Endometriosis in Adolescence

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12.1 Prevalence and Epidemiology

In 1948, Meigs reported the incidence of endometriosis in adolescents to be 6% [1]. Others have attempted to estimate the prevalence of endometriosis in adolescents, although these estimates vary depending on symptoms and the modality used for diagnosis. The prevalence of endometriosis in adolescents who present for investigation, however, appears to be high. The prevalence among adolescents undergoing laparoscopic investigation for pelvic pain not responsive to nonsteroidal anti-inflammatory drugs and oral contraceptive pills is 50–70% [2–4]. A 2013 systematic review by Janssen et al. [5] sought to review the prevalence of endometriosis diagnosed by laparoscopy in adolescents; based on 15 selected studies, they identified the overall prevalence of visually confirmed endometriosis was 62% in all adolescents undergoing laparoscopic investigation, 75% in girls with chronic pelvic pain resistant to treatment, and 70% in girls with dysmenorrhea. Although laparoscopy has been the gold standard for confirming endometriosis, other studies have included the use of imaging, such as magnetic resonance imaging (MRI) or ultrasound, to aid in the diagnosis or as an alternative to laparoscopy [6–8]. A 2020 systematic review by Hirsch et al. [9] included studies diagnosing endometriosis via both laparoscopy and imaging in adolescents, and the prevalence ranged from 25% to 100%, with a mean prevalence of 64%.

Prevalence estimates are unfortunately limited as some adolescents are asymptomatic or have atypical presentations leading to underdiagnosis. Delays in diagnosis from the onset of symptoms are common worldwide, ranging from 4 to 11 years [10–14]. In a registry of 4000 adult women with endometriosis, two-thirds of women responded to a survey and reported their first pelvic symptoms started before age 20, and 1 in 5 had pain before age 15 [15]. Symptomatic cases have been cited at earlier ages, including prior to menarche [16] and in others soon after menarche [17, 18]. The early manifestations of endometriosis suggest the origin of endometriosis is likely multifactorial and not simply after years of retrograde menstruation.

12.2 Risk Factors

Several predisposing factors make adolescents uniquely vulnerable to endometriosis. A family history of endometriosis may predispose young women to the disease, although the precise mechanism or mechanisms remain unclear. In a systematic genetic study of 234 cases of histologically confirmed endometriosis, endometriosis occurred at a 6.9% rate in first-degree relatives of women with the disease, compared to a 1% rate in relatives of controls [19]. Endometriosis that occurs in families tends to be more severe compared to sporadic cases, and a similar and earlier age of onset of symptoms occur in affected families [20, 21]. Due to the demonstration of familial clustering of endometriosis, the disease is considered by most investigators to be inherited in a polygenic or multifactorial mode [20].

Endometriosis has also been reported in up to 40% of adolescents with reproductive tract anomalies [22]. Obstructive anomalies that have been implicated include imperforate hymen, transverse vaginal septum, and vaginal agenesis [23, 24]. The presence of an obstructive anomaly supports the concept of retrograde flow as predisposing an adolescent to endometriosis. Although repair or relief of the obstruction has been associated with resolution of endometriosis [25], a case series demonstrated that endometriosis may not always resolve following repair of an obstructive anomaly [26]. This may be due to the obstruction seeding the peritoneal cavity or to other risk factors.

Increased exposure to menstruation and endogenous estrogen may predispose adolescents to acquiring endometriosis. Identified risk factors include earlier menarche (before age 11–13), nulliparity, shorter menstrual cycle intervals, and heavy menstrual bleeding [27–29]. In a laparoscopy cohort, women diagnosed with endometriosis were found to be a taller height and a leaner body habitus since adolescence [30]. Sociodemographic factors include ethnicity, with Caucasian/white and Asian women having higher reported rates of endometriosis in comparison to Hispanic and black women, although this underreporting may be contributed by implicit bias, potentially different presenting symptoms of endometriosis, and racial disparities in healthcare access [31, 32]. Childhood sexual and physical abuse are associated with an increased risk of endometriosis [33].

Modifiable and early life risk factors may also contribute to the development of endometriosis in adolescents. Prior studies have postulated lower birth weight, prematurity, and maternal diethylstilbestrol as increase risk factors for endometriosis; intense physical activity, passive smoke exposure, and skin sensitivity have also been raised as increased risk factors but remain understudied [34]. In an investigation of in utero and early life factors in relation to endometriosis, exposure to breastfeeding in early life was associated with lower odds of surgically diagnosed endometriosis and secondhand smoke during childhood was associated with greater odds of endometriosis in adolescents [35]. Exposures in adolescence may also further impact endometriosis risk into adulthood. Even dietary exposures seem to be implicated; in a longitudinal cohort study, lower rates of laparoscopically confirmed endometriosis were diagnosed among adult women who in adolescence consumed greater amounts of total dairy foods [36]. These findings support the need for further investigation of early life influences, and if early life interventions may reduce endometriosis burden in later life.

