Endometriosis is an estrogen-dependent disorder defined as the presence of endometrial tissue outside of the uterine cavity. A leading cause of infertility, endometriosis has a prevalence of 0.5–5% in fertile and 25–40% in infertile women. The optimal choice of management for endometriosis-associated infertility remains obscure. Removal or suppression of endometrial deposits by medical or surgical means constitutes the basis of endometriosis management. Current evidence indicates that suppressive medical treatment of endometriosis does not benefit fertility and should not be used for this indication alone. Surgery is probably efficacious for all stages of the disease. Controlled ovarian hyperstimulation with intrauterine insemination is recommended in early-stage and surgically corrected endometriosis when pelvic anatomy is normal. In advanced cases, in vitro fertilization is a treatment of choice, and its success may be augmented with prolonged gonadotropin-releasing hormone analog treatment. Further randomized clinical trials focusing on diverse etiopathogenic mechanisms and therapeutic innovation are necessary to find more conclusive, evidence-based answers regarding this enigmatic disease.

Key words: endometriosis; infertility; epidemiology; evidence-based treatments

Introduction

Infertility is a distressing and frustrating symptom associated with endometriosis, and the optimal choice of management in the context of this disease remains obscure. Endometriosis, defined as the presence of endometrial tissue outside the uterine cavity, is in itself an enigmatic and multifaceted pathology, a puzzle whose manifold pieces remain largely disconnected despite some decades of investigation. Although infertility and endometriosis are clearly connected, uncertainty persists over the causal relation between the two.

It is somewhat easy to understand how moderate–severe endometriosis is associated with infertility, as it is a destructive disorder that results in considerable pain and anatomical distortion of pelvic organs.1,2 Yet it is less clear how mild–minimal endometriosis might impair fertility without pelvic distortion,3–5 although a number of theories exist.6–8 To what extent can the treatment of the clinical manifestations of endometriosis improve fertility? What course of treatment is most suitable for a subfertile woman presenting with endometriosis? Answers to these questions will define the primary scope of this review, but first we provide a brief overview of the epidemiology of this perplexing disease and its relationship to infertility.

Epidemiology

Prevalence

The true prevalence of endometriosis remains obscure. Variations in patient populations, methods and criteria of diagnosis, and an overall lack of well-designed epidemiologic studies have made it difficult to arrive at confident figures for this disease. Estimates of prevalence range up to 10% among the general population,9 and large-scale studies suggest a prevalence of 0.5–5% in fertile and 25–40% in infertile women.10 Other studies quote figures of 5–50% among the infertile population,11 and it has been reported that infertile women are 6–8 times more likely than fertile women to have the disease.12 A review by D’Hooghe et al. concluded that the prevalence of endometriosis is significantly higher in infertile than fertile women, and that infertile women are more likely to have advanced stages of the disease.13
Risk Factors

A growing body of evidence suggests that age, genetic factors, menstrual parameters, anthropometric measures, body habitus, lifestyle factors, environmental exposures, and a number of other characteristics may play roles in the etiopathicgenetic mechanisms of endometriosis.

Endometriosis can be identified in women from premenarche to postmenopause, and diagnoses have been made in women ranging from 12 to 80 years of age. Regardless, endometriosis is foremost a disease of reproductive-age women, which may be explained by the estrogenic milieu strongly implicated in its pathogenesis, and it carries an average age of diagnosis of 28 years. A positive correlation between age and risk of the disease has been noted, particularly at ages above 30 and peaking in the early-to-mid 40s.

A genetic predisposition to endometriosis has been supported by the high concordance of the disease among identical twins. A familial predisposition with no clear Mendelian inheritance, but rather with multifactorial polygenic traits, has been identified in severe endometriosis, and a number of genetic polymorphisms have been investigated. Although Chatman et al. reported that there is no known racial or socioeconomic bias for the disease, it has been suggested that Asian women are at higher risk than other races, with Black women at lower risk. However, this latter finding was attributed to a frequent misdiagnosis of Black women as having pelvic inflammatory disease rather than endometriosis.

