Chapter 10
Management of Endometriosis

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Treatment of endometriosis is broadly classified into pharmacological and surgical methods. Because the etiology of the disease is not well established, none of the currently available treatments can prevent or cure endometriosis. Rather, treatment is aimed mainly at providing symptom relief or improving fertility rates [1]. Therefore, one should consider how treatment options affect pain levels and infertility when investigating whether endometriosis treatment improves quality of life.

Medical therapy is usually started as an empirical treatment, mainly proposed as a temporary aid for pain management [2]. The effect of pharmacological treatment on fertility is minimal. The surgical approach aims to address both pain and fertility. Surgical treatment is the treatment of choice for ovarian endometriomas, mostly due to the ineffectiveness of pharmacological therapy in these cases. Nevertheless, ovarian surgery reduces the ovarian reserve and its long-term implications are not yet well-known [3, 4].

10.1 Pharmacological Treatment

Several pharmacological agents including oral contraceptives, danazol, GnRH agonists, progestogens, anti-progestogens, non-steroidal anti-inflammatory agents and aromatase inhibitors have been used to treat endometriosis [5]. In many cases, chronic pelvic pain, a major endometriosis symptom, is the reason for the initiation of empirical treatment even before endometriosis is diagnosed [2]. The following section will summarize the pharmacological treatments for endometriosis.
10.1.1 **Hormonal Therapies**

10.1.1.1 **Oral Contraceptives**

Combined estrogen-progestogen contraceptive pills are commonly used to control endometriosis-related pelvic pain and dysmenorrhea [6]. These agents were initially used to maintain a “pseudo pregnancy regimen” to relieve symptoms [5]. Cyclical use of oral contraceptives is the only treatment for endometriosis that permits regular uterine bleeding [7]. However, because dysmenorrhea is a major symptom of endometriosis, the regular use of oral contraceptives has a limited advantage. Continuous use is more effective at addressing pelvic pain [8, 9].

Harada et al. [10] conducted a multi-center, placebo-controlled, double-blind randomized trial to assess the use of oral contraceptives in the treatment of dysmenorrhea. Pain was measured using verbal rating scales (VRS) and visual analogue scales (VAS). Ultrasonic examination was used to diagnose endometriomas. The authors noted that dysmenorrhea significantly improved in the oral contraceptive group. The volume of endometrial tissue and the average diameter of the endometriomas decreased significantly more so in the oral contraceptive group than in the placebo group. Nevertheless, side effects of oral contraceptives, mainly irregular uterine bleeding and nausea, were significantly increased in the oral contraceptive group. Although oral contraceptives have long been used to treat endometriosis related pain, their effectiveness is debatable [5].

10.1.1.2 **Progestogens**

Progestogens help alleviate pain either by inducing decidualization and atrophy of endometrial tissue [4] or suppressing matrix metalloproteinases—enzymes that play a central role in the development and implantation of ectopic endometrium [11]. Several progestogens have been evaluated in the treatment of endometriosis such as medroxyprogesterone acetate [12], norethisterone [13], and newer progestins such as dienogest [14]. Progesterones can be taken orally or via a levonorgestrel-releasing intrauterine device—both are effective at providing pain relief [15, 16]. Oral progesterones are highly effective at treating symptomatic endometriosis and relatively inexpensive, but they can cause significant side effects, which negatively impact quality of life [15].

Petta et al. [17] investigated the effect of a levonorgestrel-loaded intrauterine device (IUD) on chronic pelvic pain and uterine bleeding. Six months after the insertion of the IUD, most patients reported a significant decrease in chronic pelvic pain, and 70% of the patients reported no bleeding. Lockhat et al. [15] reported promising results concerning pain symptoms and disease staging after intrauterine-administered levonorgestrel use. At 3 and 6 months after the IUD insertion, a significant decrease in pain scores was noted. Moreover, the proportion of patients with moderate or severe dysmenorrhea decreased from 96% of patients pre-treatment to 68% at 3 months post-insertion (p=0.001) and to 50% at 6 months post-insertion (p<0.001). The mean number of days per month during which patients experienced pain decreased from 15±6.9 to 10.7±8.7 days after the 6-month therapy (p<0.05) [15].
10.1.1.3 GnRH Agonists