12.3 Pathophysiology

The pathophysiology of endometriosis remains controversial despite decades of research. The most recognized theory behind endometriosis is Sampson's theory [37] of retrograde menstruation, but it alone cannot explain the wide ranges of manifestations of endometriosis, including endometriosis in early adolescence. Retrograde menstruation is a common physiologic event in nearly all menstruating

women with patent tubes, with or without endometriosis present [38]. Early-onset or adolescent endometriosis therefore appears to be distinct from adult endometriosis, or at least contributed by other mechanisms [39]. One of the theories behind adolescent endometriosis is the seeding of naive endometrial progenitor cells into the pelvic cavity at the time of neonatal uterine bleeding. Neonatal uterine bleeding is a less common phenomenon affecting only 5% of newborn girls, characterized by decidual transformation and endometrial shedding in the neonatal uterus [40, 41]. The implantation model via neonatal uterine bleeding was described in a case report by Arcellana et al. [42], of a demised female infant with McKusick-Kaufman syndrome. The infant's postmortem examination revealed an intact transverse vaginal septum, hemorrhagic endometrial reflux, and implantation of epithelial fragments on the bowel serosa and adhesions around the ovaries and upper uterus. It is postulated that the relatively longer neonatal cervix and thick cervical secretions may facilitate retrograde seeding of endometrial mesenchymal stem cells and stromal fibroblasts during the early neonatal period [38, 43]. Other theories on the origins of endometriosis include Halban's [44] theory on vascular or lymphatic spread of endometrial cells, Meyer's [45] theory of embryologically totipotent cells undergoing metaplastic transformation, innate or acquired properties of the endometrium, and defective immune clearance [46]. No unifying theory explains all cases of endometriosis, and challenging cases such as premenarcheal endometriosis supports alternative theories to Sampson's theory, such as coelomic metaplasia and Müllerian embryonic rests. [17]

As part of a pursuit to further characterize adolescent endometriosis, studies have attempted to describe its physiologic environment and distinguishing features. Increasing evidence has pointed to endometriosis being a pelvic inflammatory condition. A multicenter nested case-control study demonstrated significant differences in peritoneal fluid cytokines when comparing adolescents with endometriosis to adults with and without endometriosis [47]. A more pro-invasive cytokine profile was observed in adolescents compared to adults, despite greater use of hormones for treatment. Whether observed cytokine profiles are a source or a result of endometriosis remains to be definitively determined. But, these findings at least suggest adolescents with endometriosis have a unique inflammatory milieu that may contribute to greater and/or earlier symptomatology [47].

12.4 Clinical Presentation

Endometriosis is the leading cause of secondary dysmenorrhea in adolescents, and it is also the most common finding in young women undergoing laparoscopy for chronic pelvic pain [48]. Unlike adults, endometriosis is less likely to present as the classic symptom of dysmenorrhea, or as infertility or endometriomas. In a retrospective study by Laufer et al. [2], the classic symptom of cyclic pain was present by itself in 9.4% of adolescent subjects, whereas 28.1% of subjects had acyclic pain alone, and 62.5% had both cyclic and acyclic pain. Therefore, the majority (90.6%) of adolescents with endometriosis experienced acyclic pain. In a 2018 prospective

study by DiVasta et al. [49], general acyclic pain was common for adolescents (66%) and lasted for days at a time (40%). Most participants also experienced moderate-severe menstrual pain, commonly starting at menarche.

Inquiring about general pelvic pain is crucial as it is the predominant symptom in premenarcheal endometriosis. A small case series by Marsh and Laufer [17] identified five premenarcheal girls with chronic pelvic pain who had been evaluated with a standard medical and gastrointestinal evaluation without definitive findings for an etiology for their pain. All five subjects were laparoscopically confirmed to have stage I endometriosis based on the standard American Society for Reproductive Medicine Classification of Endometriosis [50], and none of them had an obstructive anomaly of the reproductive tract. Thus, premenarcheal girls and postmenarcheal adolescents should be asked about their pelvic pain symptoms, even in the absence of menstruation. A pain diary may be helpful for the patient and/or caregiver in documenting the frequency and character of pain.

Another manifestation of pelvic pain commonly reported by women with endometriosis is dyspareunia. Adolescents and young adults with endometriosis experience dyspareunia twice as often as their peers without endometriosis; the burden of dyspareunia has an additive negative impact on physical health and mental health [51]. A thorough review of systems in adolescents with endometriosis may reveal multiple pain symptoms including non-gynecologic sources. In a case series of 25 female individuals (mean age, 17.2 years) with laparoscopically confirmed endometriosis, 52% of patients reported at least 1 genitourinary symptom, and 56% reported at least 1 gastrointestinal symptom [52]. Genitourinary symptoms reported were bladder pain, flank pain, back pain, dysuria, urinary frequency and urgency, incontinence, hematuria, and nocturia; gastrointestinal symptoms included nausea, constipation, diarrhea, and hematochezia. More adolescents with endometriosis than adults report nausea accompanying their general pelvic pain, and they experience general pelvic pain relief after a bowel movement [49]. The presence of urinary or gastrointestinal symptoms may in part be secondary to overlap with functional pain syndromes such as interstitial cystitis and irritable bowel syndrome (IBS) [53, 54]. A large prospectively enrolled cohort study showed that the odds of IBS was fivefold higher among adolescents with endometriosis than without, and the presence of acyclic pelvic pain was a strong predictor of the likelihood of IBS [55]. Another commonly reported pain disorder among adolescents with endometriosis is migraines. A cross-sectional study found a higher prevalence of migraines among adolescents with endometriosis compared to those without endometriosis [56]. The study also demonstrated a linear relationship between migraine pain severity and the odds of endometriosis, suggesting heightened pain sensitivity for adolescents with endometriosis.

