Management of Endometriosis in Teenagers

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6.1 Introduction

Endometriosis in adolescents needs unique considerations for treatment approaches, as it presents particular challenges in terms of diagnosis, variable presentation and symptoms, and choice of treatment [1]. Dysmenorrhea is the most common gynecologic issue among adolescents, occurring in 50–80% of these and causing limitation in sports and activities, poor academic performance, and long duration of resting (Fig. 6.1). In about 10% of adolescents with severe dysmenorrhea symptoms, pelvic abnormalities such as endometriosis or uterine anomalies may be found and the incidence of endometriosis has been reported between 45% and 70% in adolescents with chronic pelvic pain (CPP) [2].

About the correlation between endometriosis and chronic pelvic pain, evidence supports an increased awareness among adolescents and their health care providers about the need for early clinical diagnosis of endometriosis and timely treatment of severe dysmenorrhea/pelvic pain, usually with medical therapy as first line and surgery as second line if the pain is not responsive to medical therapy and complication such as torsion or breakage risk of endometrioma occur [1, 3].

The targets for analgesic treatment fall into the usual categories of prevention or limiting the disease: peripherally acting and centrally acting medications, psychological approaches, and non-invasive procedures such as focused ultrasound. For chronic pain, the target is to reset the brain state using one or a combination of approaches (Fig. 6.2). Once the disease is diagnosed and treated, these patients have favorable outcomes with hormonal and non-hormonal therapy [4]; however, for those who do undergo surgery, about 30% of women still report ongoing pelvic pain after surgery despite taking medications. For these reasons in endometriosis,

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A. R. Genazzani et al. (eds.), *Endometriosis Pathogenesis, Clinical Impact and Management*, ISGE Series, https://doi.org/10.1007/978-3-030-57866-4_6

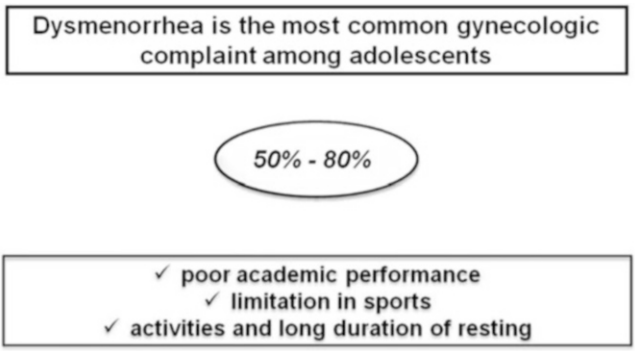

Fig. 6.1 The impact of dysmenorrhea in teenagers

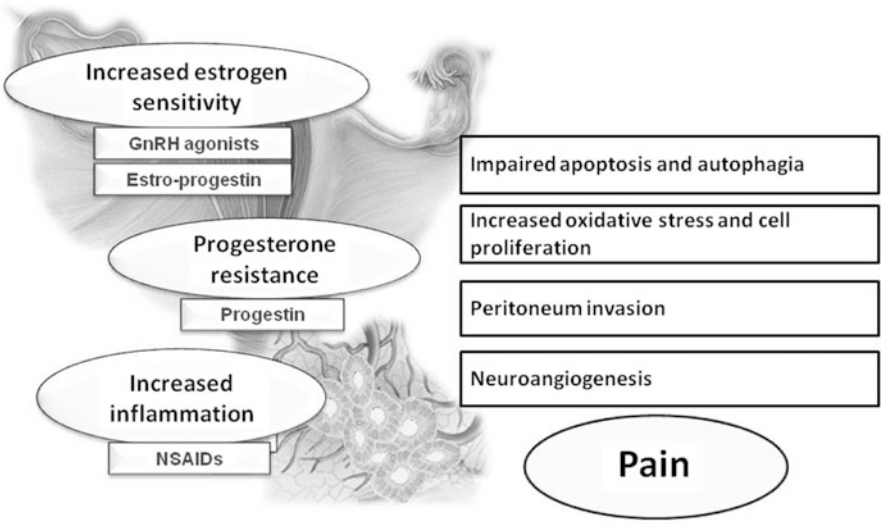

Fig. 6.2 The pathogenesis of endometriosis and its treatment options

multidimensional and personalized pain treatment has been difficult to achieve. There is a great need for a specific conceptual model for adolescents with endometriosis, in consideration that the younger the woman at onset of symptoms, the longer the duration until diagnosis is made [1].

