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REVIEW

Endometriosis in adolescents: a systematic review

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ABSTRACT

Introduction: The aim of this manuscript is to present a systematic review of characteristics and management of endometriosis in adolescents in order to gain some relevant insight into the most appropriate clinical management of the disease.

Methods: The literature review was done using electronic database PubMed focusing on the terms 'adolescents', 'endometriosis', 'teenagers', 'pain', 'infertility', 'quality of life', 'medical' and 'surgical management' from 1980 onward and was limited to articles in English. Articles were only included if they reported original relevant research.

Results: The 24 studies selected for review included 1148 adolescents with laparoscopic proven endometriosis. The diagnosis of endometriosis was histologically confirmed in 39.02% (448/1148) of cases. The results from trials have been tabulated and main results presented in a question and answer format.

Conclusions: The majority of adolescent girls with chronic pelvic pain not responding to conventional medical therapy have endometriosis (up to 80%). Laparoscopy with biopsy is the only way to diagnose endometriosis in the adolescent population, and depends on recognition of atypical manifestations of the disease. Surgical management (especially by an expert surgeon) has been shown to be beneficial in reducing pain, improving infertility, and preventing progression or recurrence of disease. Postoperative hormonal suppression helps reduce pain symptoms and recurrence of endometriomas, but it does not seem to prevent disease recurrence or progression of peritoneal endometriosis, and has not been shown to improve future fertility. Postoperative suppression until pregnancy is based on expert opinion only. There is a need for good quality properly randomized trials.

Keywords: Adolescents, Endometriosis, Laparoscopy

Introduction

Endometriosis is a gynecological condition defined by the presence of endometrial glands and stroma outside the uterus, associated with pelvic pain and subfertility (1). Various theories have been proposed regarding the pathogenesis of the disease, which represents a complex multifactorial origin involving hormonal, environmental, genetic, and immunological factors. Endometriosis can only be diagnosed by visual inspection during laparoscopy, ideally confirmed by histology (2). Delays in the diagnosis of endometriosis often occur because the gold standard for disease confirmation consists of visual assessment (laparoscopy) and histological confirmation. Such delays can adversely affect reproductive potential and functional outcomes (3). Although endometriosis was first described in teenagers as early as the 1940s (4), early studies suggested that endometriosis was rare during adolescence (5). Since endometriosis can only be diagnosed at laparoscopy, the true prevalence of endometriosis among adolescents remains unknown. Furthermore, there has been limited research on endometriosis in adolescents. The aim of this paper is to present a systematic review of characteristics and management of endometriosis in adolescents.

Materials and methods

The literature review was done using the electronic database PubMed focusing on the terms 'adolescents', 'endometriosis', 'teenagers', 'pain', 'infertility', 'quality of life', 'medical' and 'surgical management'. The search of literature was set from 1980 onward because the international classification of endometriosis was revised in 1979 by the revised American Fertility Society (rAFS). It was limited to articles in English language that addressed the research question at hand. Articles were only included if they reported original research. The reference lists of all selected articles were reviewed to identify additional papers.

Results

Abstracts and full manuscripts were reviewed for detailed evaluation after screening the titles and excluding studies that

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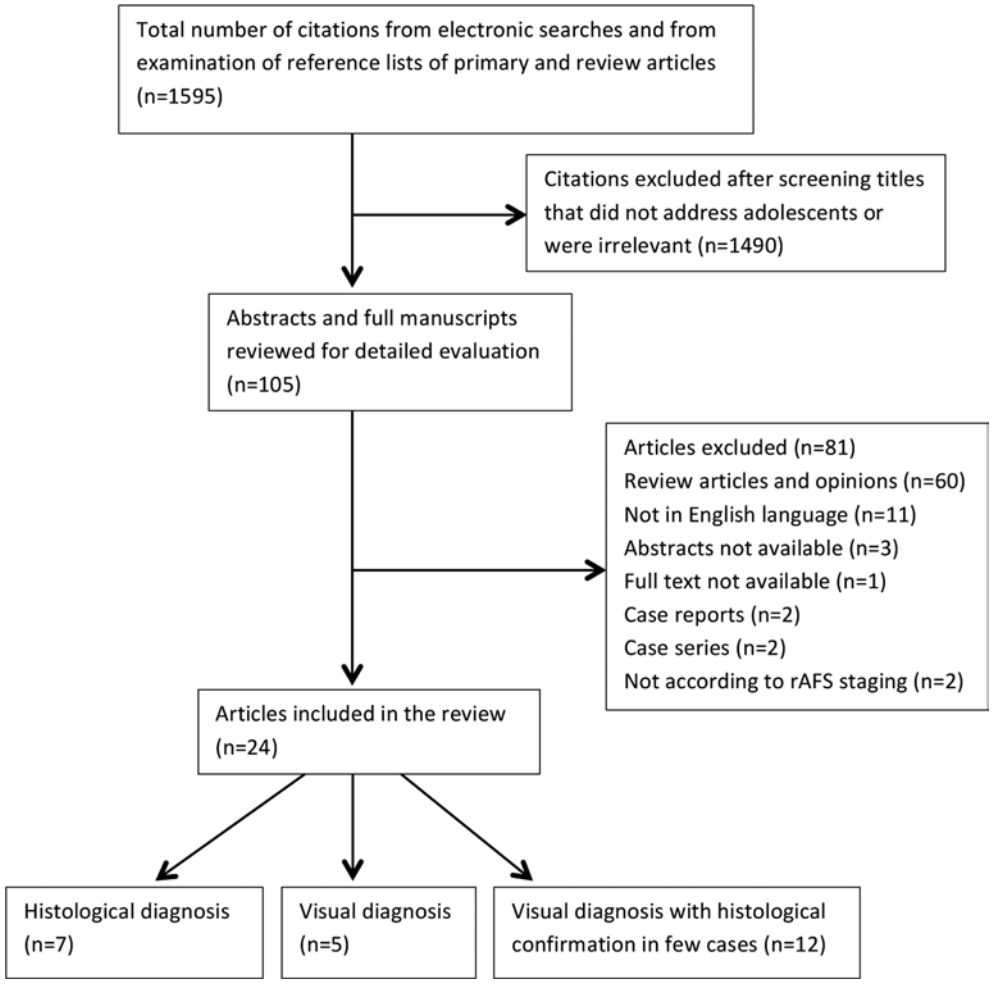