Interestingly, there is a higher self-reported rate of autoimmune diagnoses in women with endometriosis compared to the general female population. Thus, adolescents may exhibit non-pain symptoms and should be screening by their provider for other comorbidities so as to receive comprehensive healthcare [57]. A 2019 systematic review and meta-analysis suggested an increased risk of autoimmune diseases including systemic lupus erythematosus, Sjögren's syndrome, rheumatoid

arthritis, autoimmune thyroid disorder, celiac disease, multiple sclerosis, inflammatory bowel disease, and Addison disease [58]. However, only a few studies were of high quality and well-designed. It is unclear whether endometriosis is a risk factor or a consequence of autoimmune disease, but this adds evidence to the chronic and inflammatory nature of endometriosis.

Adolescents with endometriosis commonly report their symptoms as interfering with their functionality and quality of life. There is a high prevalence of pelvic pain that negatively impacts work, school, daily activities, exercise, and sleep to a moderate-extreme degree [49]. In a study of 250 adolescents with dysmenorrhea and symptoms suspicious for endometriosis, 12% of those age 14–20 years lost days of school or work each month due to pain [59]. A population-based study by Gallagher et al. [60] provided evidence that adolescents and young adults with endometriosis experience deficits in physical health-related and mental health-related quality of life. In addition to pain, participants had difficulty completing daily activities (e.g., "climbing several flights of stairs," "bathing or dressing yourself") and trouble engaging in social activities with family, friends, and groups. Unfortunately, diagnostic delay is common, despite the significant impact on quality of life. In the study by Gallagher et al. [60], the mean age at surgical diagnosis was 16.3 years (SD = 2.5), representing an average diagnostic delay of 2.8 years from onset of first symptoms.

Diagnostic delay is contributed by multiple factors. Firstly, many healthcare providers, including pediatricians, gynecologists, and family medicine practitioners, may not be aware of the many symptoms of endometriosis in adolescents. In addition, many women perceive their symptoms as an extreme of normality and consider themselves to be "unlucky" rather than ill. Women may not come forward with their pain symptoms partly due to embarrassment and in order to avoid stigmatization [61]. Lastly, knowledge of endometriosis is low among adolescents and those around them, including their family members and school personnel [62]. In a cross-sectional study by Zannoni et al. [59], 82% of 250 adolescents had never heard about endometriosis, and 80% expressed interest in learning more about it; these underscore the need for research on measures to create a supportive and informed social climate.

12.5 Evaluation

Evaluation of the adolescent patient first begins with a comprehensive history and review of systems. If the initial description of pain is vague or limited, a pain diary should be considered. The use of diaries recording pain, mood, menses, diet, medication, and other non-gynecologic symptoms can help discern the pattern of pain [63]. Since keeping a physical journal at all times may not be feasible, adolescents may find it easier to utilize pain diary and symptom tracker mobile applications. After the history, a physical examination should be performed. A physical exam is unlikely to reveal endometriosis but is helpful for assessing for other gynecologic sources of pain, such as a pelvic mass or a reproductive anomaly, or non-gynecologic

etiologies of pain; these may include gastrointestinal, urinary, or musculoskeletal etiologies. Evaluation of the skin may reveal erythema ab igne, or "hot water bottle rash." Erythema ab igne presents as a reticulated hyperpigmented erythematous eruption at sites of prolonged heat exposure, and it is commonly seen in those who use of heat for relief of pain from chronic diseases such as Crohn's disease [64, 65]. An abdominal exam should be performed to locate any tenderness and palpable hernia or masses. A musculoskeletal exam can assess for abdominal wall tenderness (e.g., Carnett's sign), range of motion of the hips and spine, symptoms with pelvic compression, and bone tenderness [57].

A pelvic exam is not always necessary, particularly as adolescents are less likely to have uterosacral nodularity or distorted anatomy from advanced or deep infiltrating disease. If a pelvic examination is offered, this should be approached with sensitivity and with the goals of minimizing discomfort and anxiety [66]. The adolescent should be given the choice of having a parent or caregiver as a chaperone during the examination. If the patient consents and is sexually active, the smallest size speculum should be utilized, typically a pediatric speculum. A single digital exam or a Q-Tip (cotton swab) can be inserted into the vagina to assess for vaginal length and patency and exclude a reproductive tract anomaly. A rectal-abdominal examination may also be better tolerated than a vaginal-abdominal examination, particularly in the patient who has never been sexually active.

12.6 Laboratory/Imaging Studies

There is currently no specific blood test or biomarker that has been validated as a noninvasive diagnostic test for endometriosis. Many attempts have been made to identify and validate specific biomarkers, such as Cancer Antigen 125 (CA125) [67]. A recent evaluation of CA125 by Sasamoto et al. [68] demonstrated that average CA125 values were low in adolescents and young women with or without endometriosis, and CA125 did not correlate with pain type, severity, or frequency. Laboratory studies may include a complete blood count or an erythrocyte sedimentation rate to assess for an inflammatory or infectious process resulting in pain. A pregnancy test or sexually transmitted infection testing should be considered in the sexually active patient. Urinalysis or urine culture are helpful in excluding urinary causes of pain.