6.1.1 Treatment Approaches

The World Endometriosis Society consensus states that early diagnosis and treatment—both medical and surgical modalities—have the potential of improving quality of life, alleviating symptoms, preventing the development of more severe

disease later in life and minimizing the likelihood that future fertility may become compromised [5].

Although surgery is effective in treating endometriosis in adults, few studies have been conducted on adolescents and surgery should be carefully considered in these patients. Apart from the increased risk of premature ovarian failure caused by surgical treatment of ovarian endometriomas [6], recent animal and epidemiological studies indicate that surgery, in and by itself, may encourage the development of endometriosis [7]. In fact, a history of surgery for endometriosis is correlated with the presence and severity of deep infiltrating endometriosis, underlining the necessity of a thorough preoperative assessment and the need for providing comprehensive information to these patients before undertaking further surgery [8]. This is why medical treatments take special importance in treating adolescents. In principle, the same drugs can be used in adolescent and adult patients. The critical issue, however, is the progressive and dynamic nature of endometriosis, shown both in spontaneous and induced disease [9]. Once diagnosis is posed, no delay in treatment together with a combined medical–surgical approach, represent the key points to slow its progression. At any rate, an attempt with a medical regimen should be the first choice [10].

6.1.2 Medical Treatment

As there is a high prevalence of dysmenorrhea in adolescents, it is reasonable to empirically treat these patients with NSAIDs and/or COCPs, unless the patient has no contraindications to these therapies. The provider may choose to initiate at first COCPs cyclically. The duration of this initial treatment should generally be three menstrual cycles with close symptom follow-up to conclude if the patient has an appropriate response to therapy [11]. The use of a pain diary to assess possible changes in the pain is a good approach for this concern [12].

If this initial approach does not demonstrate adequate symptom improvement, then a change to continuous dosing of COCPs may be considered with the goal to induce amenorrhea and further diagnostic testing or examinations may also be considered. Indeed, it is important to remember that symptomatic improvement does not necessarily rule out endometriosis, so these patients must be counseled appropriately. Should the patient fail initial empiric therapy, it is important to maintain a high suspicion for a diagnosis of endometriosis.

It may be reasonable at this time to proceed with diagnostic laparoscopy and excision of endometriosis (if present), as 35–73% of these adolescents do have endometriosis at the time of surgery [11].

However, the provider should counsel the patient and her family on the role of attempting additional hormonal medical therapy with either progestin-only therapy or gonadotropin-releasing hormone (GnRH) agonists. These treatment modalities are options in patients who are not ideal candidates for surgical intervention or feel strongly about avoiding surgery altogether [11].

Because there is no surgical cure for endometriosis, all adolescents with endometriosis should be managed with long-term medical therapy to prevent the recurrence

of symptoms and/or disease progression. An upstaging of disease at the time of second laparoscopy can occur if the patient was noncompliant with menstrual suppressive therapy [10].

Combination estrogen/progestin or progestin-only therapy serves to create a progestin-dominant environment, leading to decidualization and subsequent atrophy of intrauterine and extrauterine endometrial tissue [13].

