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Endometriosis and Infertility: A review of the pathogenesis and treatment of endometriosis-associated infertility

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Synopsis

Endometriois has been associated with infertility, however the mechanism by which it affects fertility are still not fully understood. This manuscript reviews the proposed mechanisms of endometriosis pathogenesis, it affects on fertility and treatments of endometriosis-associated infertility. Theories on etiology of disease include retrograde menstruation, coelomic metaplasia, altered immunity, stem cells, and genetics. Endometriosis affects gametes and embryos, the fallopian tubes and embryo transport, and the eutopic endometrium; these abnormalities likely all impact fertility. Current treatment options of endometriosis-associated infertility include surgery, superovulation with IUI, and IVF. We also discuss potential future treatments for endometriosis related infertility such as stem cells transplantation and immune therapy.

Article Keywords

Endometriosis; Infertility; Treatment; Pathogenesis; Stem cell; In-Vitro Fertilization

Endometriosis has been estimated to affect up to 10–15% of reproductive aged women (1). The association between endometriosis and infertility is well supported throughout the literature, but a definite cause-effect relationship is still controversial. The prevalence of endometriosis increases dramatically to as high as 25%–50% in women with infertility and 30–50% of women with endometriosis have infertility (2). The fecundity rate in normal reproductive age couples without infertility is estimated to be around 15% to 20%, while the fecundity rate in women with untreated endometriosis is estimated to be anywhere from 2% to 10% (3, 4). Women with mild endometriosis have been shown to have a significantly lower probability of pregnancy over 3 years than women with unexplained fertility (36% vs. 55%, respectively) (5). IVF studies have suggested that women with more advanced endometriosis have poor ovarian reserve, low oocyte and embryo quality, and poor implantation (6, 7).

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Despite the well supported association between endometriosis and infertility, the difficulty in proving a causal relationship likely stems from the multiple mechanisms by which endometriosis can impact fertility and the heterogeneity and variations in the phenotype of the disease. This article will discuss endometriosis-associated infertility including a basic background on endometriosis, its presumed pathophysiology in causing infertility, and both current and potential treatments.

Endometriosis: Overview

Endometriosis is an estrogen-dependent benign inflammatory disease characterized by the presence of ectopic endometrial implants (8). Implants typically occur in the pelvis but have also been seen in the upper abdomen, peripheral and axial skeleton, lungs, diaphragm, and central nervous system. The most common sites of endometriosis, in decreasing order, are the ovaries, anterior/posterior cul-de-sac, broad ligaments and uterosacral ligaments, uterus, fallopian tubes, sigmoid colon and appendix.

Because the growth of the implants is dependent on ovarian produced steroids, it is a disease that most severely affects women ages 25–35 years (9). Patients can present with a wide-range of symptoms ranging from being asymptomatic to infertile. In addition to infertility, it is commonly associated with symptoms such as dyspareunia, dysmenorrhea, bladder/bowel symptoms, and chronic pelvic pain.

Pathogenesis of Endometriosis

The definite pathogenesis of endometriosis is still unknown but there are a number of leading theories including retrograde menstruation, altered immunity, coelomic metaplasia, and metastatic spread. Newer research is also proposing stem cell and genetic origins of the disease.

Retrograde Menstruation

The most well accepted theory, retrograde menstruation, was proposed by Sampson in the 1920's and states that endometrial tissue is transported in a retrograde fashion through patent fallopian tubes into the peritoneal cavity (8, 10). The endometrial cells then attach to the peritoneal mesothelial cells, establish a blood supply, proliferate and produce endometrial implants. This theory has been well supported by subsequent research. Women with endometriosis have higher volumes of refluxed menstrual blood and endometrial-tissue fragments than women without the disorder (11). In addition, endometriosis is observed when the cervix of baboons is ligated and endometrial fragments have access to the pelvis (12). The incidence of endometriosis is much higher in young girls with outflow obstruction, thereby leading to increased tubal reflux and retrograde menstruation (13). However, the incidence of retrograde menstruation is similar in women with and without endometriosis so the pathogenesis appears to be a multi-factorial mechanism.

Coelomic Metaplasia and Metastatic Spread

In the 1960's, Ferguson proposed that coelomic metaplasia may also contribute to the development of endometriosis. It stems from the theory that the peritoneum contains undifferentiated cells that can differentiate into endometrial cells (14). Another theory argues that menstrual tissue travels from the endometrial cavity through lymphatic channels and veins to distant sites, which could attribute to implants found outside the pelvic cavity.