Adolescents with dysmenorrhea do not routinely need to be imaged, as most adolescents experience primary dysmenorrhea, or painful menstruation in the absence of pelvic pathology [48]. However, imaging may be helpful in patients who either present initially with symptoms suggesting secondary dysmenorrhea or they fail empiric treatment for primary dysmenorrhea and require further evaluation. Ultrasound imaging can exclude the presence of an ovarian cyst, tumor, adnexal torsion, or a reproductive tract anomaly. A pelvic ultrasound can be performed trans-abdominally instead of trans-vaginally to minimize discomfort. Alternatively, trans-rectal imaging may also be performed. In a retrospective observational study by Martire et al. [69], 270 women aged 12–26 years underwent trans-vaginal

ultrasound if sexually active, and trans-rectal in never sexually active adolescents. At least one finding of endometriosis was identified in 36 (13.3%) of 270 cases; ovarian endometriomas were found in 22 (11%) patients, adenomyosis in 16 (5.2%), and deep infiltrating endometriosis in 10 (3.7%). In patients with dysmenorrhea, the detection rate of pelvic endometriosis with ultrasound increased to 20%. If the ultrasound or physical examination is concerning for an anomaly, magnetic resonance imaging should be ordered because of its high accuracy in detecting and accurately characterizing Müllerian duct anomalies [70].

12.7 Trial of Medical Therapy

A trial of medical therapy is reasonable after a thorough evaluation excludes non-gynecologic causes of pain and suggests a non-acute gynecologic source, such as primary dysmenorrhea or endometriosis. First-line treatment options include non-steroidal anti-inflammatory agents (NSAIDs), combined hormonal contraceptives, and progestin-only therapies. NSAIDs interrupt cyclooxygenase-mediated prostaglandin production and are significantly better than placebo in providing pain relief from primary dysmenorrhea, although there is no individual NSAID that is demonstrated to be superior [71]. Patient education of NSAIDs is critical, as adolescents often report little or no improvement with NSAIDs. As self-directed use of NSAIDs by adolescents is high, they have likely used subtherapeutic treatment with incorrect interval dosage and timing [48]. Providers should therefore instruct adolescents on the proper interval dosage and advise starting NSAIDs 1–2 days before menstruation and through the first 2–3 days of bleeding [72]. As each method has benefits and potential adverse effects, the decision to use one method should be patient-driven so as to improve adherence.

Hormonal therapies include combined hormonal contraception (pill, patch, ring), or progestin-only therapies (oral, injectable, or implantable). Hormonal methods prevent endometrial proliferation or ovulation, or both, and thus help to decrease prostaglandin and leukotriene production [72]. The choice of medication should be individualized and tailored to the patient, as the patient may have a prior treatment history, specific desires, or certain unacceptable adverse effects. A shared decision-making approach to hormonal contraception will improve adherence to the treatment. Combination estrogen-progestin oral contraceptive pills or progestin-only pills are most commonly prescribed as they are easily initiated and short-acting; however, there is no data suggesting one formulation is better than another for the management of dysmenorrhea. A continuous regimen may provide more rapid pain reduction than cyclic use of oral contraceptive pills, but both provide similar long-term success for managing primary dysmenorrhea [73]. Continuous regimen users should be cautioned about potential unscheduled bleeding or spotting, which generally decreases over longer treatment use.

Empiric gonadotropin-releasing (GnRH) agonists or antagonists are often considered in adult women with chronic pelvic pain and clinically suspected endometriosis. Empiric GnRH agonists for adolescents 18 years of age or younger should

be avoided because of the potential adverse long-term effects on bone mineral density [74]. Patients and their parents may additionally feel uncomfortable with the potential side effects and risks of empiric GnRH agonist therapy without a definitive diagnosis. The American College of Obstetricians and Gynecologists does not endorse the use of empiric GnRH agonist therapy for treatment of adolescents with suspected primary dysmenorrhea but suggest it as an option for patients with diagnosed endometriosis and pain refractory to conservative surgical therapy and hormonal therapy [48].

A trial of 6 months of medical therapy is often conducted in adults with pelvic pain; however, this may not be practical for adolescents. Symptoms may cause significant impact an adolescent's quality of life and limit their social activities and learning. Therefore, if a patient does not experience clinical improvement with empiric treatment, treatment adherence should be assessed and a definitive diagnosis can be pursued after 3 months. The American College of Obstetricians and Gynecologists recommends the use of laparoscopy for diagnosis of endometriosis in adolescents [48]. A clinical diagnosis of endometriosis, however, can also be considered if the evaluation of symptoms, patient history, physical examination, and/or imaging raise suspicion. There has been a movement to increase the use of clinical diagnosis and treat endometriosis-associated pain without the need for a surgical diagnosis, to help remedy diagnostic delay and promote earlier intervention. A 2019 call to action by Agarwal et al. [14] proposes moving endometriosis from a histological to a clinical definition, and emphasizes the chronic, inflammatory, and progressive nature of endometriosis.

12.8 Diagnostic Surgery

Laparoscopy is an opportunity to diagnose endometriosis and treat any identifiable disease. If a gynecologist is going to proceed with laparoscopy, he or she must feel comfortable operating on adolescent patients and be familiar with the appearance of endometriosis implants in this age group. Endometriosis is staged using the revised American Society of Reproductive Medicine (ASRM) Classification of Endometriosis [50]. The staging is based on a point system that was developed to aid in fertility interventions and not pain management; thus, the extent of disease does not always correlate with the severity of symptoms [75]. Most adolescents are diagnosed with stage I or II endometriosis at laparoscopy, although some observational studies have described rates as high as 40% of stage III or IV disease [76].