There are no data suggesting that one pill formulation is better than another for the treatment of dysmenorrhea or endometriosis-associated pain. Thus, if one pill induces amenorrhea and pain persists, a different class of therapy should be considered. Alternatives for combined hormonal contraception include the vaginal ring or transdermal patch. All of these methods are safe and effective if given in a cyclic, extended, or continuous manner, but when treating endometriosis-associated pain, extended continuous use with menstrual suppression is recommended [13]. Progestin-only methods include the "mini-pill" (norethindrone only) or norethindrone acetate. It should be noted that there is a small peripheral conversion of norethindrone acetate to ethinyl estradiol, as opposed to norethindrone, which does not demonstrate conversion. Norethindrone acetate has been shown to be an effective treatment for endometriosis and tolerated by most adolescents [14]. Medroxyprogesterone acetate can also be used, and it is administered every 3 months in intramuscular or subcutaneous form. Progestin-only therapy has side effects that may not be well tolerated, such as irregular bleeding, acne, weight gain, and emotional lability. Providers should consider oral progestins prior to injectable therapy, to address side effects or to quickly discontinue the regimen. Depot medroxyprogesterone acetate (DMPA), in particular, can result in loss of bone density in some patients [4]. Alternative therapies include the etonogestrel implant and the levonorgestrel intrauterine system (LNG-IUS). A small trial of 41 women demonstrated that the implant was not inferior for treating endometriosis-related pain in comparison to DMPA, but no other studies have been conducted among adolescents. There is limited but consistent evidence that LNG-IUS reduces dysmenorrhea in adults and adolescents. The systemic level of hormone from the LNG-IUS may not be high enough to successfully suppress endometriosis-associated pain. Therefore, it is suggested the LNG-IUS with an oral progestin or estrogen/progestin pill and not the LNG-IUS alone. When counseling on the LNG-IUS, its placement could be done at the time of laparoscopy, to eliminate the possible insertional pain in the outpatient setting [15].

More recently, one compound that seems to have yielded good results without appreciable untoward effects in women aged between 18 and 52 years of age is dienogest [16]. The conventional dose is at present 2 mg daily. Eber et al. [17] evaluated the use of Dienogest in adolescents aged 12–18 years with clinically suspected endometriosis. After 52 weeks of treatment, endometriosis-associated pain improved, along with a decrease in lumbar bone mineral density, which partially recovered after 6 months of treatment discontinuation.

Methyltestosterone and danazol are both exogenous androgens, and they treat endometriosis by inhibiting follicular development and inducing atrophy of endometriotic implants.

Danazol, a 17-a-ethinyltestosterone derivative, has been demonstrated to be just as effective as GnRH agonist in treating endometriosis, but with worse quality-of-life scores reported. Side effects are dose-dependent and typically considered intolerable, such as acne, hirsutism, and weight gain, and maybe permanent, such as deepening of the voice. Transgender male patients with endometriosis may find these side effects desirable, and it can be used danazol for the treatment of endometriosis in transmale clients [1].

If a patient has a suboptimal response to combined hormonal or progestin-only therapies, the provider may consider GnRH agonists such as nafarelin or leuprolide. Continuous GnRH stimulation downregulates the pituitary and creates a hypoestrogenic environment that is highly successful in suppressing endometriosis. GnRH agonists come in many forms, including nasal spray, subcutaneous or intramuscular injection, and implant. The 3-month injectable agonist can improve patient compliance and decrease office visits. The 3-month formulation also provides ample time to trial the therapy beyond the "flare effect," which is when there is initial production of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) prior to downregulation. The "flare" results in a surge of estradiol and causes pain and withdrawal bleeding 21–28 days postinjection. Importantly, it is recommended to limit GnRH agonist therapy to above the age of 16 years because of the potential long-term adverse effects on bone, during a critical period in adolescence for accrual of bone density [13]. For this reason, "add-back therapy" is suggested for all adolescents receiving GnRH agonists, beginning within the first month. Sex steroid add-back therapy aims to decrease the hypoestrogenic effects without stimulating endometriosis. Add-back regimens include norethindrone acetate daily, or conjugated estrogens plus medroxyprogesterone acetate or norethindrone acetate daily. Combination norethindrone acetate (5 mg/day) plus conjugated equine estrogen (0.625 mg/day) add-back seems to be superior to norethindrone acetate alone for increasing bone density and quality of life [18]. Combined oral contraceptives are not appropriate to use as add-back therapy, as they negate the effects of the GnRH agonist. For surveillance, we recommend obtaining dual-energy X-ray absorptiometry at the conclusion of 9–12 months of GnRH agonist use, and repeating bone density testing at least every 2 years if the patient remains on therapy. We recommend discontinuation of GnRH agonist therapy if a decrease in bone density occurs despite add-back therapy.