Altered Immunity

Women with endometriosis have altered immunity; preventing them from clearing the refluxed endometrial cells/fragments that appear in retrograde menstruation (15). This would help explain why some women with retrograde menstruation develop endometriosis while others do not. Cell-mediated immunity is thought to be deficient in patients with the disease; leukocytes are unable to recognize that the endometrial tissue is not in its normal location (15). There have also been studies showing decreased cytotoxicity to endometrial cells secondary to defective NK-cell activity (16). Once endometriosis develops, the immune system has also been to shown to potentiate the development and increase the severity of the disease. In women with endometriosis there are increased numbers of leukocytes and macrophages in and around endometrial implants and in the peritoneal fluid. These cells secrete cytokines and growth factors (IL- 1,6 and 8, TNF, RANTES, VEGF) into the peritoneal milieu, which then recruit surrounding capillaries and leukocytes (17–19). The ultimate effect is proliferation of endometriosis implants with increased vascular supply.

In addition to retrograde menstruation, coelomic metaplasia and altered immunity, newer research is increasingly showing that stem cells and genetics may play a role in the etiology of endometriosis.

Stem Cells

It is presumed that de-novo development of endometrial tissue occurs from endogenous stem cells in the endometrium (20, 21). Over the last decade, we have studied the possibility that bone marrow-derived cells may also differentiate into endometrial cells, and pertinently, may be implicated in the development of ectopic endometrial implants. If true, this would help explain how ectopic tissue can occur in locations outside the peritoneal cavity such as the lung and CNS system. Proof that endometrial cells can be derived from bone marrow mesenchymal stem cells comes from the study of female allogenic bone marrow transplant recipients who received marrow from a single antigen mismatched related donor, allowing the cells to be identifiable by HLA type. The study remarkably showed the presence of donor-derived endometrial cells in endometrial biopsies of the recipients (22). This finding suggested that bone marrow derived stem cells can differentiate into human uterine endometrium. An additional study in 2007 used a murine model and transplanted male-donor derived bone marrow cells into female bone marrow (21). After transplantation, male-donor derived bone marrow cells (recognizable by the Y chromosome) were found in the uterine endometrium and had differentiated into both epidermal and stromal cells. This is evidence that proves that bone-marrow stem cells, from male donors can generate endometrium *de novo* and proves their mesenchymal origin. This study also showed the ability of stem cells to engraft endometriosis by showing the presence of bone marrow derived cells in ectopic endometrial implants in previously hysterectomized mice. The endometrial tissue must be capable of attracting stem cells despite its ectopic location. The above evidence shows that a non-endometrial stem cell source can result in endometrial cells in both the uterus and ectopic implants. This suggests an alternative origin of some endometriosis, specifically, from bone-marrow derived cells (21).

Genetics

For over 20 years it has been known that endometriosis has a familial tendency. Women who have a first degree relative affected by the disease have a 7 times higher risk of developing endometriosis than women who do not have a family history of the disease (23). Familial aggregation has also been shown in studies of monozygotic twins and studies involving non-human primates(24, 25). Genetic polymorphisms may lead to aberrantly expressed genes identified in the endometrium of both human and non-human primates, but their contribution to the etiology of endometriosis is not yet well defined (26–28).

Alternatively, these alterations in gene expression are more likely acquired and indeed are seen in animal models of the disease where normal endometrium (without genetic predisposition to the disease) is transplanted to the peritoneal cavity (29, 30).

The only mouse model of spontaneous endometriosis is obtained by engineering the expression of an oncogenic variant of the KRAS gene (31). KRAS is a signal transduction molecule that is mutated in several cancers and can lead to increased cell proliferation, survival and migration. Mice expressing this gene develop spontaneous endometriosis. Recently a polymorphism in the KRAS gene has been reported in a group of women with resistant endometriosis (32). Specific genetic alterations may allow the identification of endometriosis sub-types, which may allow risk stratification, individualized therapy and personalized medicine for endometriosis.