Endometriosis lesions has historically been described as blue/black/gray "powder burns"; however, these may represent older and more advanced implants that are seen in adults. Adolescents typically have nonclassical or "atypical" and superficial implants such as white implants, clear vesicular lesions, and small hemorrhagic or petechial spots of the peritoneum [77] (Figs. 12.1 and 12.2). The clear and red lesions more commonly identified in adolescents may be more painful lesions of endometriosis in comparison to black lesions [78]. Moving the laparoscope closer to the peritoneum and adjusting the magnification, a "close tip technique," may be

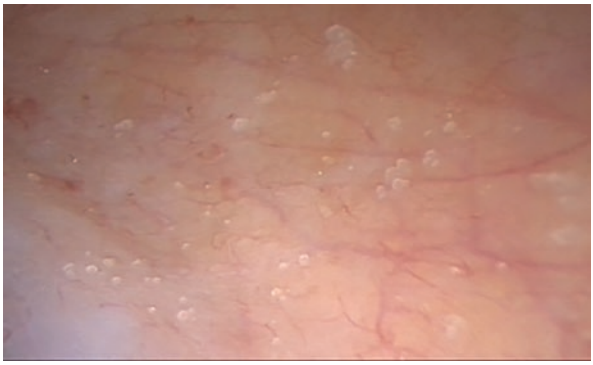

Fig. 12.1 Clear superficial lesions of endometriosis. (Reprinted from Emans [132])

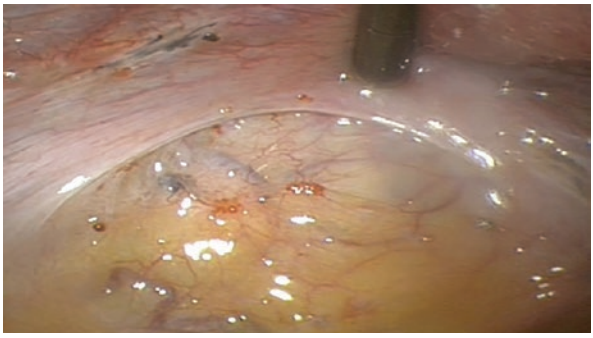

Fig. 12.2 Red peritoneal lesions of endometriosis. (Reprinted from Emans [132])

helpful in identification [79]. Another technique for visualization of lesions is by filling the pelvis with irrigation fluid (e.g., normal saline or lactated Ringer's) and submerging the laparoscope underneath the fluid; the more subtle clear lesions may be seen floating in the fluid [80]. After the lesions are identified, the fluid is removed for subsequent ablation or excision. Peritoneal windows or defects are also common in adolescents and diagnostic of endometriosis.

If no obvious or suspicious lesions are identified, a posterior cul-de-sac biopsy should be done to exclude the presence of microscopic disease. A prior retrospective study by Laufer et al. evaluated adolescents younger than 22 years of age who underwent operative laparoscopy for chronic pelvic pain unresponsive to conventional therapy; of those with a visually normal pelvis, 20% were found to have pathologically proven endometriosis from a nondirected posterior cul-de-sac biopsy [2].

12.9 Surgical Treatment

During surgery, after identification of endometriotic lesions in the pelvis, the surgeon should feel comfortable with removing or destroying as much of the disease as possible. Lysis of adhesions should also be performed if present, with the goal to

restore as much of the normal anatomy as safely feasible. The gynecologist should consider surgery as one of the many tools within their "toolbox" of options for the treatment of endometriosis. Both ablation and excisional surgery have been demonstrated to be more effective than placebo at reducing pain in adult women with endometriosis [81, 82]. A retrospective cohort study by Song et al. [83] included 85 adolescents with surgically confirmed endometriosis younger than 19 years of age; pelvic pain disappeared in 41.7% of patients and improved in 38.3% of patients.

Endometriosis implants can be treated via endocoagulation, laser ablation, excision, or electrocautery [84, 85]. A combination of techniques can be utilized and tailored to the type of lesions present. In example, a surgeon may opt to use electrocautery with a monopolar L-hook electrode instrument for destroying superficial peritoneal disease, whereas he or she may excise deeper infiltrating lesions. There does not appear to be a significant difference in pain reduction between ablation and excisional treatments for stage I and II disease [86–88].

There are no data supporting the use of radical excisional surgery, or "peritoneal stripping," for superficial endometriosis. Firstly, complete excisional surgery has not been demonstrated to be curative. In a study of 17 adolescents who had complete laparoscopic excision of their endometriosis, 47% of the patients had return of pain to a level that required a subsequent laparoscopy [89, 90]. Secondly, radical excisional surgery might be overtreatment in adolescents and lead to the development of new symptoms. Laufer and Einarsson [91] published a case report on a 15-year-old young woman with ASRM-defined stage I endometriosis who underwent radical excision of the peritoneum of the anterior cul-de-sac, posterior cul-de-sac, and both pelvic sidewalls. Unfortunately, the radical excisional surgery was not curative and resulted in increased pain, extensive adhesive formation, and recurrent lesions of superficial peritoneal endometriosis. The American College of Obstetricians and Gynecologists does not recommend radical excisional surgery in adolescents due the lack of short-term and long-term outcome data about the procedure, and the potential for adhesion formation contributing to future sequelae such as bowel obstruction and infertility, and persistent pain [48].