6.1.3 New Pharmacological Options

New medications under active investigation include GnRH antagonists, selective estrogen receptor modulators (SERMs), selective progesterone receptor modulators (SPRMs), progesterone antagonists, aromatase inhibitors, statins, angiogenic inhibitors, and botanicals.

GnRH antagonists may also be considered as an alternative. These agents are a newer class of drugs, available in oral or injection form. They are effective immediately without an LH surge or "flare." The oral antagonist Elagolix is approved for

moderate to severe endometriosis-related pain; however, it has not been studied in trials including teenagers [19]. Elagolix is administered as a 150-mg tablet once daily or 200 mg twice a day. Elagolix is not approved as a contraceptive because it does not always suppress ovulation. Furthermore, the incidence of amenorrhea varies widely, from 13.9% to 65.6% in clinical trials; reductions in dysmenorrhea, nonmenstrual pelvic pain, and dyspareunia are observed with this drug [19, 20].

SERMs represent another treatment option through ERa activity suppression, which is essential for endometriosis progression. SPRMs such as asoprisnil, with mixed agonist–antagonist properties suppressing ovulation and endometrial bleeding with antiproliferative effects on the endometrium, have been shown to be effective in inducing amenorrhea and decreasing pain [20]. While aromatase inhibitors block the key enzyme in the extra-ovarian biosynthesis of estrogens, very high dosages to overcome the expression of aromatase are needed, suggesting that they could be more effective as adjuvants to suppress the increase of endogenous gonadotropins with the use of the GnRH agonist. Small studies show pain reduction with recurrence after treatment termination [20]. Botanicals with a possible role in the treatment of endometriosis include the Chinese multiherb Yiweining, which decreases cytokine levels and expression of COX2 and Curcuma, which decreases cytokines and angiogenic factors. Botanicals under investigation include Chinese angelica, red sage root, corydalis, cinnamon, myrrh, peach kernel, frankincense, red peony, persica, prunella vulgaris, and white peony [21].

While current therapies include hormonal agents, new treatments may focus on the inflammatory response in the diseases. The effects on nerves from endometriosis involve physical “entrapment” and chemical “irritation.” Both activate immune responses. The immune response to tissue damage and its role in pain has been extensively documented. In endometriosis, not only can there be a response to tissue damage, but the immune response can be altered and indeed dysfunctional, creating a state of hypersensitivity to pro-inflammatory stimuli or molecules [22]. As such, the condition can respond to treatments that target specific immune processes [23]. Consequently, this condition can respond to treatments that target specific immune processes [23]. These treatments involved non-specific immune modulators such as ketamine up to more targeted pharmacotherapies and the current development of novel targets [1]. There is a clear disappointment over the slow progress in the development of new therapeutic agents, and few new drugs have been approved for the treatment of endometriosis in the past decade. At the same time, several experimental drugs have undergone preliminary evaluations and appear to show promising results. One option is to use dopamine receptor agonists (DRAs), compounds capable of activating signaling pathways that lead to changes in gene transcription. In a small clinical study, the administration of quinagolide DRA in patients with hyperprolactinemia led to the reduction of peritoneal endometriotic lesions in two-thirds of cases and the elimination in the other third [24]. Histologically, degeneration was supported by downregulation of the vascular endothelial growth factor (VEGF) and its receptor-2 (VEGFR2), three proangiogenic cytokines, and the plasminogen inhibitor-activator (PAR-1). DRAs reduced inflammation, interfered with angiogenesis, and improved fibrinolysis. Indeed, numerous

compounds are capable of exerting anti-angiogenic effects on endometriotic lesions in vitro and in vivo, including progestogens, GnRH agonists, and danazol, although convincing clinical evidence for their efficacy has not been reported [1]. Since the endometrium also undergoes cyclic physiological angiogenesis, it is not clear how angiogenesis can be targeted without causing unwanted collateral damage. Another possible option is the inhibition of histone deacetylase through the administration of valproic acid [25], a pre-prescribed drug approved for the treatment of epilepsy and bipolar disorders. Numerous preclinical studies indicate that this compound is promising and two clinical studies have shown that valproic acid is effective in the treatment of symptomatic and drug-resistant adenomyosis [1]. For both DRAs and valproic acid, large clinical trials have never been conducted. Since these are old drugs and their patents have expired, any large-scale clinical trials are unlikely to be conducted.