GnRH agonists bind to pituitary receptors and have a longer half-life than native GnRH. GnRH agonists induce down-regulation of the pituitary-ovarian axis and as a result, lead to hypoestrogenism [4]. Hypoestrogenism, in turn, induces amenorrhea and endometrial atrophy [11]. On the other hand, GnRH agonists induce menopausal symptoms such as hot flushes, vaginal dryness, decreased libido, mood swings, headache, and bone mineral depletion [18, 19]. GnRH agonists can be delivered via a daily nasal spray or with daily or monthly subcutaneous injections [7].

Petta et al. [17] investigated 37 endometriosis patients treated with a GnRH agonist for 6 months. The pain score decreased significantly after the first month of GnRH analogue treatment with further reduction in those who completed the 6-month therapy. It is also worth noting that GnRH analogue treatment reduced bleeding more than the IUD-administered progestin treatment.

10.1.1.4 Danazol

Androgens are steroid hormones that promote male secondary sexual characteristics [20]. Danazol is one androgen that is commonly used for endometriosis treatment. It is a derivative of 17α-ethinyltestosterone, which inhibits steroidogenesis and the LH surge, thereby increasing free testosterone levels [11]. Due to the increase in androgen levels, hirsutism, acne, and deepening of the voice are potential side effects [20]. When comparing danazol and high-dose medroxyprogesterone acetate in the treatment of endometriosis, Telimaa et al. [21] reported that a slight increase in resolution of peritoneal implants in patients receiving danazol compared to patients receiving medroxyprogesterone acetate. Compared to placebo, both danazol and medroxyprogesterone acetate significantly improved pelvic pain.

Rotondi et al. [22] compared a group of endometriosis patients who underwent danazol therapy for 24 weeks with a group of patients who underwent GnRH analogue therapy for the same period. The authors reported comparable results between the groups regarding endometriosis growth and symptoms during treatment. However, symptoms recurred after treatment in both groups, although symptom severity was lower than at admission. Danazol had androgenic side effects such as weight gain, acne, and edema.

10.1.1.5 Aromatase Inhibitors

Aromatase is an enzyme that converts steroidal precursors into estrogens. The estrogens cause ectopic tissue to grow, leading to the onset of pelvic pain [23]. The inhibition of aromatase reduces estrogen levels [24]. Only a small number of studies have assessed the use of aromatase inhibitors as a treatment for endometriosis [25]. The main concern in using these agents is osteopenia and osteoporosis, which can result in bone fractures [26]. The blockage of estrogen production in premenopausal women increases FSH levels, which may lead to ovarian follicular cysts [27]. Therefore, in
Premenopausal women, both an “add-back therapy” and oral contraceptive use are advised with aromatase inhibitors. This combination therapy significantly decreases abdominal and pelvic pain and diminishes endometriotic lesions at second-look surgery [27, 28].

10.1.2 Analgesics

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to be effective in the treatment of primary dysmenorrhea [29, 30]. These agents have been investigated extensively and are widely used for pain relief; they have an added desired anti-inflammatory effect in endometriosis [31]. Despite being the most commonly used medications for pelvic pain, their efficacy in treating endometriosis-associated pain is not conclusive [32].

10.1.3 Melatonin

As discussed in previous chapters, anti-oxidants can be used in the treatment of endometriosis to prevent disease progression. Melatonin, a broad spectrum antioxidant secreted from the pineal gland, is a scavenger of free radicals [33]. Animal studies have already shown that it significantly reduces the size of endometrial lesions [34, 35]. In a recent randomized, double-blind, placebo-controlled trial, Schwertner et al. [36] reported a significant decrease in endometriosis-related pelvic pain and an improvement in sleep quality.