Ovarian endometriomas are an uncommon presentation of endometriosis in adolescents that requires surgical therapy [92]. The prevalence of endometriomas in adolescents is unknown, but when present, the disease is upstaged to stage III or IV according to the ASRM classification [50]. First-line treatment of endometriomas in adolescents is cystectomy because cystectomy removes the endometriosis and leaves ovarian tissue behind versus oophorectomy. Laparoscopic cystectomy is more effective than cyst drainage or cyst wall ablation in reducing the recurrence of endometrioma or pain symptoms [93]. Attention is crucial to preserve as much of the native ovarian tissue or ovarian function.

Laparoscopy for endometriosis in adolescents should ultimately be as therapeutic as possible, with the objective of conserving as much of the normal anatomy. Unfortunately, without data-driven treatment guidelines, there is a wide variation in the use of surgical treatment for chronic pelvic pain in adolescents across the country and between types of institutions. Hung et al. [94] conducted a retrospective population-based analysis of the Nationwide Inpatient Sample in the United States

from 1998 to 2016 and found the overall inpatient intervention rate was 45% for excision/ablation, 15.7% for hysterectomy, 9.5% for diagnostic laparoscopy, and 1.2% for biopsy in adolescents and young adults with chronic pelvic pain. Alarmingly, the rates of hysterectomy increased in the late 2000s while all other interventions decreased. Conservative surgical treatment should be considered first-line for adolescent women as opposed to definitive (hysterectomy with or without oophorectomy) because it is less invasive and preserves fertility and hormone production. Adolescents should be counseled that endometriosis is an extrauterine disease, therefore removal of the uterus and/or ovaries may not be curative. The reoperation rate after hysterectomy is as high as 19% [95], and women who undergo hysterectomy for endometriosis at younger than 30 years of age are more likely than older women to have residual symptoms, report a sense of loss, and to report more disruption from pain in different aspects of their lives [96].

12.10 Postoperative Medical Therapies

Because surgery is not curative, adolescents with endometriosis should be counseled on long-term medical therapy to prevent the recurrence of symptoms and the progression of disease, which could subsequently impact fertility. Medical or hormonal therapies inhibit prostaglandin production that contributes to pain, and also results in decidualization and atrophy of ectopic endometrial tissue. Long-term follow-up data in adolescents show that surgically destroyed endometriosis and postoperative medical therapy tends to retard disease progression in adolescents and young adults. In a retrospective review of adolescents with surgically destroyed endometriosis and exacerbation of pain on conventional medical therapy, no stage change was observed in 70% of patients at their subsequent laparoscopy [97]. Furthermore, this study also reported no increase in the rates of adhesion formation from the initial surgical procedure. In the absence of postoperative medical treatment, endometriosis has been demonstrated to progress to a higher stage on subsequent laparoscopy [98]. Most adolescents who remain on medical therapy do not require a subsequent surgical procedure [80]. Patients should be counseled on continuing hormonal treatment unless they are actively trying to become pregnant.

12.11 Combined Hormonal Contraception

Combined hormonal contraception is commonly utilized prior to laparoscopy and postoperatively. Combined estrogen and progestin therapy can be used long term, is generally well tolerated, inexpensive, and provides contraceptive benefits. If a pill is chosen, a monophasic regimen should be selected in the event that the pill is used continuously and withdrawal bleeds are eliminated. Oral contraceptives with ethinyl estradiol greater than 30 μg should be used in preference since there is some evidence of impaired bone accrual with lower-dose (less than 30 μg ethinyl estradiol) preparations [99]. In addition, lower ethinyl estradiol formulations are more

likely to result in irregular, prolonged, frequent bleeding, or breakthrough bleeding or spotting, an undesirable symptom for those with endometriosis [100]. Alternatives to combined hormonal contraception include the transdermal patch or the vaginal ring; certain conditions may restrict use of the transdermal patch such as obesity with a body mass index greater than 30 kg/m^2 [101], and adolescents may not be willing or feel comfortable with inserting a vaginal ring. All methods are effective and safe when given in a cyclic, extended, or continues manner, but extended or continuous use is recommended for the treatment of endometriosis-associated pain.