Menstrual and reproductive factors associated with increased risk of endometriosis include early menarche (≤11 years of age), short menstrual cycles (≤27 days), heavy and long-lasting bleeding, reduced parity, and reduced lifetime duration of lactation. Cramer and Missmer proposed a possible endometriosis phenotype of early menarche, short cycles, painful periods, subfertility, and tall stature.

Taller and thinner women appear to have endometriosis more frequently, consistent with higher follicular-phase estradiol levels in taller women. Body weight, body mass index, and waist-to-hip ratio have been inversely correlated with endometriosis, although Missmer et al. did not find a relation with waist-to-hip ratio. Interestingly, women with naturally red hair may have an increased risk of endometriosis, possibly associated with altered coagulation and immune functions. Missmer et al. found no association with red hair, although they concluded that this may depend on infertility status.

Lifestyle factors, such as smoking, exercise, and consumption of alcohol and caffeine, have been related to altered risk of endometriosis. Smoking has been found to create a hypoestrogenic state inversely related with endometriosis, but others have found no association. Increased caffeine and alcohol consumption has been associated with increased risk, whereas regular exercise reduces the risk of endometriosis.

Although Signorello et al. did not find any relationship to alcohol or smoking, they confirmed that exercising more than 4 h per week decreases the risk of endometriosis.

Exposure to polychlorinated biphenyl (PCB) and dioxin has been associated with endometriosis in studies with rhesus monkeys, possibly through effects on the immune system. In humans, studies of toxin exposure as measured by serum levels have been contradictory. Positive associations of PCB congeners, heavy metals, chlorinated pesticides, and dioxin with endometriosis have been reported, although other studies found no association with organic pollutants, or found only a nonsignificant doubling of risk with dioxin.

In utero exposures may also determine a woman’s risk of having endometriosis. Greater birth weight and breast-feeding were found to decrease endometriosis risk, while diethylstilbestrol exposure and multiple pregnancies increased it.

Despite the fact that little is definitely known regarding the epidemiology of endometriosis, risk factors for the disease appear to be related to increased exposure to menstruation and body estrogen levels. Further epidemiologic research is required to establish new insights with respect to the etiopathogenesis of this puzzling disorder.

Endometriosis and Infertility

Although endometriosis is generally accepted to be related to infertility, its actual impact on fecundity and the mechanisms underlying this effect are less clear. Unfortunately, well-designed scientific studies are lacking on this issue. Fecundity, defined as the probability of a woman achieving a live birth in a given month, ranges from 0.15 to 0.20 in normal couples and 0.02 to 0.10 in untreated women with endometriosis. Significantly lower 3-year cumulative conception rates in women with endometriosis compared with controls (36% vs. 54%), and reduced conception rates in women with endometriosis who had donor inseminations to control for male and coital factors have consistently shown a relation between decreased fertility and endometriosis. A variety of animal and human studies, including those involving assisted reproductive technology (ART), have also suggested lower pregnancy rates in cases of endometriosis. A meta-analysis by Barnhart et al.
reported an endometriosis pregnancy rate that is half that for tubal factor infertility.40

Experience from IVF has indicated poor pregnancy outcomes in endometriosis patients are associated with poor sperm function, poor ovarian reserve, reduced oocyte retrieval, lower oocyte and embryo quality, impaired implantation with decreased endometrial receptivity, and luteinized unruptured follicles, particularly in advanced-stage disease.41–43 However, contradictory studies exist.44–46 ART outcomes in patients with endometriosis are also contradictory, with some reporting decreased numbers of preovulatory follicles, reduced embryo transfers, decreased fertility rates, and increased miscarriages,47 whereas others suggest similar results with control cases.48 Additionally, adverse pregnancy outcomes, such as pregnancy loss, preterm delivery, preeclampsia, and intrauterine growth restriction, have been demonstrated to occur more frequently in subjects with endometriosis.49