10.2 Surgical Treatment of Endometriosis

The aims of surgical treatment are to remove endometriomas, relieve pain and improve fertility rates via adhesiolysis [37]. Laparoscopy is the preferred surgical approach for the treatment of endometriomas [38]. Laparoscopy is associated with shorter hospitalizations, more rapid recovery, less use of analgetic agents [39], decreased costs [40], and less damage to a patient’s ovarian reserve when an ovarian procedure is carried out subsequently [38].

10.2.1 Ovarian Endometriomata Surgical Management

Several surgical techniques are available to manage ovarian endometriomas including aspiration, ablation, and ovarian cystectomy. A combination of these procedures may be used as well.
Endometrioma removal (either by excision or ablation) was more effective than non-invasive techniques at reducing pain [41]. When comparing excisional cytoreductive surgery with ablative surgery, Hart et al. found that excision was more advantageous than ablation in the management of ovarian endometrioma particularly, in regards to endometrioma relapse and pain relief [42]. Other studies showed similar results in terms of pain relief after surgical intervention [43]. The previous consensus on endometriosis management recommended laparoscopic excision over laparoscopic ablation [37, 41]. The biggest concern about ovarian cystectomy for endometriosis patients is a reduced ovarian reserve [44]. The effect of different surgical approaches on fertility will be discussed later in this chapter.

10.2.2 Ovarian Endometriomata Aspiration

A surgical approach is typically applied prior to IVF/ICSI cycles. With this technique, a trans-vaginal ultrasound guided ovarian cyst aspiration is performed on an outpatient basis [45]. Aspiration is considered a relatively safe procedure [46].

The main potential advantage of aspiration is that it leaves the pseudocapsule of the cyst intact, thereby preserving follicles in the ovarian tissue. Moreover, compared to laparoscopy, this procedure is less invasive. Nonetheless, recurrence of ovarian endometriomas is invariably higher because the ectopic endometriotic tissue is not resected [47]. To address this problem, a sclerosing agent can be used during aspiration [46, 48].

10.2.3 Deep Endometriosis Surgical Treatment

Deep endometriosis refers to endometriotic lesions that penetrate the retroperitoneal space by at least 5 mm leading to severe symptoms. Several treatments have been used in patients with deep disease to relieve those symptoms. Of them, the surgical approach is still debatable. A careful partial resection of the lesions may result in unsatisfactory symptom management and a complete resection is associated with larger potential for complications involving the urinary, reproductive and gastrointestinal systems [37]. The practice of using a surgical laparoscopic approach in cases of endometriosis is well established. Nevertheless, the ideal management of deep infiltrating endometriosis is still unknown [49].

10.3 Treating Endometriosis to Improve ART Outcomes

10.3.1 Introduction

Infertility and subfertility are commonly associated with endometriosis [50]. Many mechanisms have been proposed to explain the association between endometriosis and infertility in women such as inflammation, decreased ovarian reserve, difficulty
of oocyte retrieval in severe endometriosis, poor egg quality, and decreased implantation rates [50]. Although medical and surgical treatment options can reduce symptom severity, their effect on infertility is limited [51–53]. A negative correlation between decreased pregnancy rates and increased severity of endometriosis has been reported as well [50]. Thus, these factors may be overcome by the use of assisted reproductive techniques [53, 54].

A study by Gupta et al. reported that patients with ovarian endometriomas had a decreased response to ovarian stimulation during IVF treatment cycles [55]. In a systematic review and meta-analysis that looked at the effect of surgical treatment on IVF outcomes in patients with endometriomas, Tsoumpou et al. [56] concluded that surgical management of endometriomas does not significantly increase IVF pregnancy rates or the ovarian response to ovarian stimulation compared with no treatment. The authors advised using a practical approach to manage endometriomas prior to IVF cycles, suggesting that treatment be based on endometrioma size; patients with small endometriomas (less than 3 cm) do not require any preliminary measures and can start IVF cycle. In cases of larger (3–5 cm) endometriomas, a GnRH agonist treatment for 3 months prior to the IVF cycle is advised. For endometriomas larger than 5 cm, laparoscopic ovarian cystectomy is recommended [56].