Endometriosis Associated Infertility

Here we discuss the current evidence and proposed mechanisms of how endometriosis adversely impacts fertility. It is clear how severe disease can cause infertility. Pelvic anatomy becomes distorted and fecundity is reduced via mechanical disruptions such as pelvic adhesions. These disruptions impair oocyte release or pick-up, alter sperm motility, cause disordered myometrial contractions, as well as impair fertilization and embryo transport (33). Women who are infertile are more likely to have advanced stages of the disease (34). However, there is still much speculation about the proposed mechanisms by which mild disease impacts fertility (1). Inflammatory cytokines, growth and angiogenic factors, and aberrantly expressed genes are all being explored as potential etiologic factors of endometriosis-associated infertility.

Effect on Gametes and Embryo

Altered ovulation and oocyte production is seen in endometriosis and is associated with the increased inflammatory cells in the peritoneal fluid and endometriomas. Inflammatory effects resulting from the presence of endometriomas have been shown to affect both oocyte production and ovulation in the affected ovary (33). There is also a luteal phase disruption in endometriosis that may result from progesterone receptor dysregulation as well as an effect on progesterone target genes, which in turn leads to decreased endometrial receptivity (8, 33). Sperm quality or function is also decreased and has been proposed to be from the inflammatory/toxic affects of the peritoneal fluid and increased activated macrophages (35). The increased number of inflammatory cells in the peritoneal fluid not only damage the oocytes and sperm, but have also been shown to have toxic effects on the embryo (36). In addition, studies have shown aberrant expression of glutathione peroxidase and catalase in the endometrium of patients with endometriosis and it can be suspected that there is also an increase in endometrial free radicals and subsequently a negative affect on embryo viability (37, 38).

Effect on Fallopian Tube and Embryo Transport

Gamete transport is also affected by the inflammatory environment and increased cytokines found in endometriosis; inflammation impairs tubal function and decreases tubal motility. Disordered myometrial contractions associated with endometriosis can also impair gamete transport and embryo implantation (33).

Effect on the Endometrium

In addition to the above-mentioned inflammatory effects of endometriosis, there is increasing evidence supporting endometriosis affects the eutopic endometrium and causes implantation failure, however the mechanism of cellular or molecular signaling from the

lesion to the uterus is unknown. As described above, numerous genes are aberrantly expressed in the endometrium of women with endometriosis, many known to be necessary for endometrial receptivity. The mechanism and specific signal that leads to alterations in the endometrium of women with endometriosis is not well characterized. We recently published data demonstrating that cells migrate from ectopic endometrial implants to the eutopic endometrium (39). Experimental endometriosis was established by implanting endometrial tissue from green fluorescent protein (GFP) mice into the peritoneal cavity of DS-Red mice. The study showed that GFP+ cells were found in the eutopic endometrium, preferentially the basalis layer, of mice with experimental endometriosis. In addition, gene expression profiling of the GFP+ cells showed increased expression of pan-epithelial markers and more interestingly, up-regulation of Wnt7A expression along with 17 other genes in the *wingless pathway*. Wnt7a is essential to estrogen-mediated uterine growth and implantation in mice, likely by signaling between the epithelium and stroma (40–42). It has been theorized by Liu *et al.* that aberrant activation of the Wnt pathway disturbs endometrial development during the implantation window (43). We theorize that the increased expression of ectopic Wnt7a outside of the gland likely disrupts the normal epithelial-stromal polarity required for normal fertility (39). There is likely bidirectional movement of cells between the eutopic and ectopic endometrial tissue. The reprogrammed and abnormally located cells likely that have ‘returned’ to the endometrium generate the signal that leads to aberrant gene expression and implantation failure.

There are a number of other studies proposing that aberrant gene expression in eutopic and ectopic endometrium may be related to infertility or the establishment of the disease.

An example of aberrant gene expression is the Hoxa10/HOXA10 gene (27). This gene is directly involved in the embryogenesis of the uterus and subsequently in endometrial regeneration in each menstrual cycle. Expression of this gene is necessary for endometrial receptivity. Mice with a targeted disruption of the Hoxa10 gene show complete loss of endometrial receptivity. Similarly, women with lower levels of expression of HOXA10 have lower implantation rates. In women, cyclical endometrial expression of this gene peaks during the window of implantation in response to estrogen and progesterone. Women with endometriosis, however, do not exhibit the mid-luteal rise as would be expected, which may partially explain their infertility(28).

Aromatase, the enzyme that converts androstenedione and testosterone to estrone and estradiol, has also been extensively studied in endometriosis. It has been shown that abnormal levels of aromatase are present in both endometriotic implants as well as eutopic endometrium where it is normally absent, resulting in increased estradiol production (44). The role of aromatase in the pathophysiology of endometriosis is clear given that it is an estrogen-dependent disease; increased estrogen production in the endometrium may also affect endometrial development and receptivity.