**Evidence-based Management in Endometriosis-associated Infertility**

Primary aims of endometriosis treatment are the removal or reduction of ectopic endometrial implants, restoration of normal anatomy, hindrance of disease progression, and alleviation of symptoms. A broad spectrum of therapeutic options, including expectant management, medical and surgical interventions alone or in combination, and ART, have been used to address the clinical sequelae of endometriosis.2,50,51 However, the efficacy of these options with regard to achieving conception success in endometriosis-associated infertility is considerably variable and remains inadequately explored, as reviewed below.

**Expectant Management**

In spite of a significantly impaired pregnancy rate in comparison with the general population, patients with early-stage endometriosis without severe pelvic adhesions are able to conceive spontaneously. A prospective multicenter cohort study assessing 168 patients with endometriosis undergoing expectant management found that the monthly fecundity rate of 2.52 per 100 person-months did not differ significantly from the fecundity of 263 women with unexplained infertility.52 Other studies have found monthly fecundity rates ranging between 0.14 and 0.43.53–55 Hull et al. reported a cumulative pregnancy rate of 55% in 56 cases of minimal–mild endometriosis after an expectant management of 18 months.56 However, cases of advanced-stage endometriosis complicated with extremely disrupted pelvic anatomy have been reported to have pregnancy rates near 0%; this disparity in fecundity between stages of endometriosis may confound the interpretation of various therapeutic modalities.

**Medical Treatment of Endometriosis-associated Infertility**

Medical treatment of endometriosis typically involves hormonal manipulation of the menstrual cycle to create an amenorrheic state, thus producing an environment unfavorable to endometrial tissue. Danazol, progesterational drugs, gestrinone, oral contraceptives, and gonadotropin-releasing hormone (GnRH) agonists (GnRHa) are conventionally used medical agents. In addition, experimental medications, such as selective estrogen receptor modulators, selective progesterone receptor modulators, aromatase inhibitors, GnRH antagonists, pentoxifylline, tumor necrosis factor-α inhibitors, angiogenesis inhibitors, and matrix metalloproteinase inhibitors, hold the potential for greater efficacy and flexibility with fewer side effects. Evidence to date indicates that medical therapy is not of benefit for endometriosis-associated infertility. A comprehensive 2007 Cochrane review by Hughes et al. examining 24 randomized controlled trials (RCTs) concluded that pregnancy outcomes did not improve from treatment with ovulation-suppression agents (including danazol, GnRHa, medroxyprogesterone, gestrinone, and oral contraceptives) compared to placebo (odds ratio [OR]: 0.79, 95% confidence interval [CI]: 0.54–1.14, \( P = 0.21 \)) or no treatment (OR: 0.80, 95% CI: 0.51–1.24, \( P = 0.32 \)), and that none of the medical agents was more efficacious or better than any other.57 These drugs merely serve to delay fertility instead of increasing pregnancy rates; further, they are, in themselves, detrimental for fecundity and carry significant costs and side effects. Therefore, they should be discouraged in the management of endometriosis-associated infertility, with the possible exception of use in *in vitro* fertilization (IVF). European Society of Human Reproduction and Embryology (ESHRE) guidelines for the treatment of endometriosis-associated infertility state that hormonal suppression of ovarian function does not improve fertility in minimal–mild or more severe endometriosis, and should not be offered for this reason alone (recommendation grade A, evidence level 1a).57

Experimental medications that do not inhibit ovulation can be used without a delay of attempted conception. Pentoxifylline is a phosphodiesterase inhibitor with anti-inflammatory properties and has been investigated in infertile women with endometriosis. A single small-scale RCT with 60 cases reported
a nonsignificant increase in pregnancy rates with pentoxifylline use (31% vs. 18.5% with placebo in a 12-month period), whereas a prospective, double-blind, randomized, placebo-controlled study did not find any fertility improvement with the same medication. This latter study concluded that pentoxifylline did not enhance fertility or lessen recurrence in any stage of endometriosis. Other emerging drugs that do not suppress ovarian function and instead selectively target endometriotic lesions may yet hold promise, but current evidence based on the established pharmacopoeia indicates that medical treatment of endometriosis-associated infertility is not effective and should not be pursued.