10.3.2 Endometrioma Aspiration

Pabuccu et al. [47] investigated whether aspiration of ovarian endometriomas prior to controlled ovarian hyper-stimulation (COH) would improve the outcome of intracytoplasmic sperm injection (ICSI). They reported that the duration of COH was longest in the non-aspirated group. Nevertheless, the clinical pregnancy rates and implantation rates were similar among the four factions of patients: those who had aspiration at the beginning of COH, those who did not have aspiration, those with a history of ovarian surgery but no current endometriomas, and those with tubal factor infertility. Essentially, aspiration of the ovarian endometriomas did not improve the number of follicles or diminish the dosage of gonadotropins needed or the number of mature oocytes. It also did not increase the rate of implantation. Most importantly, since all groups had comparable clinical pregnancy and implantation rates, the authors concluded that aspiration and previous resection of endometriomas (1–6 cm in diameter) is not of value prior to IVF cycles [47].

Suzuki et al. [57] evaluated the outcome of IVF in patients diagnosed with endometriosis in the presence of an ovarian endometrioma. They compared three groups of patients (50 women in each). The first group consisted of patients who underwent aspiration and examination of the aspirated fluid to verify the presence of endometriosis. The second group was composed of patients who did not have endometriomas but had endometriosis diagnosed laparoscopically. The last group was composed of women with tubal factor infertility. The results revealed that ovarian endometrioma did not affect the quality of embryos or lower pregnancy rates but it did negatively impact the quantity of viable oocytes. Additionally, the number of mature
oocytes retrieved in the first group of patients who had one affected and one normal ovary were comparable, thus demonstrating that endometriosis did not impact oocyte development [57].

Aspiration of ovarian endometrioma during oocyte retrieval may also be considered. However, this procedure may place the patient at a higher risk for ovarian or pelvic infection [58, 59]. Also, if chocolate cyst fluid comes into contact with the oocytes, it may contaminate them. These are potential theoretical complications, however, that have not been supported by a definitive RCT as large-scale RCTs that examine women affected by ovarian endometriosis do not exist. Essentially, this type of RCT would be extremely difficult to conduct as endometrioma-affected women only represent a minority of patients who seek IVF.

### 10.3.3 Endometrioma Ablation

Endometrioma ablation is another surgical option. During an ablation procedure, the internal cyst wall is destroyed with bipolar coagulation or a CO2 laser following drainage. This is one of the most frequently used techniques. This procedure has favorable results in terms of IVF outcomes and is also advocated because it is thought to cause less anatomic damage and disruption than cystectomy [60].

Donnez et al. [61] investigated the effect of laparoscopic ablation of ovarian endometrioma on the ovarian response to stimulation. Specifically, they vaporized the internal cyst wall using a CO2 laser. The study group consisted of 85 patients who failed to become pregnant for 1 year following the ablation, at which point IVF was performed. A control group of 289 patients with tubal factor infertility who also underwent IVF was included. The clinical pregnancy rate was similar between the two groups. The two groups were statistically comparable across a number of important variables, including number of ampoules used for stimulation, the number of follicles aspirated, the number of follicles >15 mm in diameter, the number of mature oocytes aspirated, E2 peak levels, fertilization rate, number of embryos/cycle, number of transferred embryos/cycle, implantation rates, and ongoing pregnancy rates.

### 10.3.4 Ovarian Cystectomy

Besides ablation, cystectomy is another surgical approach for endometrioma management. The effectiveness of cystectomy as a surgical technique is still controversial. Although cystectomy is known to have the lowest recurrence rates, it is also reported to have a negative impact on ovarian reserve and ovarian responsiveness to hormonal stimulation. The emergent pattern from the literature is that while cystectomy may reduce ovarian response, this deficiency is compensated for through increased ovarian stimulation [62], which results in overall cumulative pregnancy rates that are similar to those of other techniques [63].
Performing laparoscopic cystectomy prior to an IVF cycle did not improve the number of oocytes retrieved, the number of mature oocytes, fertilization rate, and clinical pregnancy rate [64]. Although laparoscopic cystectomy did not damage ovarian reserve or function, it also did not help patients achieve pregnancy in a significant way. Because cystectomy of ovarian endometriomas prior to IVF does not improve pregnancy rates, there is no incentive for the patient to undergo this procedure [64].