Progesterone resistance and dysregulation of progesterone receptors also appear to play a role in implantation failure. Because progesterone induces endometrial decidualization during the luteal phase, its presence is crucial for a normal pregnancy. Progesterone receptors have been shown to be dysregulated in both eutopic and ectopic endometrium. Down-regulation of receptors is seen prior to implantation in normal endometrium, but is delayed in the endometrium of endometriosis (45). In addition, both eutopic and ectopic endometrium have been shown to be resistant to progesterone, causing an unopposed estrogen state which is likely not suitable for implantation (46, 47).

Recent studies have also shown an association with the abnormal progesterone resistance and inappropriately persistent expression of matrix metalloproteinase (MMP), which

degrade extracellular matrices (48). MMPs are normally inhibited by progesterone in the secretory phase but in the setting of endometriosis, they remain elevated during inappropriate periods such as implantation. The disinhibition of these proteins could theoretically lead to an environment of constant matrix breakdown not conducive to implantation.

Around the same time progesterone receptors are down regulated during implantation, epithelial expression of αβ-integrin, a marker of uterine receptivity, is normally increased (49). Patients with endometriosis have lower expression of this adhesion molecule, which may interfere with embryo attachment in implantation (8, 49).

There is a well-established association between endometriosis and infertility; however, as evidenced above, it appears to be multi-factorial involving mechanical, molecular, genetics, and environmental causes. As newer research identifies alterations in gene expression and genetic defects, it is appropriate to consider testing of endometrial adequacy to diagnose and treat endometriosis-associated infertility.

Treatment of Endometriosis-Associated Infertility

Current treatment of endometriosis-associated infertility focuses on improving fecundity by removing or reducing ectopic endometrial implants and restoring normal pelvic anatomy(50). A wide spectrum of treatment options have been examined including expectant management, medical treatment, surgical treatment, and assisted reproductive technology. Current research is also examining novel promising non-hormonal treatment options for endometriosis such as ICON, VEGF antagonists, and stem cells, which may also prove to increase fecundity by decreasing the extent of ectopic implants or improving the eutopic endometrium (51, 52).

Expectant Management

Despite the significantly lower fecundity rate when compared to women without endometriosis, women with mild-moderate endometriosis are still able to conceive in the absence of any medical or surgical intervention. Multiple studies evaluating patients with endometriosis who undergo expectant management report their fecundity rate to be around 2.40–3.0 per 100-person months (53, 54). However, in women with more severe disease, pregnancy rates are far lower (50). While the option of expectant management may be reasonable for patients with mild-moderate disease, it is only delaying the start of effective treatment in those with severe disease. Patient counseling must take into account the severity of endometriosis.

Medical Treatment

It is well known that endometriosis is an estrogen dependent disorder. Endometriotic lesions have been shown to have an increased production and decreased inactivation of estradiol. This is due, in part, to abnormal expression of both aromatase and 17-beta hydroxysteroid dehydrogenase (44, 55). Common medical therapies used to treat symptoms of endometriosis such as pelvic pain, dyspareunia and dysmenorrhea target ovarian estrogen production. Medications used as endometriosis therapy are hormonal medications including combined oral contraceptives, progestins, danazol and gonadotropin-releasing hormone agonists or antagonists (GnRH analogs). Although these medications may help treat pain, they have shown no benefit in the treatment of endometriosis-associated infertility. A 2010 Cochran review looked at 25 trials of ovulation suppressive agents (danazol, progestins, oral contraceptives, GnRHa) in women with endometriosis-associated infertility who wished to conceive. The odds ratios (OR) for pregnancy following ovulation suppression versus placebo or no treatment was 0.97 (95% confidence interval (CI) 0.68 to 1.34, P = 0.8) for all

women randomized and 1.02 (95% CI 0.70 to 1.52, P = 0.82) for subfertile couples (56). Not only was there no benefit from ovulation suppression, but it also delayed the patient from having a live birth while taking the suppressive agents.