12.12 Progestin-Only Therapies

Progestin-only therapies should be offered to those who decline estrogen-containing therapy or are not candidates to receive estrogen. Progestin-only methods include oral, injectable, and implants. While there are many formulations of combined estrogen-progestin contraceptive pills, norethindrone, desogestrel, and drospirenone are the main progestin-only oral contraceptive pills. Norethindrone is commonly available as 0.35 mg tablets daily (commercial names include Camila and Micronor). It is important to remember that the overall incidence of ovulation is 42.6% with norethindrone, in comparison to 1.1–4.6% with combined oral contraceptives [102]; therefore, norethindrone may not be an ideal choice for adolescents with recurrent functional cyst formation or ovulation pain. Drospirenone (commercial name Slynd) was approved for use in the United States in 2019 [103], and is dispensed as 24 tablets containing 4 mg drospirenone, followed by 4 placebo tablets. In contrast to norethindrone, drospirenone does consistently suppress ovulation [103]. Desogestrel (commercial names include Cerazette and Mircette) is dispensed as 75 mcg tablets daily and also inhibits ovulation [104]. Desogestrel is available in many countries excluding the United States. Norethindrone acetate (NA) is another progestin-only oral pill that is not FDA approved as a contraceptive but is indicated for the treatment of endometriosis and abnormal uterine bleeding [105]. NA can be used in a dosage from 5 to 15 mg per day and can be titrated to suppress menses and pain, although a dose greater than 10 mg per day might increase risk of hepatic adenoma formation [106]. This potential risk is likely in part by the small peripheral conversion of NA to ethinyl estradiol [107]. NA monotherapy has been demonstrated to be a well-tolerated and effective treatment for endometriosis-associated pain and bleeding in adolescents [108].

Depot medroxyprogesterone (DMPA) is another progestin-only contraceptive that is highly effective and well-received by the adolescent population [109]. DMPA is administered every 3 months in intramuscular or subcutaneous form. Adolescents should be appropriately counseled on bone health with long-term use of DMPA due to the potential loss of bone mineral density, which is temporary and reversible after discontinuation. Long-acting reversible contraceptive methods include the etonogestrel implant and the levonorgestrel intrauterine system (LNG-IUS), and both appear to improve pelvic pain, dysmenorrhea, and health-related quality of life in endometriosis [110]. While the etonogestrel implant is a very effective form of

contraception, unscheduled bleeding is common and the primary reason for discontinuation [111]. As far as the LNG-IUS, there is limited but consistent evidence that it can successfully treat endometriosis-associated symptoms in adults [112]. The efficacy of the LNG-IUS for adolescent endometriosis, however, does not appear to be the same as that seen in adults. Yoost et al. [113] performed a retrospective chart review of 18 adolescents with endometriosis and LNG-IUS. Contrary to results from adult studies, the majority of patients in this adolescent cohort (67%) needed additional hormonal medications after LNG-IUS placement to achieve adequate suppression of pain or bleeding. A possible explanation is that the systemic level of hormone from the LNG-IUS may not be high enough to successfully suppress endometriosis-associated pain. A progestin-only or combination pill may therefore need to be recommended in conjunction with the LNG-IUS.

Inability to tolerate a pelvic exam should not be a limiting factor for LNG-IUS insertion. The LNG-IUS should be offered at time of diagnostic/therapeutic laparoscopy to eliminate the possible pain with insertion performed in the outpatient setting. The LNG-IUS can also be offered at a sequential date under sedation or anesthesia. While never sexually active adolescents are more likely to have an unsuccessful intrauterine device insertion in the office, insertion in this population is still successful overall with an insertion rate as high as 98.7% [114].

12.13 Androgens

Exogenous androgens are an uncommon but an accepted method of treating endometriosis. Danazol is a 17-a-ethinyltestosterone derivative that produces a high androgen/low estrogen environment, inhibiting follicular development and inducing atrophy of endometriotic implants [115]. Danazol has been demonstrated to be just as effective as GnRH agonist therapy in the treatment of endometriosis-associated symptoms [116, 117]. However, its use is limited by the occurrence of androgenic side effects, including hirsutism, acne, and weight gain. Permanent side effects are also possible, such as deepening of the voice [118]. Transgender male adolescents may therefore be more inclined than cisgender female adolescents in utilizing danazol for management of their dysmenorrhea or endometriosis symptoms.

Transmasculine adolescents may utilize testosterone for gender-affirming treatment. Testosterone should not be considered a conventional therapy for endometriosis as there may be incomplete ovulatory suppression and persistent endometrial activity [119, 120]. Shim et al. [121] reported described a cohort of 35 transmasculine adolescents who were diagnosed with dysmenorrhea. Only seven (20%) were laparoscopically evaluated for endometriosis, and it was confirmed in all seven patients. Five of the adolescents with endometriosis initiated testosterone treatment, and two continued to experience endometriosis-associated symptoms while on testosterone and concomitant progestin therapies. Transmasculine persons affected by dysmenorrhea or endometriosis should be counseled that exogenous testosterone use might not completely mitigate their symptoms, and other hormonal therapies

might need to be used in conjunction with purposes including bleeding, pain, or contraception [121].

12.14 Gonadotropin-Releasing Hormone Agonists and Antagonists

If patients experience endometriosis symptoms refractory to conservative surgery and postoperative medical therapy, GnRH analogues may be advised. GnRH agonists and antagonists are both currently available for the treatment of endometriosis. Continuous GnRH by these medications downregulates the pituitary and creates a hypoestrogenic environment highly successful in suppressing endometriosis. GnRH agonists can be administered via nasal spray (nafarelin), subcutaneous or intramuscular injection (includes leuprolide), and implant (includes goserelin). The adolescent should be engaged in the decision-making process when selecting the mode of administration; the 3-month injectable agonist may be more desired as it improves patient compliance and decreases office visits. The adolescent should also be counseled on the potential "flare effect," which is when there is an initial upregulation of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) prior to downregulation. The "flare effect" temporarily increase estradiol production, causing pain and withdrawal bleeding 21–28 days after initiation of therapy [80].