Fig. 1 - The process of literature identification and selection. rAFS = revised American Fertility Society.

were irrelevant. Manuscripts such as review papers, opinions, case reports, and case series were excluded. The 24 studies selected for review included 1148 adolescents with laparoscopic proven endometriosis. In these 24 studies, 7 had a histologically proven diagnosis of endometriosis in all cases, 5 studies only had visual diagnosis and 12 had visual diagnosis followed by histological confirmation in few patients. The diagnosis of endometriosis was histologically confirmed in 39.02% (448/1148) of cases (Fig. 1). The results are presented in a question and answer format, along with tables, to make the information more easily interpreted.

Prevalence of endometriosis in adolescents

Is the prevalence of endometriosis in adolescents known?

Estimated to be about one-third of adolescents with chronic pain, increasing to up to 80% in adolescents with chronic pelvic pain who fail to respond to medical treatment.

With the introduction of laparoscopy, it was suggested that endometriosis may not be uncommon in adolescent girls. But it was still difficult to discern the incidence of endometriosis as the physicians were reluctant to operate on this age group. In recent studies, endometriosis was found in 25%-32.5% of adolescents with chronic pain (6, 7). This increases to 69.6%-79.4% for adolescents who presents with chronic pelvic pain that was unresponsive to oral contraceptive pills (OCPs) and non-steroidal anti-inflammatory drugs (NSAIDs) (8-10). Endometriosis was diagnosed as an incidental finding in 10% of adolescents without symptoms in a study by Bai et al (11) (Tabs. I, II).

TABLE I - Studies evaluating the prevalence of endometriosis in adolescents with pain

Study	Prevalence	Aim of study
Kontoravdis et al (6)	25.0%	Laparoscopic evaluation and management of chronic pelvic pain during adolescence
Vercellini et al (7)	32.5%	Laparoscopy in the diagnosis of gynecologic chronic pelvic pain
Bai et al (11)	10.0%*	To evaluate the age distribution, diagnosis, clinical stage, and treatment of endometriosis in adolescents of Korea

* Incidental finding.

TABLE II - Studies evaluating the prevalence of endometriosis in adolescents with chronic pelvic pain not responding to medical treatment

Study	Design	No. (pos/ cases)	Method of evaluation	Duration	Prevalence	Age (y)	Aim of study
Ragab et al (10)	Cross-sectional	27/34	Biopsy	2012-14	79.4%	15.2 ± 3.5*	To determine the prevalence of endometriosis among adolescent school girls with severe dysmenorrhea
Stavroulis et al (37)	Retrospective analysis	9/11	Biopsy	2001-03	35.5%	13-20	To determine the frequency and severity of endometriosis in adolescent and teenager girls with chronic pelvic pain who fail to respond to medical management and to evaluate the outcome of radical laparoscopic surgery for severe endometriosis
Laufer et al (8)	Retrospective analysis	31/46	Visual or biopsy	1990-94	69.6%	<20	To evaluate adolescent girls with chronic pelvic pain not responding to conventional medical therapy
Reese et al (9)	Retrospective analysis	3/49	Biopsy	1992-94	73.0%	11-19	To determine the incidence, clinical stage, and lesion type of endometriosis in adolescent girls

* Mean and standard deviation.

TABLE III - Studies evaluating a delay in diagnosis of endometriosis, especially among adolescents

Study	Design	Number	Duration	Age (y)	Aim of study
Greene et al (14)	Cross-sectional study	4334	1998	36.2 ± 0.1*	To determine whether first physician seen and symptoms beginning in adolescence have an impact on the diagnostic experience of endometriosis
Ballard et al (15)	Qualitative analysis	28	2004-2005	16-47	To investigate the reasons women experience delays in the diagnosis of endometriosis and the impact of this on women's experiences
Arruda et al (17)	Qualitative analysis	200	2000-2001	All age groups	The study aim was to assess the time elapsed between onset of symptoms and diagnosis of endometriosis, and to identify the factors associated with diagnostic delay in a group of Brazilian women
Ballweg (13)	Qualitative analysis	4000		<15-45	Comparative historical data show endometriosis is starting younger, and is more severe
Emmert et al (12)		37	1996-1997	11-19	Endometriosis diagnosed by laparoscopy in adolescent girls
Hadfield et al (16)	Qualitative analysis	218		10-46	Delay in the diagnosis of endometriosis: a survey of women from the USA and the UK

* Mean and standard deviation

Is there a delay in diagnosis of endometriosis, especially among adolescents?