In one study, drainage was cited as being more advantageous than ablation of ovarian cysts in regards to dysmenorrhea, dyspareunia, chronic pelvic pain, recurrence of the ovarian endometriomas, and ability to achieve spontaneous pregnancy [42]. However, this analysis did not include women who underwent IVF after surgery.

Previously [65], Canis et al. performed a retrospective study to assess ovarian response during IVF cycles after laparoscopic cystectomy. All of the ovarian endometriomas were >3 cm. Of note, the pregnancy rates during the first cycle of IVF for Group A (endometrioma >3 cm), Group B (no endometrioma), and Group C (tubal infertility) were 35.9 %, 31.2 %, and 30.5 %, respectively. When comparing the three groups, the number of oocytes and embryos attained were similar, demonstrating that laparoscopic cystectomy is a beneficial method to treat ovarian endometriomas. Nevertheless, reduced ovarian reserve following ovarian cystectomy was shown in other studies [66]. Kahyaoglu et al. compared two groups of patients: 22 women who underwent laparoscopic cystectomy and cauterization before IVF and 22 women with tubal factor infertility who proceeded directly to IVF. Fewer follicles and oocytes were retrieved in the cystectomy endometrioma-operated group. The clinical pregnancy rate in the endometrioma group exceeded that of the tubal factor group by 9 %, with rates of 45 % and 36 %, respectively. When comparing the operated and contralateral normal ovary, the normal ovary produced more mature follicles for retrieval than the affected one [66].

While it is evident that cystectomy does in fact have a negative effect on ovarian function [67], a new technique that combines cystectomy by stripping with ablation through a CO2 laser may have favorable results in preserving ovarian reserve [68]. Although this is a laparoscopic modification of traditional cystectomy, it is effective and has immense potential for future development. With this integrative approach, 80–90 % of the cyst is excised and the remaining 10–20 % of the endometrioma wall is vaporized. The ablated portion is proximal to the ovarian hilum and thus, vaporization is the preferred technique for this location as it contains the vasculature most prone to damage in the ovary [68].

In order to increase IVF success rates, women with ovarian endometrioma may first undergo treatment to minimize the presence of the disease. Although laparoscopic surgery has long been considered the first-line treatment for minimal and mild (stage I and II) endometriosis [62], a new approach claims that surgery may not be beneficial in terms of pregnancy rates and disease management if the ovarian endometriomas are <3 cm in diameter [69]. Nevertheless, it is noteworthy that for patients who do not require IVF and want to procreate naturally, surgery may be their best option as Donnez et al., 2004 reported a postoperative pregnancy rate of 50 % [63].

While the surgical technique that yields the best results for IVF is still being debated, a careful review of recent studies shows that laparoscopic removal of ovarian endometriomas that are less than <3 cm in diameter does not increase pregnancy
rates naturally or with IVF and may in fact cause irreparable damage to the affected ovary. Surgery should be considered only when the cysts are large and painful, when medical therapy fails or once malignancy cannot be excluded [70].

10.4 Recent Advances in Management of Endometriosis

10.4.1 Introduction

More recent research has focused on conservative management of endometriosis rather than surgical approaches [71]. Numerous studies have suggested that ovulation plays a crucial role in the pathogenesis of endometriosis and medical management that inhibits ovulation alleviates the symptoms of endometriosis and decreases the rate of recurrence [2].

Endometriosis is a chronic and long-term disease; repeated therapy is needed to treat the symptoms and to limit its recurrence. However, the side effects of long-term therapy also should be considered. The primary aim of medical management is to stop the growth of the endometriotic lesions and to control symptoms, hence improving the patient’s quality of life. Hereby, some of the advances in the management options will be briefly viewed by groups.