6.1.4 Surgical Treatment

In a mini-review of dysmenorrhoea in adolescence, Harel [26] state: "If dysmenorrhea does not improve within 6 months of treatment with non-steroidal anti-inflammatory drugs (NSAID) and oral contraceptive pill, a laparoscopy is indicated to look for endometriosis."

In fact, 25–45% of adolescent patients who underwent laparoscopy for chronic pelvic pain had endometriosis and laparoscopy when performed, should not only be for diagnosis but should also include a therapeutic surgical treatment [27].

Pathologic findings in patients with endometriosis visible on laparoscopy are manifold, including the classic endometrial glands and stroma, chronic inflammation, fibroconnective tissue, reactive mesothelial cells, hemosiderin deposition, endosalpingiosis, and adhesions. The natural progression of the disease leads to fibrosis [1].

The endometriosis revised scoring system of the American Society for Reproductive Medicine (rASRM) applied in an adolescent patient can vary widely. In general, no correlation between the stage of disease and the amount of pain experienced was found. Earlier studies tend to demonstrate a higher prevalence of minimal (rASRM stage I) or mild (rASRM stage II) disease. More recently, however, several authors have reported severe (rASRM Stage III or IV) endometriosis in adolescents. Endometrioma has been found in 16–32.7% of adolescents undergoing surgery for endometriosis [28]. In the Dun et al. [2] series, of 25 adolescents with surgically diagnosed endometriosis, most had Stage I (68%) endometriosis, followed by Stages II (20%) and III (12%). None of the adolescents had Stage IV endometriosis. Matalliotakis et al. [29] reported that 22/55 (45.4%) of the adolescents with endometriosis in their cohort had Stage I disease, 20/55 (36.4%) had Stage II disease, 8/55 (14.5%) had Stage III disease, and 2/55 (3.7%) had Stage IV disease. In the Audebert et al. [30] series, 33 (60%) of the cases were classified as Stages I–II, 22 (40%) as Stages III–IV, and 6 (10.9%) were classified as deep infiltrating endometriosis (DIE). Smorgick et al. [28] observed a prevalence of advanced stage (moderate to

severe) endometriosis of 23% in women aged ≤22 years at the time of surgery. Overall, the literature on the prevalence of advanced disease varies widely, from 8.1% to 88.9%.

In view of its proven benefits in the adult population, such as less postoperative analgesia and a shorter hospital stay, laparoscopy should be the standard operating technique used in the assessment and treatment of endometriosis in the adolescent patient. Patient positioning during laparoscopy is similar to that used in adults. The adolescent patient must be placed in a dorsal lithotomy position, using the Allen stirrups if the patient is tall enough, with the arms folded to the sides and the thumb oriented superiorly [31]. For shorter patients, a frog leg position can be assumed. In many instances, uterine manipulation can be used, after a cervical dilatation, if necessary. A Foley catheter should be placed to maintain bladder decompression during surgery.

The abdominal entry technique remains at the discretion of the surgeon, although the recommended entry point remains at the midpoint of the umbilicus [31]. It is important to keep in mind that many adolescent patients are smaller and thinner than adults, with a shorter distance between the umbilicus and the underlying great vessels. The pneumoperitoneum should be based on a maximum filling pressure and not on the volume of gas. Adolescents can generally tolerate pressures of 10–15 mmHg [31].

The first surgical treatment is most important, with excision and destruction of all visible endometriosis and lysis of adhesions; all deep infiltrating lesions more than 5 mm have to be excised [32]. Implants can be destroyed via electrocautery, endocoagulation, laser ablation, or excision. Large studies have not been performed in adolescents; however, studies in adults have demonstrated that surgical treatment can provide significant pain relief. In stage I or II endometriosis, there is no difference in pain relief with ablation or excision during laparoscopy [33].

