limits the evidence base available to guide governing bodies such as the European Society of Human Reproduction and Embryology (ESHRE) and the American College of Obstetrics and Gynecology (ACOG) in making evidence-based recommendations. A committee opinion from ACOG (no. 760: Dysmenorrhea and Endometriosis in the Adolescent) suggests that the majority of presentations will represent primary dysmenorrhea without pathology. The committee recommends that empirical treatment of dysmenorrhea should be offered for 3-6 months. However, use of empirical combined hormonal contraceptives for dysmenorrhea under the care of a family physician has been associated with a delay in diagnosis and higher rates of severe endometriosis in later life.[43,44] This association may suggest that combined hormonal contraceptives improve symptoms but do not halt disease progression. Importantly, the committee

Table 3
Critical Appraisal of the Articles Included in the Review Using the CASP Classification

Authors and Year	(A) Are the Results of the Study Valid?						(B) What are the Results?			(C) Will the Results Help Me Locally?	
	Did the Study Address a Clearly Focused Issue?	Did Authors Use an Appropriate Method to Answer Their Question?	Was/Were the Cohort/Cases Recruited in an Acceptable Way?	Was the Outcome Accurately Measured to Minimize Bias?	Is the Disease Status of the Tested Population Clearly Described?	Have They Taken Account of the Confounding Factors in the Design and/or Analysis?	Are the Results of the Study Clear?	Were the Results Precisely Presented?	Do You Believe the Results?	Can the Results be Applied to the Local Population?	Were all Important Outcomes Considered (Policy Makers, Professional Family)?
Goldstein et al 1980	+	+	+	+	+	+	+	+	+	+	+
Chatman and Ward 1982	+	+	+	+	+	+	+	−	+	−	+
Vercellini et al 1989	+	+	+	+	+	+	+	+/−	+	+	+
Davis et al 1993	+	+	+	+	+	+	+	+	+	+	+
Reese et al 1996	+	+	+	+	+	+	+	+	+	+	+
Emmert et al 1998	+	+	+	+	+	−	+	−	+/−	+	+
Laufer et al 1997	+	+	+	+	+	+	+	+/−	+	+	+
Kontoravdis et al 1999	+	+/−	+	+/−	+	+/−	+/−	−	+/−	+	+
Bai et al 2002	+	+	+	+/−	+	+	+/−	+/−	+/−	−	+
Stavroulis et al 2006	+	+	+	+	+	−	+	−	+/−	+	+
Ventolini et al 2005	+	+	+	+	+	+	+	−	+	+	+
Kalu et al 2008	+	+	+	−	+	+	+	+	+/−	+/−	+
Doyle et al 2009	+	+	+	+/−	+	+	−	+	+/−	+	+
Roman 2010	+	+	+	+	+	+	+	+	+	+	+
Vicino et al 2010	+	+	+	+	+	+	+	+	+	+	+/−
Ragab et al 2015	+	+	+	+	+	+	+	+	+	+	+
Fong et al 2017	+	+	+	+	+	+	+	+	+	+	+
Al-Jefout et al 2018	+	+	+	+	+	+	+	+	+	+	+
Knox et al 2019	+	+	+	+	+	+	+	+	+	+	+

+, Yes; +/−, cannot tell; −, no.

recommend that further investigations of possible secondary causes, such as endometriosis, be considered if there is no improvement with empirical treatment.[45]

Recommendations

Adolescent endometriosis–associated pelvic pain is common. Primary and secondary care physicians have a role in acknowledging and treating adolescent pelvic pain. The prompt referral to a pediatric gynecologist if empirical treatment has failed may decrease delays in the diagnostic pathway and possibly reduce disease progression. Earlier recourse to advanced diagnostic tests can provide adolescents and their families with relief, liberation, and legitimization of their symptoms, together with access to support and an opportunity to discuss tailored medical or surgical management.[46]

A coordinated approach from leading endometriosis organizations is required to generate greater research on effective diagnostic and therapeutic interventions for adolescents with pelvic pain. Clinicians should consider MRI prior to laparoscopy, as this may be a useful noninvasive imaging technique in adolescents. This unique population are in the peak of their educational study and require expedited, structured, and organized care to minimize absence from study. For this to be achieved, further research is needed to develop appropriate protocols for adolescents, who are more likely to have earlier-stage disease.

Conclusion

The prevalence of endometriosis in adolescents with pelvic pain is high. There is a paucity of high-quality studies evaluating endometriosis in this population. The sequalae of chronic pain during educational study warrants greater vigilance, including prompt referral of patients from primary to secondary care if empirical treatments fail.

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