Adolescent Endometriosis: Diagnosis and Treatment Approaches

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Abstract. Objectives: To review the etiologies, diagnosis, and treatment options of adolescent endometriosis.

Methods: Review of publications relating to adolescent endometriosis.

Results: Endometriosis occurs in adolescents as young as 8 years of age; furthermore, there have been documented cases of endometriosis occurring prior to menarche. Adolescents presenting with pelvic pain are treated with cyclic combination oral contraceptive pills and nonsteroidal anti-inflammatory agents. If the pain does not respond to these therapies, then in adolescents as in adults, an operative laparoscopy is recommended for the diagnosis and surgical management of endometriosis. The operating gynecologist should be familiar with the appearance of the complete spectrum of various morphologies of endometriosis, as adolescents tend to have clear, red, white, and/or yellow-brown lesions more frequently than black or blue lesions. Subtle clear lesions of endometriosis may be better visualized by filling the pelvis with irrigation fluid so that the clear lesions can be appreciated in a three-dimensional appearance. Young women who are found to have endometriosis by laparoscopy may present with acyclic, cyclic, and constant pelvic pain. Adolescents with pelvic pain not responding to conventional medical therapy have approximately a 70% prevalence of endometriosis. It is known that endometriosis is a progressive disease and since there is no cure, adolescents with endometriosis require long-term medical management until the time in their lives when they have completed childbearing. Psychosocial support is extremely important for this population of young women with endometriosis.

Conclusions: Endometriosis occurs in adolescents, and presenting symptoms may vary from those seen in adult women with the disease. All health care providers must be aware of the existence of adolescent endometriosis. They should also be aware of the presenting symptoms so that the adolescent can be appropriately referred to a gynecologist comfortable with medical and surgical treatment options in this patient population. If laparoscopy is to be undertaken, the gynecologist must be prepared not only to diagnose but to surgically manage endometriosis. In addition, the subtle laparoscopic findings of endometriosis in adolescents must be recognized for an appropriate diagnosis. Long-term medical therapy will hopefully decrease pain and the progression of the disease, thus decreasing the risk of advanced-stage disease and infertility.

Introduction

Adolescents frequently complain of dysmenorrhea and pelvic pain. Studies have shown that 25% to 38.3% of adolescents with chronic pelvic pain have endometriosis.\textsuperscript{1,2} Traditionally, nonsteroidal anti-inflammatory drugs (NSAIDs) and oral contraceptive pills (OCPs) are the first line of treatment; however, many adolescents continue to describe pelvic pain despite these medications. For these young women, it is important to include endometriosis in the differential diagnosis. Endometriosis in adult women is commonly associated with cyclic pelvic pain; however, the symptoms in adolescents may demonstrate acyclic and cyclic pain. It is estimated that 4% to 17% of postmenarchal females have endometriosis.\textsuperscript{3} Although in the past it was assumed that endometriosis presented only after many years of menstruation, studies have described endometriosis prior to menarche,\textsuperscript{4} and 1\textsuperscript{5} and 5\textsuperscript{6} months after menarche. Numerous series have shown rates of endometriosis at 50% to 70% of adolescents undergoing laparoscopy for pelvic pain who did not have control of pelvic pain with OCPs and NSAIDs.\textsuperscript{7-9}

With education of young women, their families, pediatricians, nurse practitioners, family practitioners, gynecologists, and pediatric surgeons, we may be able to decrease the length of time from the onset of symptoms to presentation, and from the time of presenta-
tion to diagnosis. In addition, with early diagnosis of endometriosis it may be possible to decrease the long-term effects of the disease (pain, masses, and infertility), and thus improve affected young women’s quality of life.

The Origin of Endometriosis

It is important to note that some patients may have a genetic predisposition towards developing endometriosis. This is suggested by the observation that 6.9% of first-degree female relatives of patients with endometriosis are affected, as compared to 1% or less of controls. We commonly see young women in consultation who are brought in by their mothers, who have suffered with endometriosis symptoms since adolescence but were not diagnosed until later in life. Although a tendency to develop endometriosis may be inherited, the source of endometrial tissue outside the uterus is still debated.