**Surgical Treatment in Endometriosis-associated Infertility**

Restoration of disrupted pelvic anatomy is the mainstay of surgical treatment of endometriosis-associated infertility and involves the destruction of endometriotic deposits, removal of endometriomas, and adhesiolysis. Laparotomy and laparoscopy are efficacious routes of access for surgery, but laparoscopy has shorter hospitalization, recovery, and return-to-work times, fewer adhesions, and greater patient comfort. Surgery is usually the treatment of choice to restore disrupted pelvic anatomy and remove endometriomas in advanced stages, whereas the question of optimal treatment remains more controversial in early stages of the disease without anatomical distortion.

**Advanced Endometriosis**

Although few RCTs have examined the efficacy of surgical approaches in advanced endometriosis, some evidence indicates that surgery can be of value. Several nonrandomized trials involving cases of severe endometriosis have found a rise in pregnancy rates after reparative surgery compared with rates of approximately 0% in untreated cases. A meta-analysis of one quasi-randomized and five cohort studies reported that surgery may be of value to improve pregnancy rates compared with no treatment or medical therapy, but the heterogeneity of these studies unfortunately reduces the confidence of such a conclusion. Moreover, two prospective randomized studies by Busacca et al. and Soong et al. concluded that operative laparoscopy was beneficial for infertile women with advanced-stage endometriosis, although the latter study found a reduced postoperative conception rate in women with stage IV compared with stage III disease. ESHRE guidelines state that data are insufficient regarding the efficacy of surgical treatment in cases of moderate–severe endometriosis. Regardless, it seems intuitive that a structural normalization of severely distorted pelvic anatomy can improve conception outcomes, as supported by the above studies. Future RCTs are needed to reach definitive answers on the efficacy of surgery in advanced endometriosis.

**Minimal–mild Endometriosis**

The value of surgical treatment in minimal–mild endometriosis is more controversial. In a Canadian RCT of 341 infertile women (20–39 years of age) with stage I–II disease, 169 underwent diagnostic laparoscopy with no treatment and 172 underwent operative laparoscopy with ablation or excision of endometrial implants. Subjects were followed up for 36 weeks postoperatively and for up to 20 weeks of gestation if they conceived. The cumulative pregnancy rates and fecundity rates were found to be significantly higher in surgically managed patients (30.7% vs. 17.7% for those with no treatment, OR: 1.7, CI: 1.2–2.6 and 4.7% vs. 2.4%, OR: 1.9, CI: 1.2–3.1, respectively). There was no evidence that outcomes were affected by method of ablation by electrosurgery or laser delivery systems. However, contradictory conclusions were made by an Italian study, which involved a similar design but examined a smaller number of early-stage patients (n = 101), and followed pregnancies 1 year after laparoscopic intervention proceeding to live births. Live birth rates were comparable in surgically treated and nontreated subjects (19.6% vs. 22.2%, respectively). Neither of these studies was free of confounding factors. In the Canadian study, subjects were informed about the randomization, 10% of women in each group received fertility treatment or adhesiolysis, pregnancy rates in control cases were lower than expected, the follow-up period was less than 1 year, no distinction was made between active red lesions and nonactive black or fibrotic white lesions, vascularization and mitotic activity were not taken into account, and mapping of lesions was not considered in the selection at the time. The Italian study had a lower statistical power because its series was small (n = 54 operative surgeries vs. n = 47 diagnostic laparoscopies), with patients distributed among seven different centers. The patients had a longer duration of infertility and slightly more extensive disease; histologic confirmation was not requested; rates of red, white, or black lesions were not recorded; and vascularization and mitotic activity were not considered. Regardless, a meta-analysis of these two studies concluded that surgery was of significant benefit in infertile patients with early-stage endometriosis (OR: 1.7, 95%, CI: 1.1–2.5). However, the degree of the conferred benefit appears to be small: the number of women who must undergo surgery to achieve a single
additional pregnancy in these cases has been calculated as 7.7, which may be unacceptably high for some patients. ESHRE guidelines state that endometriotic lesion ablation with adhesiolysis improves fertility in minimal–mild endometriosis compared with diagnostic laparoscopy alone (recommendation grade A, evidence level 1a).57,70