We recently reviewed several novel medical therapies being tested for the treatment of endometriosis(51). Some are hormonal, such as selective estrogen receptor modulators and selective progesterone receptor modulators, while others target inflammation and angiogenesis such as statins, VEGF receptor antagonists, and immunoconjugate (ICON). Other trends in the treatment of endometriosis include the use of Aromatase inhibitors, Cox-2 inhibitors, Omega-3 fatty acids, and cannabinoid agonists (57). Despite increasing research on the novel therapies, evidence to date is primarily limited to experimental animal models; further trials in women will be needed to define their role and utility in endometriosis-associated infertility.

As a general rule, medical therapy should be discouraged in patients with endometriosis and subfertility who desire a live birth (50). The exception to this rule is in patients undergoing in-vitro fertilization (IVF). Multiple studies have shown that prolonged GnRHa treatment prior to IVF may improve fertility rates in advanced endometriosis (58–60). Proposed mechanisms are by means of increased retrieved oocytes, higher implantation rates, and reduced preclinical abortions (61, 62). A Cochran review looked at 3 RCT and concluded that the administration of GnRH agonists for a period of three to six months prior to IVF or ICSI in women with endometriosis significantly increases the odds of a clinical pregnancy (OR 4.28, 95% CI 2.00–9.15) (63). Similar to GnRHa, the use of oral contraceptives has also been shown to improve outcomes when given for 6–8 weeks prior to ART. A randomized controlled trial by de Ziegler *et al.* showed outcomes comparable to age-matched controls of women who did not have endometriosis (64).

Data regarding GnRH and OCP therapy in patients with endometriomas has however remained controversial. A 2010 Cochran review by Benschop *et al.* concluded that administration of GnRHa does not significantly affect the clinical pregnancy rate when given prior to assisted reproductive technology (ART) in patient's with endometriomas, however there was improved ovarian response and a greater number of mature oocytes aspirated (65). Conversely, the study by de Ziegler *et al.* showed improvement using pre-ART continuous OCP for 6–8 weeks even in those with endometriomas (64). Needless to say, data regarding suppressive therapy pre-ART in patients with endometriomas is still evolving but shows promise for improving endometriosis related infertility when used in conjunction with IVF.

In women with moderate-severe endometriosis, prolonged GnRHa administration should be considered prior to IVF (66). It is also reasonable to consider the use of continuous oral contraceptive therapy prior to ART in patients with all stages of endometriosis.

Surgical Treatment

Surgery for endometriosis can be both diagnostic and therapeutic. Laparoscopic surgery is preferred to laparotomy; it is more cost effective, has a shorter hospital stay and shorter recovery (67). Surgical treatment of endometriosis-associated infertility has proposed benefits in both severe and minimal-moderate disease. Benefits of surgery in severe disease include restoration of pelvic anatomy, removal of implants and endometriomas, and resulting decreased inflammation. There are few randomized controlled trials studying the effects of surgery on fecundity in advanced stage disease and there is insufficient evidence to recommend surgery for the treatment of infertility in severe disease. However, as long as ovarian resection is limited to avoid substantial reduction in ovarian reserve, surgery in severe disease should still remain an option in patients with severe endometriosis associated

infertility desiring a live birth. Surgery in minimal-moderate disease is a little more controversial, but evidence to date supports surgical intervention. Marcoux *et al.* conducted a randomized, controlled trial on 341 women to determine whether laparoscopic surgery enhanced fecundity in infertile women with minimal-mild endometriosis. They concluded that either resection or ablation of minimal and mild endometriosis significantly enhanced fecundity in infertile women when compared to diagnostic laparoscopy alone (cumulative probabilities, 30.7% and 17.7%, respectively; P=0.006). The corresponding fecundity rates were 4.7 and 2.4 per 100 person months, respectively and the absolute increase in the 36-week probability of a pregnancy carried beyond 20 weeks that was attributable to surgery was 13 percent. They also showed no significant difference between excisional vs. ablative techniques (53). However, contradictory evidence was seen by an Italian study of similar design but with a smaller number of subjects that found no significant difference in conception rates (68). A meta-analysis was subsequently performed by Olive and later re-affirmed by a Cochran review concluded that surgery had significant benefits in infertile patients with early-stage endometriosis who desired fertility. The number of women who needed to undergo laparoscopic surgery for one additional clinical pregnancy was approximately 7.7 and the OR was 1.66 (95% CI 1.09 to 2.51) in favor of laparoscopic surgery versus diagnostic surgery only (69, 70). However, given the relatively small increase in pregnancy, alternative therapies should also be considered.