There are many proposed theories to explain the origin of endometriosis, and no one theory accounts for all presentations of endometriosis. In a classic 1927 article, Sampson suggested that retrograde menstruation through the fallopian tubes results in seeding the all presentations of endometriosis. In a classic 1927 article, Sampson suggested that retrograde menstruation through the fallopian tubes results in seeding the pelvis with endometrial tissue. This theory is supported by the observation that endometriosis occurs most commonly in the dependent portion of the pelvis. Furthermore, obstructive anomalies of the female genital tract that enhance retrograde flow have been associated with endometriosis in the adolescent population. Schifrin and colleagues identified 6 adolescents with müllerian anomalies associated with endometriosis, the youngest being a 12-yr-old with vaginal atresia and bicornuate uterus leading to a hematocolpos. Furthermore, repair of this type of obstructive anomaly has been associated with resolution of endometriosis.

Other theories seeking to explain the origin of endometriosis have proposed that metaplastic cells transform into endometrial cells, and endometrial cells metastasize through lymphatic and vascular channels, resulting in endometriosis. This last theory helps to explain the finding of endometriosis in tissue remote from the pelvis such as the lung, brain, and skin. The most recent theories implicate an immune mechanism and suggest that a deficiency in cellular immunity allows the ectopic endometrial tissue to proliferate. Additionally, environmental exposures have been hypothesized to influence the development of endometriosis.

All these theories help explain some aspects of endometriosis. No single theory explains all cases of endometriosis, especially when relating to adolescents. One very challenging scenario is that of postpubertal/prenormarcheal endometriosis. Most likely the cause of endometriosis is multifactorial, and all proposed mechanisms may contribute to the etiology of this disease process.

Diagnosis of Endometriosis

Evaluation of Pelvic Pain

In adult women endometriosis is suspected when a patient presents with chronic pelvic pain, dysmenorrhea, dyspareunia, a pelvic mass, or infertility. In adults the pain of endometriosis is most often cyclic pain. In the adolescent endometriosis population, the presenting pelvic pain is often both acyclic and/or cyclic (see Table 1). In addition, bowel and bladder symptoms may be common in adolescents found to have endometriosis. Ovarian endometriomas are rare prior to the age range of the mid-twenties.

Initial evaluation of an adolescent with pelvic pain should include a thorough history (see Fig. 1). A pain diary documenting frequency and character of pain will help the adolescent and her caregiver to determine whether pain is cyclic, and if it is related to bowel or bladder function. Complaints of difficulty participating in normal activities, missing school, or avoiding extracurricular activities secondary to pain suggest that medical intervention is appropriate. A family history of endometriosis is correlated with a higher likelihood of endometriosis in the patient. A history of sexual abuse or physical abuse may also be associated with chronic pelvic pain but should not preclude further evaluation.

The physical exam is very important, but it may not be able to be performed for all adolescents. The goal of the physical exam should be to try to determine the etiology of the pain and to rule out an ovarian tumor or anomaly of the reproductive tract. For an adolescent who is not sexually active, a rectal-abdominal exam may be better tolerated than a vaginal-abdominal exam. A Q-tip can be inserted into the vagina to document a patent vagina without an obstructive or partially obstructive anomaly such as a transverse vaginal septum, an imperforate or microperforate hymen, or an obstructed hemi-vagina. An ultrasound should be utilized to exclude the possible existence of a pelvic mass or structural anomaly. A common finding on pelvic exam in the setting of endometriosis in-

<table>
<thead>
<tr>
<th>Presenting Symptoms</th>
<th>Percent</th>
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<tbody>
<tr>
<td>Acyclic and cyclic pain</td>
<td>62.5</td>
</tr>
<tr>
<td>Acyclic pain</td>
<td>28.1</td>
</tr>
<tr>
<td>Cyclic pain</td>
<td>9.4</td>
</tr>
<tr>
<td>Gastrointestinal pain</td>
<td>34.3</td>
</tr>
<tr>
<td>Urinary symptoms</td>
<td>12.5</td>
</tr>
<tr>
<td>Irregular menses</td>
<td>9.4</td>
</tr>
<tr>
<td>Vaginal discharge</td>
<td>6.3</td>
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</table>
Excludes cul-de-sac tenderness. If an exam is declined by the young adolescent then a “Q-tip” evaluation to document a patent lower reproductive tract and a pelvic ultrasound may be adequate.