Destruction/ablation for superficial peritoneal disease and excision for deeper lesions that grow through the peritoneum can be performed. There is no data to support the use of radical excisional surgery (also called peritoneal stripping) for superficial endometriosis, and since it may increase extensive adhesive formation, it should not be used in the adolescent population [34]. Rectal "shaving" versus excision and endometrioma aspiration versus cystectomy are associated with an increased recurrence rate [32].

6.1.5 Outcome of Surgery

Data on pain improvement or cure rates are limited in adolescent patients with no published comparative trials. However, most adolescents do not require more than one laparoscopy in their lifetime as long as they are compliant with medical menstrual suppressive therapy.

It is not possible to predict in which patient the disease will progress. The main risk factor for recurrence is incomplete destruction or excision, whether it is

laparoscopic destruction or excision in stage 1–2 endometriosis [33] or full excision in stage endometriosis 3–4.

Surgery alone is not a definitive and adequate treatment; the recurrence rate is 5% in 1 year, 5–14% in 2 years, and 20–50% in 5 years [35].

In a small study of 20 adolescents, Yeung et al. [36] suggested that, in the hands of a skilled laparoscopist, complete excision of all areas of abnormal peritoneum with typical and atypical endometriosis may be sufficient to eradicate the disease. A statistically significant decrease in dysmenorrhea, constipation, dyschezia, pelvic examination tenderness, intestinal cramping, exercise pain, and bladder pain were reported. The authors investigated long-term outcomes up to 66 months (on the average 23.1 months) of patients who were not specifically advised to take postoperative hormonal suppression. Although the rate of repeat surgery was 47.1%, the rate of recurrent endometriosis at surgery was zero [36].

Rimbach et al. [37] agreed with this surgical strategy but claimed that the possibility of achieving this goal is limited by the difficulty of detecting all foci and the risks associated with radical surgical strategies. A small retrospective series of adolescents undergoing laparoscopic excision of endometriosis showed that 73% of adolescents had no pain or significantly improved after surgery, and 9% had partial improvement with a median follow-up of 65 weeks.

In the study by Dun et al. [2], the mean age at the time of surgery was 17.2 (±2.4) years (range, 10–21), and patients were followed up for 1 year. At 1 year, 64% reported resolved pain, 16% improved pain, 12% continued pain, and 8% recurrent pain. The authors stated that once the disease is diagnosed and treated by a skilled gynecologist, these patients have favorable outcomes with hormonal and non-hormonal follow-up treatment.

A cohort of 20 adolescent patients in New Zealand who underwent laparoscopic excision of endometriosis demonstrated a statistically significant improvement in dysmenorrhea, pelvic pain, and quality of life as assessed by the EuroQol Group's EQ-5D questionnaire after a mean follow-up time of 2.6 years [38].

In the Audebert et al. [30] study of 55 cases, symptom recurrence or persistence after excision or ablation of endometriosis was identified in 74% of adolescent patients with a mean follow-up of 97.5 months. This is similar to the rate reported in the retrospective cohort study by Tandoi et al. [39], which noted a 56% rate of symptom recurrence at 5 years of follow-up of patients 21 years or younger who underwent excision of endometriosis. Moreover, a case series by Yang et al. [40] confirms the recurrence of symptoms after the excision of endometriosis, noting a recurrence rate of 55.6% with an average time to recurrence of 33.4 months, although these patients were also treated with postoperative medical therapy.

In comparison, Shakiba et al. [41] investigated the rate of reoperation as a surrogate marker for endometriosis recurrence after both laparoscopic excision of endometriosis and hysterectomy with or without bilateral salpingo-oophorectomy for endometriosis-associated pain in adults. In the subgroup of patients who had laparoscopic excision of endometriosis, the authors found that the percentage of patients who were surgery-free at 2, 5, and 7 years was 79.4, 53.3, and 44.6%, respectively, which tends to mirror that seen in the adolescent population.