Yes, up to 12 years.

In an older 1998 study with a series of 34 adolescents with endometriosis, the interval between onset of symptoms and laparoscopy was only 1.7 years (12). However, more recent studies which may include the diagnosis of atypical lesions indicate a greater delay to surgical diagnosis. Ballweg et al (13) state that as the age of the onset of symptoms decreases, the number of doctors having to be seen to reach a diagnosis increases. Specifically, an average of 4.2 doctors were seen for patients whose symptoms began before age 15 years compared with an average of 2.64 doctors for patients whose symptoms began between the ages of 30 years and 34 years. There are, on average, 9.28 years from the onset of symptoms to the diagnosis. Another study by Greene et al (14) concluded that women and girls who reported seeing a gynecologist first for symptoms related to endometriosis were more likely to have a shorter time to diagnosis, to see fewer physicians, and to report a better experience overall with their physicians as compared to generalists. Several studies on women undergoing surgery for endometriosis have reported that pelvic pain existed for 6-12 years on average, with time to diagnosis and treatment being independent of health-care system type and cost reimbursement (15-17) (Tab. III).

Clinical and surgical characteristics of endometriosis in adolescents

What are the main clinical features of endometriosis in adolescents?

The main symptoms are chronic pelvic pain and dysmenorrhea. Acyclic pain seems to be more common in adolescents than in adults.

The main presenting symptoms in the studies included were chronic pelvic pain (27%-96%) and dysmenorrhea (18%-100%). Other presentations included gastrointestinal symptoms, urinary symptoms, irregular menses, dyspareunia, pelvic mass, subfertility, constitutional symptoms and depression/anxiety (18, 19). A study by Smorgick et al (19) describes a high prevalence of comorbid chronic pain syndromes (56%) and mood disorders (48%) in adolescents and young women with endometriosis. Irritable bowel syndrome was found in 25%, interstitial cystitis/painful bladder syndrome in 16% and chronic headaches in 19% of adolescents and young women with endometriosis. The quality of life (QOL) was described as awful or poor by 64.75% patients (20). A multivariate analysis of over 1000 patients concluded that the association between endometriosis stage and severity of pelvic symptoms was marginal and inconsistent and could be demonstrated only with a major increase in study power (21). Fedele et al found no correlation between severity of pain symptoms and stage of the disease or site of the endometriotic lesions (22). Another study by the same author in infertile women concluded that endometriosis in infertile women is associated with pelvic pain, the severity of which is related to the extent of the disease (23).

Adolescent endometriosis may present differently from endometriosis in adults. In particular, adolescents may not present with the typical cyclic pain pattern that is found in adults with the disease. In a study by Laufer et al (8), 90.6% of adolescents with endometriosis had acyclic pain versus 69% in the adult population (24). Mullerian anomalies are unique characteristics of adolescent patients with endometriosis, especially those with outflow tract obstructions. Yang et al reported genital tract malformations in 24% (15/63) of patients (25).

Does the disease rAFS stage vary in adolescents?

The majority of adolescents have early stage disease, but a significant proportion of adolescents have advanced disease (up to one-third). An ovarian endometrioma is the most common presentation of advanced endometriosis in adolescents.

The studies included in the review were staged according to rAFS classification (Tabs. IV-V). Out of 22 studies, breakdown into all four stages could be obtained for 13 studies which are represented in tables below. The findings are similar irrespective of pre-operative hormonal suppression. Whereas older studies dealt mostly with early stages (8, 9, 26), more recent ones report a large number of cases with Stage III and IV endometriosis (25, 27). The adult literature reports Stage I disease in 30%-39%, Stage II in ~12%-13%, Stage III in 27%-35% and Stage IV in 13%-28% (21, 28). According to our findings, adolescents do present with advanced stages but in fewer numbers when compared to adults. The main presentation of advanced-stage endometriosis in this age group is ovarian endometriomas rather than extensive peritoneal or adhesive disease. Out of

TABLE IV - Staging of endometriosis according to r-AFS classification (without failure of hormonal suppression)

Study	Stage I	Stage II	Stage III	Stage IV
Wilson-Harris et al (38) (n = 28)	60.7%	28.6%	7.1%	3.6%
Smorgick et al (19) (n = 86)	67.0%	9.0%	8.0%	15.0%
Smorgick et al (29) (n = 136)	70.0%	14.0%	11.0%	4.0%
Yang et al (25) (n = 63)	7.9%	3.2%	52.4%	36.5%
Yeung et al (36) (n = 20)	29.4%	64.7%	5.9%	0%
Roman (26) (n = 20)	40.0%	45.0%	5.0%	10.0%
Vicino et al (27) (n = 38)	18.4%	13.2%	34.2%	34.2%
Bai et al (11) (n = 39)	10%	44%	28%	18%
Total n = 430	47.0% (202/430)	18.8% (81/430)	19.3% (83/430)	14.9% (64/430)

r-AFS = revised American Fertility Society.