Studies on the treatment of an endometrioma in the setting of infertility are more uniform. A 2008 Cochran review examined the current literature regarding laparoscopic ablation vs. excision of endometriomas and found that excision of the cyst was associated with a subsequent increased spontaneous pregnancy rate in women who had documented prior sub-fertility (OR 5.21 CI 2.04–13.29). Resection was clearly superior when compared to drainage or ablation. This review also identified a RCT that demonstrated an increased ovarian follicular response to gonadotropin in those who underwent excisional surgery when compared to ablative surgery (WMD 0.6 CI 0.04–1.16) (71). In addition, excisional surgery was associated with a reduced rate of recurrence and superior improvement in pain.

Combined Medical and Surgical Treatment

Many studies have looked at combined medical and surgical therapies, in specific, pre-operative and post-operative medical therapy. Pre-operative medical therapy was administered with the intent of reducing the severity of endometriosis and thereby decreasing the risk and increasing the desired outcome of the surgery. While pre-operative use of a GnRH agonist can reduce the severity of disease there is no convincing evidence that it impacts surgical success or fertility rate (50, 72, 73). Likewise, multiple randomized trials have evaluated the use of ovarian suppression post-operatively. The aim was to increase resorption of residual deposits and reduce the recurrence of disease, however no trial reported increased fertility rates (59). A 2009 Cochran review looked at 16 trials of pre- or post-operative hormonal suppression and found that there was no evidence of benefit associated with post-surgical medical therapy and insufficient evidence to determine a benefit to pre-operative therapy with regards to pain, disease recurrence or pregnancy rates (74). Given these studies, adjuvant medical therapy is not recommended.

Superovulation and Intrauterine Insemination

Multiple randomized controlled trials have shown that ovulation induction and superovulation both with and without intrauterine insemination (IUI) increase fertility rates in patients without distorted anatomy (75–78). All of these studies focused on patients with minimal-mild endometriosis. There is a lack of data for patients with more advanced endometriosis. Guznik showed that fecundity rates were highest when combining gonadotropin induction with IUI compared to with ICI or IUI/ICI alone (76). Another study

suggested benefit with clomiphene citrate and IUI compared to controls (fecundity 0.095 vs. 0. 033) (79). In addition, a recent randomized study comparing IUI with clomiphene (Clomid) vs. IUI with Letrozole showed a benefit in clinical pregnancy rates with either (14.7 vs. 15.9%, respectively) in women with surgically treated minimal-mild endometriosis and no difference between the two methods (80). An important aspect to remember is that ovarian stimulation can also exacerbate endometriosis so it should be performed in a controlled manner and be limited to 3–4 cycles (50, 81). To summarize, there is evidence to support SO/IUI in women with Stage I or II endometriosis especially if they have been surgically diagnosed and shown to be free of anatomic distortion prior to the therapy. There is not sufficient evidence to support SO/IUI in patients with severe endometriosis.

Assisted Reproductive Technology

In vitro fertilization is currently the most effective treatment of endometriosis-associated infertility. The Society of Assisted Reproductive Technology reported that in 2009, over 1400 live births were reported from 5600 IVF cycles in patients with endometriosis. However, when comparing data on the effectiveness of IVF for patients with endometriosis versus patients with other causes of infertility, there is still controversy. A recent report on the Society of Assisted Reproductive Technology data showed that the average delivery rate per retrieval of patient's undergoing IVF-ET (in vitro fertilization-embryo transfer) was 39.1% for women with endometriosis compared to 33.2% for women with all causes of infertility. This suggests that women with endometriosis seem to have similar or even slightly increased success in IVF compared to women with other causes of infertility (82). Additionally, a study by Opoien *et al.* showed that excluding women with endometriomas, women with all stages of endometriosis who underwent luteal phase GnRHa down-regulation followed by IVF/ICSI treatment had a similar pregnancy and live birth rate compared to women with tubal factor infertility (83). Patients with endometriomas, however, did show a significantly lower pregnancy and live birth rate. Similarly, an analysis of the Human Fertilization and Embryology database suggested that live birth rates were not affected by endometriosis compared to unexplained infertility (50). Additionally, a study by Bukulmez showed that no evidence suggests that the presence or extent of endometriosis affects the clinical pregnancy or implantation rate in patients that are undergoing ICSI (84).