Among patients treated for deep infiltrating endometriosis, a trend was observed for higher rates of recurrence that required repeat laparoscopy. Data on the impact of endometriosis on subsequent fertility in adolescents are overall reassuring with a limited effect on the fertility rate. Indeed 72.2% of adolescent patients desiring pregnancy achieved a successful live birth, with 69.2% of these pregnancies occurring in patients with minimal or mild disease [30]. Fertility rates strongly correlated with the stage of endometriosis and were 75%, 55%, 25%, and 0% for stages I, II, III, and IV, respectively [11].

Despite these results, there is no evidence that surgical intervention for endometriosis in the adolescent prevents disease progression or long-term consequences such as adult infertility.

6.1.6 Alternative/Complementary Treatments

There is little evidence of the effectiveness of non-pharmacological approaches to the treatment of endometrial pain [42] and empirically-based, non-pharmacological interventions for the treatment of endometriosis and CPP are rare. It is, however, well known in the literature that CPP is very distressing for women, associated with disability and other mental health conditions, and often involves inconclusive and unsatisfactory medical investigations [3].

Existing psychologically based pain treatment interventions, such as Cognitive-Behavioral Therapy (CBT) or Acceptance and Commitment Therapy (ACT), could be revised to meet the specific needs of women with endometriosis and/or CPP.

CBT has been established as a valid and effective treatment for chronic pain conditions, but CBT studies investigating specific interventions for endometriosis and/or CPP in women are lacking. A range of behavioral and medical treatments addressing CPP in women was conducted and psychological therapies are shown to be effective for CPP; however, in practice, treatment recommendations generally come from single studies, and more research is needed. Nevertheless, CBT interventions have proven to be effective in reducing pain, improving sexual function, managing discomfort, and reducing disability for a wide range of gynecological conditions that are associated with CPP [3].

Endometriosis can adversely affect women and their partners' general psychological well-being, adaptation to relationships, and overall quality of life. Significantly more sexual dysfunctions compared to healthy women were reported in women with endometriosis [3].

Research on psychosexual interventions in the treatment of endometriosis is limited but appears to be effective in reducing endometriosis-related pain and improving associated psychosexual outcomes. In particular, the goal would be to achieve an individualized, couple-centered approach to care, integrating psychosexual and medical management for endometriosis.

Alternative treatments can be helpful for treating chronic pain and merit further research. A recent systematic review identified eight studies on complementary treatments, and the authors concluded that acupuncture has been the only therapy

till now to demonstrate improvement in symptomatic endometriosis [43]. A Japanese style acupuncture was identified to be a safe, effective, and well-tolerated adjunct therapy for adolescent endometriosis through a randomized, controlled trial. A multidisciplinary approach to endometriosis, with integrative medicine and non-gynecology providers such as pain specialists, mental health professionals, and physical therapists, is a proposed model of care to improve long-term clinical outcomes and to encourage research.

6.2 Conclusions

Endometriosis in adolescents is a challenging clinical problem as it may present with a number of clinical and pathological differences versus adult women. Nevertheless, given the chronicity of the disease, the challenge is to avoid a delay in diagnosis, understand the disease and direct effective therapies at an early age. Given that endometriosis and accompanying CPP is a multi-faceted and complex problem, there is a need for a new approach from a diagnosis and treatment perspective. While endometriosis can be treated by surgical excision of the lesions and/or hormonal treatment, sometimes combined with anti-inflammatory drugs, medical treatments are not curative and approximately 30% of women who undergo surgery report ongoing pain after surgical excision of the lesions. Overall, combined medical–surgical therapy aimed at menstrual cessation results in better long-term symptom improvement, tailored according to the severity of patient symptoms, extent of disease, and compliance.

However, it should be noted that pharmacological treatments, while not curative, can be helpful following surgery and may be an effective strategy to limit the recurrence of the disease. By understanding the neural underpinnings of the disease and risk factors for chronification, research could provide a basis for evaluating novel treatments and potentially lay the foundation for successful personalized, precision medicine to shorten diagnostic delay and maximize successful pain remediation. Further research is also warranted regarding long-term sequelae such as infertility in women diagnosed with endometriosis as adolescents.

In conclusion, the goals are represented by: improvement of diagnosis, careful surgical treatment, increase in medical treatment, follow-up, and improvement of scientific data.

Conflict of Interest None.

Financial Support None.

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