**Combined Medical and Surgical Therapies in Endometriosis-associated Infertility**

Surgery combined with pre- and postoperative medical therapy represents a growing field of drug application. Theoretically, preoperative medication may reduce inflammation, vascularization, and implant size, making for faster, easier, less traumatic surgery, with the possibility of surgical scheduling in any time of cycle and the potential for complete eradication of the disease and decreased risk of postoperative adhesions. However, drawbacks of combined therapy include drug costs, side effects, and temporary regression of endometrial foci allowing escape from laparoscopic recognition and ablation.

**Preoperative Medical Therapy**

The preoperative use of medication may be useful for reducing the severity of endometriosis. A prospective multicenter clinical trial by Audebert et al. reported reductions in severity with preoperative compared with postoperative GnRHa treatment, although surgical feasibility did not differ significantly.71 Nasal application of GnRHa has revealed decreased inflammation, vascularization, and endometrioma growth,72 and a study by Muzii et al. found that preoperative GnRHa can improve surgical performance.73 However, in the absence of convincing evidence of improvements in surgical feasibility and in fertility rate, preoperative medication appears to be unjustified, as the theoretical benefits do not seem to outweigh the increased costs and rates of morbidity.

**Postoperative Medical Therapy**

Postoperative medical therapy is another option in combined therapy, aiming to achieve resorption of residual deposits that cannot be surgically removed, destruction of microscopic implants, and reduction of disease dissemination in case of endometrioma rupture. Three studies have evaluated the use of postoperative medical therapy with GnRHa and raloxifene,74–76 and other randomized trials have examined postoperative ovarian suppression.75–77 None of these studies reported increased fertility rates with postoperative medication. ESHRE guidelines conclude that postoperative danazol or GnRHa treatment is not more effective than expectant management in improving fertility for endometriosis-associated infertility (recommendation grade A, evidence level 1b).57,75,77–79

Thus, it appears that no qualified evidence indicates that fertility is enhanced by combination surgery with either preoperative or postoperative medical therapy, and the conversion of theoretical advantages into practical outcomes has hitherto been unfruitful. As with medical treatment alone, medication combined with surgery may only serve to delay fertility.

**Assisted Reproductive Technologies in Endometriosis-associated Infertility**

**Controlled Ovarian Hyperstimulation With or Without Intrauterine Insemination**

A number of randomized trials assessing the efficacy of ovulation induction with or without intrauterine insemination (IUI) have found that ovulation induction enhances fertility rates in cases of endometriosis-associated infertility without distorted pelvic anatomy or male factor infertility,4,53,80–82 Guzick compared fecundity rates after randomizing patients into intracervical insemination (ICI), IUI, gonadotropin induction/ICI, and gonadotropin induction/IUI.83 Monthly fecundity rates were highest in the gonadotropin induction/IUI group (0.09), followed by IUI (0.05), gonadotropin induction/ICI (0.04), and ICI (0.02). A study by Adamson et al. reported that monthly fecundity in infertile couples with endometriosis was doubled with clomiphene citrate to approximately 7% per month, and quadrupled with menotropins to 15%, compared with no treatment.84 However, RCTs assessing superovulation with IUI in advanced-stage endometriosis are lacking. ESHRE guidelines conclude that IUI with ovarian stimulation improves fertility in minimal–mild endometriosis, but the effect of unstimulated IUI is not clear (recommendation grade A, evidence level 1b).57 It is important to note that, because ovarian stimulation may lead to the progression of ovarian endometriosis, controlled ovarian hyperstimulation (COH) with IUI should be limited to a maximum of three to four cycles, and IVF-embryo transfer should be preferred.85