Laboratory studies should include a pregnancy test. A CBC (complete blood count) and erythrocyte sedimentation rate will help to rule out an acute or chronic inflammatory process. Urinalysis and urine culture...
help identify a urinary tract source of pain. Sexually transmitted disease testing should be obtained when appropriate. In patients with a known diagnosis of endometriosis, CA-125 may be used to follow the progress of disease, but this assay is not a useful screening test due to its high rate of false positives.\textsuperscript{21} We prefer to rely on reporting of symptoms to follow endometriosis and do not use CA-125 in clinical management.

Ultrasound evaluation of the pelvis is the most helpful radiological study in the setting of pelvic pain. In adults endometriomas may often be identified on ultrasound; however, endometriomas are rarely seen in adolescents. Ultrasound can identify other causes of pelvic pain such as ovarian cysts, torsion, tumors, genital tract anomalies, and appendicitis. CT scan with contrast may help rule out appendicitis in cases of acute pain, but is otherwise not helpful. MRI is an excellent but expensive modality for evaluation of genital tract anomalies, and appendicitis. CT scan and decreasing menstrual flow.

In cases where disabling pain persists, laparoscopy to diagnose endometriosis is essential. Chronic pelvic pain is usually defined as 3 to 6 months of pelvic pain. When working with adolescents, it is important to realize that 3 to 6 months of debilitating pain may interfere with school and social activities. It may be necessary to proceed with a surgical laparoscopic evaluation prior to the full 3 to 6 months. Upon laparoscopic evaluation, we have found that 69% of adolescents with chronic pelvic pain not responding to a trial of NSAIDs and cyclic OCPs have endometriosis.\textsuperscript{9}

Empiric Treatment

The differential diagnosis of chronic pelvic pain is extensive.\textsuperscript{22} When the evaluation of pain suggests a nonacute gynecological source such as primary dysmenorrhea, endometriosis, or adhesions, a trial of NSAIDs is recommended. The patient should begin the medication before the expected onset of severe pain if possible. A low-dose oral contraceptive may also improve symptoms of dysmenorrhea by suppressing hormonal stimulation associated with ovulation and decreasing menstrual flow.

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Empiric depot leuprolide has been utilized in adult women with chronic pelvic pain and clinically suspected endometriosis.\textsuperscript{23,24} Although controversial, the utilization of empiric GnRH agonist therapy alleviates the need for a surgical procedure. We, however, do not routinely utilize gonadotropin-releasing hormone (GnRH) agonists for women age 16 yrs or younger due to concerns of adverse effects on final bone density formation.\textsuperscript{25} Additionally, some parents are not interested in utilizing empiric therapy due to concerns of using a medication with adverse side effects without a definitive diagnosis. We thus do not routinely recommend empiric GnRH agonist therapy for treatment of presumed endometriosis for young women under age 18, but it is an option for consenting women over age 18.

Surgical Diagnosis

Operative laparoscopy can be undertaken to make a definitive diagnosis of endometriosis. If a gynecologist is going to perform the surgical procedure, he or she must feel comfortable operating on patients in this age range and be able to perform the required surgery. A diagnostic laparoscopy with subsequent referral to a “specialist” for definitive surgery places the patient at undue risk from two anesthesias. In the adolescent population it is especially important to achieve a good cosmetic result with laparoscopy. To minimize visible scarring, the laparoscope trocar can be placed through a vertical incision directly in the umbilicus. Additional operative ports should be placed symmetrically 1 to 2 cm above the pubic symphysis so that the pubic hair will grow over the incision site(s).