TABLE V - Staging of endometriosis according to r-AFS classification (with failure of hormonal suppression)

Study	Stage I	Stage II	Stage III	Stage IV
Ragab et al (10) (n = 27)	44.4%	25.9%	29.6%	0%
Dun et al (18) (n = 25)	68.0%	20.0%	12.0%	0%
Ventolini et al (40) (n = 28)	14.3%	39.2%	42.8%	3.6%
Reese et al (9) (n = 49)	79.6%	12.3%	6.1%	2.0%
Davis et al (30) (n = 36)	28.0%	22.0%	19.0%	31.0%
Total n = 165	49.7% (82/165)	22.4% (37/165)	20.0% (33/165)	7.8% (13/165)

r-AFS = revised American Fertility Society.

20 patients with advanced diseases, 14 (70%) patients had endometrioma, obliteration of cul-de-sac in 3 cases (15%) and significant adhesive disease in 2 cases (10%) (29).

What are the main characteristics of lesions in adolescents?

Atypical lesions are common in adolescents, with red lesions perhaps being the most common.

Davis et al (30) and Reese et al (9) showed a predominance of red lesions in their adolescent population, and demonstrated that adolescents with severe dysmenorrhea and those with complaints of abdominal pain, nausea, constipation, and diarrhea had the greatest number of red lesions. Another study reported atypical red vascular lesions in 60% of adolescents compared to only 20% of non-adolescents (26). Stripling et al (31) and Martin et al (32) reported an evolution pattern of subtle lesions in adolescence to more classic lesions a decade later. Redwine (33) reported that clear and red lesions occur at an average of 10 years earlier than the black lesions. Clear lesions are common in adolescent endometriosis but often difficult to visualize and evaluate. Peritoneal defects, or windows, which are possible manifestations of endometriosis, are very common in adolescents (34). The reported incidence in adolescents is around 10%-18.4% as quoted in various articles (9, 30, 35). A recent study by us showed that deep retraction pockets (DRPs) may be a manifestation of endometriosis (even with a clear surface of the pocket), so that DRPs should be excised to achieve optimal excision of endometriosis (36) (Tab. VI).

TABLE VI - Studies evaluating the clinical characteristics of endometriosis in adolescents

Study	Design	No. (pos/ cases)	Method of evaluation	Duration	Age (y)	Aim of study
Dun et al (18)	Retrospective analysis	18/25	Biopsy	2001-2009	10-21 years	To describe the experience of adolescents who underwent laparoscopy for pelvic pain and were diagnosed with endometriosis
Smorgick et al (29)	Retrospective analysis	86	Visual or biopsy	2000-2011	≤22	To describe the prevalence and characteristics of advanced-stage endometriosis in adolescents and young women treated in a tertiary referral center
Smorgick et al (19)	Retrospective analysis	138	Visual or biopsy	2001-2011	<21	To describe the occurrence of pain syndromes, mood conditions, and asthma in adolescents and young women with endometriosis evaluated at their medical center
Yang et al (25)	Retrospective analysis	63	Biopsy	1992-2010	12-20	To investigate the clinical presentations, diagnosis, treatment modalities and prognosis of endometriosis in adolescents in China
Yeung et al (20)	Retrospective analysis	17/20	Biopsy	1999-2007	12-19	To determine long-term outcomes after complete laparoscopic excision done at a tertiary referral center in a teenager population who were not specifically advised to take postoperative hormonal suppression
Roman (26)	Comparative cohort	20	Biopsy	2003-2009	<20	To describe their experience with laparoscopic excision of endometriosis on an adolescent population and to compare it with a non-adolescent population treated during the same period
Vicino et al (27)	Prospective analysis	30/38	Biopsy	2000-2006	≤21	To analyze the clinical manifestations of endometriosis in adolescents
Bai et al (11)	Retrospective analysis	39	Biopsy	1990-1999	14-21	To evaluate the age distribution, diagnosis, clinical stage, and treatment of endometriosis in adolescents of Korea
Davis et al (30)	Retrospective analysis	36	Visual	1986-1992	<20	To describe the appearance, stage, and treatment of endometriosis in adolescents undergoing laparoscopic treatment of severe dysmenorrhea and endometriosis

Surgery and hormonal treatment

Role of surgery in improving pain, fertility or progression/recurrence

Is surgery beneficial in treating pain?

Yes, in all stages of endometriosis.

An increasing number of groups have been reporting their outcomes following surgical treatment of endometriosis in teenagers. The majority of these publications were included in the systematic review by Janssen et al (1). These publications included treatment either by ablation or excision of endometriosis, and some did not specify how endometriosis was treated. Only a few of these articles gave outcome data after surgery. In a study by Stavroulis et al (37), laparoscopic "radical excision" was used to treat 11 teenagers followed by hormonal suppression. An excellent response (completely pain free or greatly improved) was seen in 72.3% with a median follow-up of 65 weeks. Roman et al (26) reported significant improvement of dysmenorrhea, pelvic pain symptoms, and QOL of adolescents as demonstrated by the EQ-5D Visual Analogue Scale after laparoscopic excision of endometriosis with a mean follow-up of 2.6 years. Yeung et al (20) concluded that there was a decrease in chronic pelvic pain (by 23.5%), dyspareunia (by 11.8%) and statistically significant improvement in QOL scores (46.4%) after complete excision with a follow-up for up to 66 months. In a study by Dun et al, 64% reported resolved pain and 16% reported improved pain at 1 year after the laparoscopic excision and ablation (18) (Tab. VII).

Is surgery beneficial for improving fertility in adolescents with infertility?

Yes, in revised American Society for Reproductive Medicine (r-ASRM) stages I and II.