**Assisted Reproductive Technologies in Endometriosis-associated Infertility**

The impact of endometriosis on IVF outcomes remains uncertain. Some studies have reported IVF success rates in cases of endometriosis comparable with those of unexplained or tubal factor infertility,46,86,87 or improved outcomes with increasing disease stage,41 whereas other studies have found reduced success rates.1,43,88 These inconsistent results
may be attributable to laparoscopic oocyte retrieval and inferior laboratory methodologies used in early studies. A meta-analysis involving 22 nonrandomized studies of IVF outcome found lower pregnancy rates in patients with endometriosis compared with those with tubal factor infertility; it was reported that women with severe endometriosis were less likely to achieve pregnancy success than those with mild disease. Reduced oocyte retrieval, fertilization, and implantation rates were also associated with endometriosis, and it has been suggested that lower implantation rates in endometriosis may be attributable to diminished ovarian reserve rather than embryo quality or uterine receptivity. An analysis of the Human Fertilisation and Embryology Authority database suggested that IVF live birth rates are not adversely affected by endometriosis compared with unexplained infertility. No evidence shows adverse effects of endometriosis on implantation and pregnancy rates in patients undergoing intracytoplasmic sperm injection.

Several studies suggest that long-term treatment with GnRHa before IVF may improve fertility rates in advanced-stage endometriosis by means of increased numbers of retrieved oocytes and transferred embryos, higher implantation and pregnancy rates, and reduced rates of preclinical abortions. ESHRE guidelines recommend that IVF treatment is suitable for endometriosis-associated infertility, particularly for cases involving impaired tubal function, male factor infertility, and/or failure of other treatments (recommendation grade B, evidence level 2b). Moreover, endometriosis is associated with lower IVF pregnancy rates than tubal infertility (recommendation grade A, evidence level 1a). Finally, prolonged GnRHa treatment prior to IVF should be considered for cases of moderate–severe endometriosis, as it has been associated with increased pregnancy rates (recommendation grade A, evidence level 1b).

Conclusions

Beset with inadequate, inconclusive, and conflicting data, it remains difficult to arrive at a consensus regarding appropriate choices of treatment for endometriosis-associated infertility. Even so, the current evidence does allow for a number of conclusions to be drawn. Despite the lack of a firmly established causal relation between endometriosis and infertility, it is clear that treatment of endometriosis can improve fertility in some cases. Expectant management may be a reasonable approach in younger patients with early-stage disease and a shorter duration of infertility. Current medical therapy is not efficacious, and its use should be discouraged as it may only serve to postpone conception. Laparoscopic surgery appears to be superior to expectant management or medical therapy in minimal–mild endometriosis and may also be of benefit for patients with advanced endometriosis. The quality of available evidence supporting the use of preoperative or postoperative medication combined with surgery is too poor to make a recommendation on such regimens. COH/IUI is a good option in mild and surgically corrected disease. In patients with early-stage endometriosis, IVF outcomes are similar to those with unexplained or tubal factor infertility, and GnRHa treatment combined with IVF may be useful for more advanced disease.

Further RCTs with rigorous scientific designs are needed to establish a comprehensive evidence-based approach to deciding among management strategies for endometriosis-associated infertility.

Conflicts of Interest

The authors declare no conflicts of interest.

References


89. Matalliotakis, I.M. et al. 2007. Women with advanced-stage endometriosis and previous surgery respond less well to gonadotropin stimulation, but have similar IVF implantation and delivery rates compared with women with tubal factor infertility. Fertil. Steril. 88: 1568–1572.