To summarize, while it is still uncertain how much endometriosis affects IVF success rates, IVF appears to be the most successful treatment option for patients with all stages of endometriosis. In addition, it is not unreasonable to consider pre-treatment ovulation suppression to help suppress inflammatory cytokines and reduce disease presence prior to any form of ART. In patients with endometriomas, more research is needed to assess their affect on IVF/ICSI and whether surgical intervention prior to ART increases their success rate.

Potential Treatments in the Future

There are a number of novel medical therapies, mentioned above, that are currently being examined for use in endometriosis and a few show potential as a medical therapy in endometriosis-associated infertility. These include but are not limited to immunoconjugate (ICON), and aromatase inhibitors. ICON targets aberrantly expressed tissue factor on endometriotic endothelium and prompts regression of the established disease, likely by devascularization (51). It has the potential to destroy preexisting implants in a nontoxic, non-hormonal manner, which could subsequently improve fertility rates. Aromatase inhibitors are another potential treatment. As described above, aromatase is found in eutopic endometrium, where it is normally absent, and may impact estradiol levels and implantation. Aromatase inhibitors are being increasingly studied for the use of endometriosis associated

pain, but clinical trials studying their potential with current fertility treatments are still needed.

As discussed above, there is currently ongoing research on the impact both genetics and stem cells may have on endometriosis. The HOXA10 gene has been implicated in the pathogenesis of endometriosis-associated infertility by affecting implantation (27). There is evidence that epigenetic modifications may play a larger role than once believed. Epigenetics is the alteration of DNA by long lasting covalent modification such as the addition of a methyl group, however without a mutation or change in any base pair. These epigenetic changes have been described in numerous studies including hypermethylation of HOXA10, progesterone receptor-β, and E-Cadherin or hypomethylation of genes for estrogen receptor-β and steroidogenic factor 1 (77, 85). Potential future treatments could involve targeting these altered molecular pathways and correcting abnormal methylation. Unfortunately, there are no safe and effective ways currently available to correct these defects. Replacement of endometrium is a potential option. Stem cell therapies (discussed below) are a potential option to replace damaged endometrium.

Finally, some of the our newest data shows great potential as future treatment strategies. We have previously shown that bone-marrow derived mesenchymal stem cells can give rise to endometrial cells, in addition, that there is likely a bidirectional communication between eutopic endometrium and endometrial implants. This information could not only help to foster a better understanding of the disease, but knowledge of this process could lead to potential therapies for treating uterine disorders, and therapeutically augmenting stem cell transdifferentiation into endometrium. Damaged endometrium can be replaced with stem cells. This is especially appealing given the epigenetic damage to endometrium seen in women with endometriosis; epigenetic alterations are persistent and there are no know therapies to reverse this damage. Replacement of endometrium with a stem cell based therapy may be the optimal way to restore normal endometrial function and implantation in women with endometriosis.

Summary of Treatment Options

Ultimately, the optimal method for treatment of endometriosis-associated infertility is an individualized decision that should be made on patient-specific basis. Many factors must be taken into account including but not limited to distorted pelvic anatomy, patient's ovarian reserve, partner semen analysis, age, presence of endometriomas, and length of infertility (77). Depending on the patient, current treatment options may include expectant management, surgical removal of implants, ovulation induction or IVF. For women with suspected stage I/II endometriosis, a decision to perform laparoscopy with surgical excision of discovered implants before offering other treatments can be discussed with each patient. If the patient is young, it is not unreasonable to discuss expectant management or SO/IUI as a first line therapy. If the patient is older and nearing 35, a more aggressive plan such as SO/IUI or IVF +/− pre-IVF ovulation suppression should be discussed with her.

For women with suspected stage III/IV endometriosis, IVF is recommended. If surgery is performed and the initial surgery does not restore fertility, IVF +/− pre-ART ovulation suppression is an effective alternative compared to repeat surgery although there is currently insufficient evidence to assess the benefit of surgery in addition to IVF on the outcomes of pregnancy (3).

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Key Points

- Endometriosis is an estrogen-dependent disease that affects between 10%–15% of reproductive aged women
- There is a well-established association between endometriosis and infertility; however, as evidenced above, it appears to be multi-factorial involving mechanical, molecular, genetics, and environmental causes
- The optimal method for treatment of endometriosis-associated infertility is an individualized decision that should be made on patient-specific basis.
- In vitro fertilization is currently the most effective treatment of endometriosis-associated infertility