10.4.2 Hormonal Agents

10.4.2.1 Selective Estrogen Receptor Modulators

Because endometriosis is an estrogen-dependent disease, selective estrogen receptor modulators (SERM) may be beneficial as a treatment. Bazedoxifene is a SERM that effectually antagonizes estrogen-induced uterine endometrial stimulation without disrupting the necessary estrogenic effects in bone or the central nervous system [72]. These advantages make it an excellent treatment. Indeed, one animal study showed that it decreased the size of endometriotic implants and levels of endometrial proliferation markers [72].

10.4.2.2 Selective Progesterone Receptor Modulators

Because endometriotic lesions contain progesterone receptors [73], treatment with selective progesterone receptor modulators (SPRM) has been suggested to deactivate the ectopic endometrium lesions. Animal studies showed that SPRMs reduced endometrial thickness; adding progesterone to the treatment regimen prevented undesirable transformation of the endometrium, and most of the glands remained tubular [74]. Indeed, Chwalisz et al. [75] reviewed two randomized, placebo-controlled studies that reported a significant reduction in pain symptoms and a dose-dependent correlation to bleeding complaints.


10.4.3 Non Hormonal Agents

10.4.3.1 Anti Inflammatory Agents: TNF-Alpha Inhibitors

Inflammation is known to be a major part of endometriosis genesis and development [76]. Anti-inflammatory agents may be beneficial in reducing endometriosis symptoms and disease progression even without suppressing ovulation as other agents do. Animal studies showed that anti-TNF alpha agents reduced endometrial lesions size [77, 78] and number [79] and endometriosis-induced infertility [80]. Lu et al. [81] recommended studying anti-TNF alpha to assess whether it offers a suitable management option for women with endometriosis.

10.4.3.2 Statins

These commonly used agents inhibit cholesterol production, lowering levels of cholesterol- a well-established ischemic heart disease risk factor. By yet poorly understood mechanisms, statins are known to inhibit proliferation in several biologic systems [82]. Animal studies showed that high-dose statin treatment significantly regressed endometriotic implants [83, 84]. Statins were also shown to exhibit anti-inflammatory [85] and anti-oxidative [83] activities, which are desirable in the treatment of endometriosis.

10.4.3.3 Apoptotic Agents: Metformin

Metformin is a commonly used oral hypoglycemic agent from the biguanide family that is used to treat type II diabetic patients. In addition to being an insulin sensitizer, metformin modulates the inflammatory response and inhibits sex steroid production [85]. Animal studies showed that it significantly reduced the size and volume of endometriotic lesions [86, 87].

10.4.3.4 Anti-angiogenic Agents: Dopamine Agonist

Because the endometrium requires a large blood supply, it is assumed that angiogenesis is essential for endometrial lesion development [88]. Hence, researchers hypothesized that inhibiting angiogenesis would be beneficial in the treatment of endometriosis. Indeed, animal studies showed decreased activity and proliferation of endometriotic lesions after dopamine agonist treatment [88]. Moreover, dopamine agonist treatment was more effective than GnRH agonist therapy in promoting lesion regression [89].
10.4.3.5 Antioxidants: Epigallocatechin-3-Gallate

Epigallocatechin-3-gallate is a major component of green tea. It has a high antioxidant capacity and has been recognized as an effective treatment for different tumors [90]. Because it inhibits cell proliferation, promotes apoptosis and has antioxidative effects, researchers have studied it as a possible treatment for endometriosis. Animal studies showed that it significantly suppressed angiogenesis in endometrial tissue without affecting blood vessel development in ovarian follicles [91] and reduced the size and activity of the endometrial implants [92]. The authors concluded that Epigallocatechin-3-gallate has the potential to be an effective treatment by inhibiting the formation of new endometriotic lesions [91].