The gynecologist operating on an adolescent with pelvic pain must be familiar with the appearance of endometriosis implants in this age group. Endometriotic implants have variable morphology, which has been described in the revised American Society of Reproductive Medicine (ASRM) Classification of Endometriosis (see Fig. 2).\textsuperscript{26} Only one series has objectively compared lesions in adolescents to those found in adults.\textsuperscript{27} This series suggests red flame lesions are more common in adolescents with endometriosis than in adult patients. Powder-burn lesions are less common in adolescents, which is consistent with the presumption that these lesions represent older, more advanced implants. It has been suggested that the clear and red lesions are the more painful lesions of endometriosis (see Table 2).\textsuperscript{28} Peritoneal Alan-Masters windows are also common in adolescents and should be recognized by the operating gynecologist. Care must be taken to identify subtle lesions of endometriosis that often appear as clear, shiny peritoneal vesicles. Visualization of lesions through a liquid distention medium may facilitate identification of clear vesicular lesions.\textsuperscript{29} If no evidence of endometriosis is identified, a cul-de-sac biopsy to rule out microscopic disease should be performed as endometriosis may be identified without visualization on laparoscopy. Although one study suggests a low prevalence of microscopic endometriosis,\textsuperscript{20} another report shows a significant rate of microscopic endometriosis in adults.\textsuperscript{30} Recent experience at Children’s Hospital, Boston suggests a significant amount (3%) of microscopic endometriosis in adolescents with a visually normal pelvis.\textsuperscript{9}

At the time of laparoscopy, endometriosis should be staged according to the revised ASRM Classification of Endometriosis\textsuperscript{26} in order to facilitate follow-up and comparison if future surgery is performed. Interestingly, although most adolescents present with Stage I–II disease,
in one reported series of 36 adolescents with endometriosis, 31% had stage IV disease. When counseling patients postoperatively, it is important to remember that the severity of symptoms has not been found to correlate with the extent or location of lesions (see Table 3).

Treatment of Endometriosis

Surgical Treatment
Operative laparoscopy is performed for definitive diagnosis, coagulation, ablation, or resection of endometriosis in the least invasive and most cost-effective fashion. Laparotomy is rarely indicated. Removal of lesions of endometriosis may be performed with electrocautery, endocoagulation, or laser. Surgery has been shown to reduce pain from endometriosis in rates of 38% to 100% of adult women. Regardless of the technique, care must be taken to avoid damage to the ureters, major vessels, bowel, and bladder. Lysis and resection of adhesions is also performed at the time of surgery. As noted previously, endometriomas are rare in adolescents; however, large ovarian cysts should be removed, taking care to preserve ovarian tissue. Surgery alone is not adequate treatment for endometriosis as there can be microscopic residual disease that must be suppressed with medical therapy. With surgery alone, studies have shown that symptoms will return in approximately 50% of adult women within 1 year.

Medical Treatment Options
Endometriosis is a chronic disease that has been shown to be progressive. Adolescent patients with endometriosis in the least invasive and most cost-effective fashion. Laparotomy is rarely indicated. Removal of lesions of endometriosis may be performed with electrocautery, endocoagulation, or laser. Surgery has been shown to reduce pain from endometriosis in rates of 38% to 100% of adult women. Regardless of the technique, care must be taken to avoid damage to the ureters, major vessels, bowel, and bladder. Lysis and resection of adhesions is also performed at the time of surgery. As noted previously, endometriomas are rare in adolescents; however, large ovarian cysts should be removed, taking care to preserve ovarian tissue. Surgery alone is not adequate treatment for endometriosis as there can be microscopic residual disease that must be suppressed with medical therapy. With surgery alone, studies have shown that symptoms will return in approximately 50% of adult women within 1 year.