Adolescents who choose to initiate GnRH agonist therapy should be advised on the long-term adverse effects on bone. As adolescence is a critical time period for bone accrual, GnRH agonist therapy should be limited to patients above the age of 16 years [57]. For this reason, all adolescents who initiate GnRH agonists should receive "add-back" therapy within the first month. Add-back therapy describes the use of sex steroids to decrease the hypoestrogenic effects of the treatment such as bone demineralization, without stimulating the growth of endometriotic tissue. The most common add-back regimens include daily use of NA (5 mg), conjugated equine estrogens (CEE) (0.625 mg) plus medroxyprogesterone acetate (5 mg), or conjugated equine estrogens plus NA (2.5 or 5 mg). Combined oral contraceptives are not an appropriate add-back regimen as they negate the hypoestrogenic effects of GnRH agonists. In a randomized controlled trial of adolescents who received 12 months of GnRH agonist therapy, the combination of NA plus CEE was more effective for increasing total body bone mineral content, areal bone mineral density, and lean mass [122]. The add-back therapy of NA with CEE was also superior to NA alone for improving physical health-related QOL in the adolescent cohort [123].

Given the potential impact on bone density, patients should be counseled on adequate dietary calcium and vitamin D intake and the benefits of weight-bearing exercise. Dual energy X-ray absorptiometry screening should be considered for adolescents concluding 12 months of GnRH agonist use, and repeating testing at least every 2 years if the patient elects to stay on the therapy beyond the recommended 12 month duration. GnRH agonist therapy should be discontinued if a significant change in the bone mineral density Z-score occurs.

Adolescents should also be thoroughly counseled on the other side effects that may occur during or after GnRH agonist treatment. Hypoestrogenic symptoms are common, such as hot flashes, vaginal dryness, and decreased libido, and may result in patient dissatisfaction or discontinuation of therapy [80]. In a survey study of adolescents with endometriosis who received leuprolide depot 11.25 intramuscular injections with add-back therapy, 24 out of 25 respondents reported side effects during treatment; 80% reported side effects lasted longer than 6 months after treatment discontinuation, and 9 out of 20 reported side effects they considered irreversible, including memory loss, insomnia, and hot flashes [124].

GnRH antagonists are also an available treatment for endometriosis, although trials have not included women less than 18 years of age. One advantage of GnRH antagonists is the absence of a "flare effect" as they initiate downregulation of pituitary gonadotropins from the beginning of administration. Elagolix is an oral short-acting competitive GnRH antagonist approved in 2018 for the management of moderate to severe endometriosis-associated pain in the United States [125]. When prescribed, adolescents should be removed that elagolix does not always suppress ovulation and is not considered a contraceptive [126]. Amenorrhea may also not be realistically achieved, as the incidence varies widely from 13.9% to 65.6% in clinical trials [127]. Further long-term data are sorely needed to assess the efficacy of elagolix and other GnRH antagonists in adolescents.

12.15 Complementary Therapies

Nonhormonal therapies can be utilized to treat endometriosis-related pain, but it is important to remind the patient that nonhormonal treatments will not retard disease progression. Complementary modalities that can be offered to the adolescent include acupuncture, exercise, electrotherapy, and yoga. In a randomized, sham-controlled trial by Wayne et al., adolescents with laparoscopically confirmed endometriosis had a significant reduction in pain after Japanese-style acupuncture therapy [128].

More studies are merited to assess the efficacy and safety of complementary interventions for endometriosis in adolescents. A meta-analysis by Mira et al. identified only eight studies assessing complementary interventions for endometriosis-associated pain, and only acupuncture has demonstrated a significant improvement in outcomes [129]. There are no proven dietary treatments for the prevention or management of dysmenorrhea or endometriosis [130].

Multidisciplinary and holistic management of endometriosis can help introduce adolescents to complementary and alternative therapies, including physical therapy and biobehavioral therapy. Non-gynecology providers may include pain specialists, mental health professionals, and physical therapists. Adolescents who may find the multidisciplinary approach helpful are those with chronic pain and experience significant disability despite aggressive medical and surgical management. In these patients, a biobehavioral approach can help emphasize the patient's

return to school, participation in social activities, and recognition of maladaptive behavior [131].

12.16 Support and Long-Term Follow-Up

As endometriosis is a chronic condition requiring long-term therapy, adolescents should be as much involved in the decision-making as possible to improve satisfaction and adherence to treatment. Their primary caregiver may be more involved with the initial treatment, but adolescents should be encouraged to ask questions and have their concerns addressed. Adolescents are very conscious of side effects and may become noncompliant with treatment, thus individualizing treatment is crucial [132]. In addition, as adolescents age and begin college or work, clinicians should assist in the transition of care and remind their patients to establish a relationship with a gynecologist familiar with the management of endometriosis.

Adolescents should be encouraged to identify family members or close friends who can support them when they are suffering from their endometriosis-associated symptoms. Exacerbations of pain may limit adolescents from activities such as hanging out with friends, leading to guilt or embarrassment. Education of family and friends may aid them in understanding the symptoms and treatment of endometriosis, and how to be supportive. In addition, adolescents with endometriosis find support from their peers very helpful. Adolescents can access peers through chat rooms, meetings, blogs, and phone conversations [132]. Monthly chat rooms and educational information for both patients and families are available at www.youngwomenshealth.org.

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