10.4.3.6 Intraperitoneal Treatment with Local Anesthetics

Lignocaine is a commonly used local anesthetic agent that has anti-inflammatory and anti-arrhythmic properties. The peritoneal cavity of women with endometriosis is subjected to a local inflammatory reaction [93]. The peritoneal endometriotic lesions in women with endometriosis also have larger numbers of nerve fibers than normal peritoneum [94]. The inflammatory substances released by macrophages in the peritoneal cavity of women with endometriosis stimulate these nerve endings and cause significant pain, which contributes to the dysmenorrhea reported by these women. A double-blind, randomized controlled trial conducted in Sweden reported that perturbation (flushing) of the uterine cavity and fallopian tubes with lignocaine significantly reduced pain symptoms and can be used as a non-hormonal treatment option for women with dysmenorrhea caused by endometriosis [95, 96].

10.4.4 Surgical Techniques Robotic Surgery

As mentioned above, laparoscopy removes endometrial implants and scar tissue, reduces pain and aids fertility. Laparoscopy is considered the gold standard for treating mild and moderate stages of endometriosis [49]. Advanced endometriosis involves neighboring organ systems, which can greatly complicate a surgical procedure.

Robotic-assisted laparoscopic techniques have been shown to be useful in the treatment of extensive endometriosis and may prove useful in the treatment of urinary tract endometriosis [97]. Robotic surgery is a relatively safe technique, especially in high risk groups such as obese women [98].
10.5 New Frontiers in Management of Endometriosis

10.5.1 Endometriosis Diagnosis

At present, the gold standard for endometriosis diagnosis is histologic inspection of an endometrial lesion obtained via laparoscopy. However, a surgical diagnosis is hazardous. Either a late diagnosis of the disease is achieved, resulting in potentially preventable complications due to the progressive nature of the disease, or an empirical symptom-based treatment is initiated, possibly targeting the wrong disease. For that reason, a better diagnostic tool is necessary [99].

In a systematic review, May et al. [100] identified more than 100 biomarkers in the literature. Unfortunately, no single biomarker or combination of biomarkers has clearly been proven to be accurate [100]. Further investigation is still required.

10.5.2 Endometriosis Treatment

10.5.2.1 Stem Cells

Stem cells have the ability to self-renew by undergoing innumerable cell divisions. They also have the potential to differentiate into specialized cell types. The mucosa of the human endometrium has a basal and functional layer. The basal layer is permanent and provides cells for regeneration each month. The functional layer is shed every month during the menstrual cycle. Human endometrium contains epithelial and mesenchymal stem/progenitor cells, which play a vital role in the regeneration of endometrial tissue during the menstrual cycle, after parturition and after surgical resection. Endometriotic lesions in women with endometriosis have a clonal origin and are initiated by retrograde movement of the shedded endometrial stem/progenitor cells [101]. The origin of ovarian endometrioma from stem cells rather than from ovarian surface epithelium [102] further enhances the role of stem cells in the pathogenesis of endometriosis. Targeting these endometrial stem/progenitor cells may prevent the development of endometriotic lesions in women with endometriosis.

10.5.2.2 Gene Therapy of Endometriosis

Gene therapy is defined as the transfer of genetic material (DNA or RNA) into target cells in order to cure or relieve disease symptoms [103]. The genetic material can be delivered using a viral vector or with a non-viral technique [103]. The lack of a real cure for endometriosis makes gene therapy a potential treatment or preventive option.

Animal models of gene therapy with angiogenesis inhibitors were found to be very effective in the treatment of endometriosis [104]. Other studies reported promising results and advances in gene therapy [105, 106]. Further studies are required before gene therapy can be applied in a clinical setting.
10.6 Key Points and Summary

Although endometriosis has been recognized and treated for many years, no treatment can cure the disease. Not knowing the etiology of the disease plays a major role in our inability to cure it. Therefore, treatment today mainly focuses on relieving pain and improving fertility.

Current research is focusing on treating different suggested etiologies such as oxidative stress. New horizons such as gene therapy and stem cell therapy are being developed in order to find a cure.

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