Table 2. Type of Lesion and Pain

<table>
<thead>
<tr>
<th>Type of Lesion</th>
<th>Association with Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear</td>
<td>76%</td>
</tr>
<tr>
<td>Red</td>
<td>84%</td>
</tr>
<tr>
<td>White</td>
<td>44%</td>
</tr>
<tr>
<td>Black</td>
<td>22%</td>
</tr>
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</table>

Pain perception 1–27 mm from lesion
dometriosis confirmed by laparoscopy should receive medical treatment of their disease. The goal of medical therapy is to treat pain from postoperative residual disease and suppress progression. The choice of treatment depends on the severity of the patient’s symptoms, the extent of disease, and compliance. The patient and the health care provider can follow success or failure of medical therapy. Adolescents should be asked to rate their pain on a scale of 0 to 10 at the time of each visit. Medical therapy should be utilized to decrease pain and permit the adolescent to function. The patient should be aware that she may not be pain free but her medications should be adjusted to maximize pain relief and promote school and social function and participation.

Although numerous options have been described for the treatment of endometriosis, at the Children’s Hospitals in Boston and Pittsburgh, continuous oral contraceptives or gonadotropin-releasing hormone agonists are usually first-line therapy. We offer either therapy to women over age 16, and only continuous oral contraceptives to women less than 16 yrs for concern of the effects of the GnRH agonist on the formation of normal bones and bone density.

Nonsteroidal Anti-inflammatory Agents. As noted earlier in this report, NSAIDs are appropriate empiric treatment for dysmenorrhea. NSAIDs are also helpful adjuvant agents for the treatment of pelvic pain associated with endometriosis.

Hormonal Suppression. Clearly, not all patients with endometriosis find relief from symptoms with NSAIDs alone. Suppression of menses, ovulation, and endometriosis generally achieves superior pain control. By hormonally decreasing stimulus to endometriotic tissue, regression of disease and improved pain control may be achieved. There are differing modalities for suppression of menses, ovulation, and endometriosis, each with differing risks, benefits, and side-effect profiles.

Combination Estrogen and Progestin Therapy. Oral contraceptives, contraceptive patch, and the vaginal ring all contain both estrogen and progestin. Continuous low-dose combination estrogen/progestin therapy diminishes pain from endometriosis by creating a hormonal “pseudopregnancy” state in which endometrial implants are relatively inactive. Gynecologists and pediatricians have extensive experience with OCP administration in adolescents. OCPs are generally well tolerated and may be safely used for at least 10 years without an associated increase in mortality. There is a lack of data on the long-term utilization of continuous hormonal therapy, although this has been a widely utilized treatment modality. There has been a recent small study showing benefits of long-term hormonal therapy. In a similar fashion to the continuous pills, the contraceptive patch (OrthoEvra) or the vaginal ring (NuvaRing) can be used in a continuous fashion without breaks to attempt to suppress menses, pain, and endometriosis.

Danazol. Danazol is a 17-α-ethinylestradiol derivative that creates an acyclic environment, and multiple studies show its efficacy in treating endometriosis to be equivalent to a variety of GnRH agonists. Danazol has significant androgenic side effects secondary to affecting sex-hormone-binding-globulin levels, resulting in an increase of free testosterone. For example, in a series by Buttram of 220 patients, complaints included weight gain, depression, muscle cramps, decreased breast size, flushing, oily skin and hair, acne, hirsutism, irreversible deepening of the voice, and skin rash. In this particular series 7% of patients discontinued the drug secondary to intolerable side effects. Compared with patients using danazol, patients using GnRH agonists reported a better quality of life. Given the side effects, this medication would likely be poorly tolerated by adolescents and is not widely utilized in management of endometriosis.