A retrospective case series to assess the long-term fertility outcomes in young women after laparoscopic surgery (excision and ablation) to treat endometriosis-associated pelvic pain demonstrated a long-term pregnancy rate of 71.4% of which >80% were achieved without assisted reproductive technology (ART) with a mean follow-up of 102.54 months (38). Patients with documented infertility as an indication for surgery or who were not trying to conceive at any time after surgery during follow-up were excluded. Subsequent medical therapy after surgery was not assessed in the study. Most of

TABLE VII - Studies evaluating the outcomes after surgical treatment of endometriosis in adolescents

Study	Design	No. (pos/ cases)	Method of evaluation	Duration	Findings	Age (y)	Aim of study
Dun et al (18)	Retrospective analysis	18/25	Biopsy	2001-2009	64% resolved pain, 16% improved pain	10-21	To describe the experience of adolescents who underwent laparoscopy for pelvic pain and were diagnosed with endometriosis
Yeung et al (20)	Retrospective analysis	17/20	Biopsy	1999-2007	Decrease in chronic pelvic pain (by 23.5%), dyspareunia (by 11.8%), improvement in QOL scores (46.4%)	12-19	To determine long-term outcomes after complete laparoscopic excision done at a tertiary referral center in a teenager population, who were not specifically advised to take postoperative hormonal suppression
Roman et al (26)	Comparative cohort	20	Biopsy	2003-2009	Significant improvement in dysmenorrhea (p value 0.0055), pelvic pain (p = 0.05), QOL improved by 19%	<20	To describe their experience with laparoscopic excision of endometriosis on an adolescent population and to compare it with a non-adolescent population treated during the same period
Stavroulis et al (37)	Retrospective analysis	11		2001-2003	Completely pain free or greatly improved in 72.3%	13-20	To determine the frequency and severity of endometriosis in adolescent and teenager girls with chronic pelvic pain who fail to respond to medical management and to evaluate the outcome of radical laparoscopic surgery for severe endometriosis

the patients who conceived had Stage I/II disease (38). Audebert et al also reported a live birth rate of 72.2% after surgical treatment (excision and ablation) with 9/13 pregnancies in patients with Stage I/II disease (39). Ventolini et al concluded that even at the earliest point in the natural life cycle of endometriosis (with no treatment for endometriosis) there is an inverse relationship between stage of the disease and fecundability (40) (Tabs. VIII-IX).

Is surgery beneficial in reducing disease progression/recurrence?

Optimal (or complete) laparoscopic excision by experts might slow disease progression.

There are few studies that emphasize that complete laparoscopic excision by experts can significantly reduce the recurrence rates of endometriosis in adolescents. Yeung et al found zero rate of recurrence (diagnosed visually or histologically) after complete laparoscopic excision of the disease in teenagers at a repeat laparoscopy for pain. During this period, 47.1% patients had a subsequent laparoscopy for persistent recurrent pain, but the rate of endometriosis (diagnosed visually or histologically) found at surgery was zero. Only one-third of patients took postoperative hormonal suppression for any length of time in the study. This is the largest prospective study after optimal excision in adolescents (20).

Similarly, a study by Kalu et al (35) found a threefold increase in symptom recurrence and need for reoperation in girls operated by generalists as compared to those operated by an endometriosis specialists team (Tab. X).

TABLE VIII - Relationship between stage of endometriosis and fecundability [(35) n = 28]

	Stage I	Stage II	Stage III	Stage IV
Fecundability rates	75% (3/4)	55% (6/11)	25% (3/12)	0% (0/1)

TABLE IX - Studies evaluating the fertility outcomes after surgical treatment of endometriosis in adolescents

Study	Design	No. (pos/ cases)	Method of evaluation	Duration	Findings	Age (y)	Aim of study
Audebert et al (39)	Retrospective analysis	49/55	Biopsy	1998-2013	Live birth rate -72.2%	<19	To report the clinical presentation and long-term issues of adolescent endometriosis
Wilson-Harris et al (38)	Retrospective analysis	28	Visual or biopsy	2000-2005	Live birth rate -71.4%	18-25	To describe the long-term fertility outcomes in young patients with endometriosis associated pelvic pain treated with laparoscopic surgery
Ventolini et al (40)	Retrospective analysis	28	Visual or biopsy	1993-1995	Fecundability rates Stage 1 = 75% Stage 2 = 55% Stage 3 = 25% Stage 4 = 0%	12-18	A long-term follow-up study comparing mild and severe forms of endometriosis and their fecundability, on 28 women diagnosed with endometriosis in adolescence

TABLE X - Studies evaluating the recurrence/progression after surgical treatment of endometriosis in adolescents

Study	Design	No. (pos/ cases)	Method of evaluation	Duration	Findings	Age (y)	Aim of study
Yeung et al (20)	Retrospective analysis	17/20	Biopsy	1999-2007	47.1% recurrence of symptoms, rate of endometriosis- zero	12-19	To determine long-term outcomes after complete laparoscopic excision done at a tertiary referral center in a teenager population, who were not specifically advised to take postoperative hormonal suppression
Kalu et al (35)	Retrospective analysis	28	Visual	2000-2005	Symptom recurrence 14% in specialist group vs. 42.8% in generalists	15-21	To describe the clinical features and treatment outcome following the laparoscopic treatment of endometriosis in teenagers and adolescents

Batt et al (41) have also suggested that adolescents with chronic pelvic pain should be referred to gynecologists who are experienced laparoscopic surgeons and who recognize congenital anomalies as well as the subtle and atypical and more common appearances of endometriosis.

Role of postoperative hormones in improving pain, fertility or progression/recurrence

Most published reviews recommend that postoperative hormonal suppression be offered to adolescents to treat symptoms and to prevent progression/recurrence (42, 43).

Does postoperative medical therapy in conjunction with surgery to treat endometriosis improve pain?

Perhaps it does, though this is a separate issue from preventing disease progression or recurrence.

Stavrolius et al (37) showed excellent response (completely pain free or greatly improved) in 72.3% (8/11) patients. Two other patients reported partial improvement. All patients were prescribed postoperative medical management (OCPs taken tricyclically, Provera and levonorgestrel intrauterine system). The overall median follow-up was 65 weeks. Dun et al (18) also showed that 64% reported resolved pain and 16% reported improved pain at 1 year after the laparoscopic excision and ablation. Postoperative medical treatment (OCPs and progestins) was taken by 76% of patients (Tab. XI).

A case series by Unger et al (44) concluded that without combined surgical-medical management, disease worsens, and places patients at risk for severe chronic pelvic pain as well as infertility. The case series reported on three adolescents who were diagnosed with Stage I endometriosis on initial surgery and had lesions cauterized. All three patients were prescribed hormonal treatment but were non-compliant. A second laparoscopy for debilitating symptoms showed worsened stage (two patients were stage IV and one was stage II). Progression of disease in these cases might be due to failure to completely treat disease at primary surgery or due to noncompliance with hormonal treatment.

Does postoperative medical therapy in conjunction with surgery to treat endometriosis improve future fertility?

Not evaluated.

Two studies in the review reported fertility outcomes after surgery in adolescents. A study by Audebert et al (39) did not prescribe post-surgery hormonal treatment to patients who wanted to conceive. Wilson-Harris et al (38) did not assess subsequent medical therapy after surgery in all their patients. Hence, it is difficult to conclude whether postoperative medical therapy in conjunction with surgery to treat endometriosis improves future fertility.

Does postoperative medical therapy in conjunction with surgery to treat endometriosis slow disease progression/recurrence?

Probably not, though this is a separate issue from treating pain.

The recurrence rate of endometriosis in young women appears to be higher than in older women. A retrospective cohort of 57 women, aged ≤21 years, who were treated initially by excisional surgery had a 56% (n = 32) rate of recurrence of symptoms during a follow up-period of 5 years. A second laparoscopy that confirmed the presence of disease was only performed in 11 out of 32 patients. The study also showed that the postoperative medical therapy did not influence the recurrence rates (45).

A retrospective chart review by Doyle et al (46) concluded that combined medical surgical-medical management retards disease progression in adolescents and young adults. No change in stage was observed in 70%, 19% improved by a single stage, 1% improved by two stages, and only 10% worsened by one stage on subsequent laparoscopy for recurrent/worsening symptoms. Regardless of the initial stage, there was not a statistically significant trend towards disease progression ($p = 0.29$). There was, however, a significant likelihood of improving in stage as observed at the second laparoscopy ($p<0.0001$), with those diagnosed as stage II or stage III at initial laparoscopy most likely to exhibit improvement (Tab. XII).

TABLE XI - Studies evaluating the pain outcomes after combined surgical-medical treatment of endometriosis in adolescents

Study	Design	No. (pos/ cases)	Method of evaluation	Duration	Findings	Age (y)	Aim of study
Dun et al (18)	Retrospective analysis	18/25	Biopsy	2001-2009	Improvement in 72.3%	10-21	To describe the experience of adolescents who underwent laparoscopy for pelvic pain and were diagnosed with endometriosis
Stavroulis et al (37)	Retrospective analysis	9/11	Visual	2001-2003	Improvement in 80%	13-20	To determine the frequency and severity of endometriosis in adolescent and teenage girls with chronic pelvic pain who fail to respond to medical management and to evaluate the outcome of radical laparoscopic surgery for severe endometriosis

TABLE XII - Studies evaluating the disease progression or recurrence after combined surgical-medical treatment of endometriosis in adolescents

Study	Design	No. (pos/ cases)	Method of evaluation	Duration	Findings	Age (y)	Aim of study
Tandoi et al (45)	Retrospective analysis	57	Biopsy	2000-2005	Recurrence rate-56%	≤21	To evaluate rate and determinants of long-term recurrence of endometriosis in a population of young women
Doyle et al (46)	Retrospective analysis	90	Visual	1995-2007	Progression in 10%, persistent disease in 70%	12-24	To evaluate the effect of combined surgical-medical treatment on endometriosis progression in adolescents as measured by disease stage

A cross-sectional study by Chapron et al (47) concluded that the knowledge of adolescent period history can identify markers that are associated with deeply infiltrating endometriosis (DIE). The study showed that patients with DIE had significantly more positive family history of endometriosis (odds ratio [OR] = 3.2; 95% confidence interval [CI]: 1.2-8.8) and more absenteeism from school during menstruation (OR = 1.7; 95% CI: 1-3). The OCP use for treating severe primary dysmenorrhea was more frequent in patients with DIE (OR = 4.5; 95% CI: 1.9-10.4). Duration of OCP use for severe primary dysmenorrhea was longer in patients with DIE (8.4 ± 4.7 years vs. 5.1 ± 3.8 years). There was a higher incidence of OCP use for severe primary dysmenorrhea before 18 years of age in patients with DIE (OR = 4.2; 95% CI: 1.8-10.0) in patients undergoing surgery for endometriosis.