Progestins. Progestational agents include norethindrone acetate (15 mg daily by mouth), medroxyprogesterone acetate (30–50 mg daily by mouth), and depot medroxyprogesterone acetate (150 mg intramuscularly every 1 to 3 months), each of which will improve symptoms in approximately 80% to 100% of patients with endometriosis. At therapeutic doses, progestins may be associated with side effects such as weight gain, bloating, depression, and irregular bleeding. However, many patients tolerate this therapy very well. Oral progestin therapy should be considered prior to long-term intramuscular injections so that side effects can be identified and addressed or the medication discontinued. The long-term utilization of depot medroxyprogesterone acetate has been shown to result in loss of bone density in some patients, and therefore monitoring of serum estradiol and/or bone density is advised. In at-risk patients, low-dose estrogen therapy can be used. The cardiovascular effects of long-term therapy remain unknown and warrant investigation.

Gonadotropin-Releasing Hormone Agonists. GnRH agonists may also be prescribed for adolescents who are over age 16. We generally prescribe depot leuprolide acetate 11.25 mg intramuscularly every 3 months. Side effects include: hot flushes, headaches, difficulty
sleeping, mood swings, depression, and vaginal dryness. With this dose more than 90% of patients will become amenorrheic and hypoestrogenic. We do not routinely utilize GnRH agonists for individuals younger than 16 due to concerns of adverse affects on permanent bone density. Upon completion of this therapy the patient begins continuous OCPs. Nafarelin (nasal spray), one puff twice daily intranasally, is an alternative GnRH agonist; however, compliance is often unpredictable in the adolescent population. The utilization of add-back therapy can help to alleviate the side effects of GnRH agonists. Add-back therapy is based on the “estrogen threshold hypothesis” and the concept is demonstrated in Figure 3.

(OCP, patch, or ring) then prolonged utilization of GnRH agonist with add-back therapy can be initiated. We have had patients with surgically diagnosed disease refractory to other medication on this prolonged GnRH agonist with add-back for over 10 years. Prior to the initiation of “retreatment” with a GnRH agonist or if therapy is to be prolonged greater than 9 months, a baseline bone density evaluation should be obtained, then repeated 6 months later and, if stable, repeated every 2 years. As noted above, the long-term utilization of GnRH agonist with add-back therapy has not been studied in the adolescent population.

If pain does not respond to aggressive medical therapy, it may be resulting from recurrent endometriosis and/or pelvic adhesions from endometriosis or prior surgery. A repeat laparoscopic procedure should be considered in this clinical situation. If surgery is to be undertaken, then lysis of adhesions should be performed laparoscopically. All visible lesions of endometriosis should be cauterized, lasered, or resected. We utilize adhesion preventive agents laparoscopically following surgical lysis of adhesions.

### Issues for Future Consideration

Early diagnosis of endometriosis and treatment will hopefully suppress progression and advancement of disease. This is an area that needs future investigation. Additionally, there are some areas that are particularly challenging. For instance, how should we treat the adolescent daughter of a woman who had no pelvic pain but who had Stage IV endometriosis and infertility? Should she have an evaluation and treatment even though she has no pelvic pain, in an attempt to avert the silent development of Stage IV endometriosis and future infertility? These areas should be addressed in future investigations.

### Conclusions

Evaluation of pelvic pain in adolescents begins with a history and physical exam, pain calendar, laboratory evaluation, and possible ultrasound. Empiric treatment of chronic pelvic pain and dysmenorrhea in adolescents may include nonsteroidal anti-inflammatory agents and hormonal therapy. A definitive diagnosis of endometriosis can only be made by laparoscopy. Forty-five to seventy percent of adolescents with chronic pelvic pain have endometriosis diagnosed at the time of laparoscopy. A gynecologist familiar with the appearance of endometriosis in adolescents should perform the surgical laparoscopic procedure. In adolescents, the laparoscopic appearance of endometriosis may be subtle, with red flame lesions and clear, shiny peritoneal vesicles. Surgical management involves diagnosis of endometriosis and ablation of lesions. Medical management of endometriosis in adolescents is achieved with hormonal suppression using continuous hormonal therapy, gonadotropin-releasing hormone agonists, or other medications. A multidisciplinary approach to pelvic pain with the assistance of pain treatment services and complementary and alternative therapies are also helpful for some adolescents.

### References


![Fig. 3. Estrogen threshold hypothesis.](image)