Is there any evidence regarding type of hormonal suppression to be used?

A range of medical therapies have been employed for the treatment of endometriosis, although data are not available for all of these options in an adolescent population. The options include estrogen/progestin combinations, progestins alone, and gonadotropin-releasing hormone agonists (GnRHa) with add-back therapy.

Gonadotropin-releasing hormone agonist (GnRHa)

A retrospective study by Yang et al (25) reported a recurrence rate of 55.6% in adolescent patients after excisional surgery with a follow-up ranging from 12-98 months. The study identified genital malformation and multifocal disease as a risk factor for recurrence. Recurrence was defined as new pelvic masses found by ultrasound or similar symptoms which recurred at least 6 months' postoperatively. They showed GnRHa to be more effective compared with OCPs and progestins to prevent recurrence. Disease recurred in 46%-50% of patients receiving OCPs and progestins when compared to 0% in patients receiving GnRH agonists.

Two randomized controlled trials assessed the hormonal add-back therapy for females treated with GnRHa for endometriosis. The trials concluded that hormonal add-back therapy successfully preserved bone health and improved QOL for adolescents and young women with endometriosis during 12 months of GnRHa therapy. Combination norethindrone acetate plus conjugated equine estrogens add-back appears to be more effective for increasing total bone mineral content, bone mineral density, lean mass and physical health-related QOL than norethindrone acetate monotherapy (48, 49).

Levonorgestrel intrauterine system (LNG-IUS)

While the LNG-IUS is accepted for use in the adolescent population for contraception and menorrhagia, there are few data regarding its effectiveness in the treatment of endometriosis, and studies are mainly from the adult population. A retrospective cohort study by Yoost et al (50) sheds insight that the LNG-IUS is indeed effective at diminishing pain and bleeding associated with endometriosis in adolescent patients (Tab. XIII).

A case report published in the *Australian and New Zealand Journal of Obstetrics and Gynaecology* journal provides some evidence that the combined therapy with LNG-IUS and an etonogestrel subdermal implant may effectively suppress endometriosis symptoms, at least on a medium-term basis in patients with pain that may be resistant to other therapies (51).

Endometrial cysts

There are very few data about endometriosis and endometriomas in adolescents and young women. A study reviewing 15 years of ovarian masses in infants, children and adolescents reported no endometriomas (52). Newer studies have reported that advanced-stage endometriosis in adolescents mainly presents with ovarian endometriomas rather than extensive peritoneal or adhesive disease (29).

Adolescents with endometrioma experience more frequent pain, but other characteristics of endometrioma do not differ with other age groups (53). A retrospective chart review of 63 adolescent patients with endometrioma found bilateral disease in 22.22% (14/63) patients. They also found that a right endometrioma was more frequent than a left endometrioma (65% vs. 57%). With regard to the clinical manifestations of the disease, chronic pelvic pain was the most common symptom (44%) reported on admission. Fifty-five (87%) patients had score <16 points for adnexal adhesions calculated according to the r-ASRM classification. The surgery performed was a combined technique of cystectomy and cauterization of the capsule in this study (54). A review by Gordts et al (55) published recently concluded that early ablative surgery can contribute to a lower morbidity, relief of symptoms, and a better QOL.

TABLE XIII - Studies evaluating the type of hormonal treatment posts surgery in adolescents with endometriosis

Study	Design	No. (pos/ cases)	Method of evaluation	Duration	Age (y)	Aim of study
Gallagher et al (48)	Randomized controlled trial	50	Visual	2000-2010	15-22	The effect of GnRHa plus add-back therapy on quality of life for adolescents with endometriosis
Yoost et al (50)	Retrospective cohort	18	Biopsy	2009-2011	14-22	To evaluate our adolescent patient population who had received a levonorgestrel intrauterine system (LNG-IUS) at or after the time of endometriosis diagnosis, and determine efficacy of the LNG-IUS in regards to pain and bleeding on follow-up exam
Yang et al (25)	Retrospective analysis	63	Biopsy	1992-2010	12-20	To investigate the clinical presentations, diagnosis, treatment modalities and prognosis of endometriosis in adolescents in China
Al-Jefout et al (51)	Case report	1		2002	13	Simultaneous use of a levonorgestrel intrauterine system and an etonogestrel subdermal implant for debilitating adolescent endometriosis

GnRHa = gonadotropin-releasing hormone agonist.

TABLE XIV - Studies evaluating the clinical characteristics of endometrioma in adolescents

Study	Design	No. (pos/ cases)	Method of evaluation	Duration	Findings	Age (y)	Aim of study
Lee et al (56)	Multicenter retrospective cohort	105	Visual	2000-2010	recurrence rates of 6.4%, 10%, 19.9% and 30.9% at 24, 36, 60 and 96 months	<20	To evaluate cumulative recurrence rates of endometriomas after a laparoscopic endometriotic cyst enucleation in adolescents and to find the factors associated with recurrence
Audebert et al (39)	Retrospective analysis	49/55	Biopsy	1998-2013	Recurrence rate of 36.84%	<19	To report the clinical presentation and long-term issues of adolescent endometriosis
Lee et al (53)	Cross-sectional	35	Biopsy	2003-2010		≤20	To evaluate the clinical characteristics of endometrioma in adolescent women compared to women of other age groups
Özyer et al (54)	Retrospective analysis	63	Biopsy	2007-2011		≤24	To 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

Treatment in early stage will result in less damage to the ovary caused by the disease itself and by a less invasive surgical procedure. Although laparoscopy is traditionally recommended, transvaginal laparoscopy has been shown to be most effective in ablating endometriomas with a maximum diameter of 3 cm.

A retrospective cohort study reported a recurrence rate of 50% for DIE and a recurrence rate of 36.84% for endometriomas during a mean follow-up of 97.5 months after excision and ablation surgery. All patients who did not want to conceive were advised to use hormonal treatment (39). A very recent study accepted for publication in the *Journal of Paediatric and Adolescent Gynecology* journal has reported cumulative recurrence rates of endometrioma per patient at 24, 36, 60 and 96 months after laparoscopic cyst enucleation for ovarian endometrioma as 6.4%, 10%, 19.9% and 30.9%, respectively. All patients were Stage III or IV disease. The diagnosis of recurrent ovarian endometrioma was based on ultrasonographic findings. Seventy-six percent of patients received postsurgical medical therapy. Surgical characteristics such as the diameter of the cyst, rAFS stage, unilateral or bilateral involvement, and coexistence of deep endometriosis were not associated with recurrence in the study (56) (Tab. XIV).

Discussion

Our review found that the prevalence of endometriosis in adolescents is estimated to be about one-third of adolescents with chronic pain, increasing to up to 80% in adoles-

cents with chronic pelvic pain who fail to respond to medical treatment. Regarding the clinical features of endometriosis in adolescents, the most common presenting symptoms in the studies included were dysmenorrhea and chronic pelvic pain. The review also concluded that the adolescent endometriosis may present differently from adult endometriosis, with acyclic pain being more common in adolescents. At the time of surgical diagnosis, most adolescents (~50%) in our study had Stage I disease irrespective of hormonal treatment. These findings are consistent with American College of Obstetrician & Gynecologists (ACOG) Committee Opinion on Endometriosis in Adolescents. Our review also found a high prevalence of comorbid chronic pain syndromes (56%) and mood disorders (48%) in adolescents and young women with endometriosis. We found that an ovarian endometrioma is the most common form of presentation of advanced disease in adolescents. Our review also showed a predominance of red lesions in the adolescent population as mentioned by ACOG.

ACOG Committee Opinion #310 states that current treatments for adolescents have been extrapolated and adapted from the literature on adult case of endometriosis. The goal of therapy should be suppression of pain, suppression of disease progression, and preservation of fertility. Our review concludes that surgery is beneficial to treat pain in all stages of endometriosis and improves fertility, especially in early stages. It also concludes that complete excisional surgery by experts can also help slow disease progression.

ACOG Committee Opinion #310 recommends long-term medical treatment for pain management of adolescent endometriosis and until a woman has completed child bearing. It also states that long-term studies are needed to determine if medical treatment can inhibit the progression of endometriosis and preserve future fertility. Through our review, we conclude that it helps delay pain recurrence, but that it is not clear if it helps prevent disease recurrence or progression and, perhaps more importantly, fertility.

ACOG suggests that GnRHa therapy should not be used as first-line treatment for adolescents younger than 16 years of age. It also says that no data exist on the long-term effects of GnRHa use with add-back therapy in the adolescent population and, thus, it should be reserved for adolescents who are refractory to continuous combination hormone therapy. Our review found GnRHa to be more effective compared with OCPs and progestins to prevent recurrent endometriomas. Add-back therapy successfully preserved bone health and improved QOL for adolescents with endometriosis during 12 months of therapy. The LNG-IUS may be effective at diminishing pain and bleeding associated with endometriosis in adolescent patients.

Conclusions

Summary of recommendations for clinical practice

- Awareness of endometriosis as a disease with significant morbidity among adolescents is of utmost importance. The majority (up to 80%) of adolescent girls with chronic pelvic pain not responding to conventional medical therapy have endometriosis. Adolescent endometriosis may not present with the typical cyclic pain pattern that is found in adults with the disease. Early identification of disease may be helpful in slowing or preventing progression.
- Laparoscopy (with biopsy) is the only way to diagnose endometriosis in the adolescent population, and surgical management has been shown to be beneficial in reducing pain, infertility, and progression or recurrence of disease. Adolescent patients with endometriosis may be best served by having surgery with a specialist who recognizes the often atypical manifestations of the disease, which are common in the adolescent population.
- Postoperative hormonal suppression helps reduce pain symptoms and recurrence of endometriomas, but it does not seem to prevent disease recurrence or progression as is commonly believed, or perhaps more importantly, to benefit fertility, Further studies are needed, and until then, postoperative suppression until pregnancy is based on expert opinion only.

Summary of recommendations for research

There is a need for good quality properly randomized and controlled trials, evaluating surgical technique, hormonal treatments and clinical outcomes. Pathological confirmation of endometriosis should be done in all cases, and should include documentation of the phenotype of lesions. Valid measurements of outcomes such as visual analog scale scores for pain and QOL scores should be included. There should be a long-term follow up for at least 1 year.

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