

Ovarian Endometriomas Infertility and in Vitro Fertilization: Review of the Literature

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Endometriosis is one of the most common cause in infertility and most commonly observed in pelvic peritoneum, on the ovaries and uterosacral ligaments. The infertility associated with endometriosis has been attributed to several mechanism such as impaired peritoneal enviroment, distored the pelvic anatomic structure, reduced endometrial receptivity.

Endometrioma is commonly found pathology of endometriosis. Endovaginal ultrasonography is relevant for the diagnosis of ovarian endometriomas with a good predictive value. The treatment of endometriomas are frequently surgical. Several surgical techniques are performed in endometrioma. Operative laparoscopic management is the 'gold standard' for surgical treatment. Surgical treatment in infertile women with endometrioma can be restored to normal anatomic structure. IVF/ICSI treatment can be recommended in this women. On the other hand, the results of this treatment is argueded.

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Introduction

Endometriosis affects an estimated 10%-15% of all women of reproductive age and 20%-50% of all women with infertility.^{1,2} Infertile women are 6 to 8 times more likely to have endometriosis than fertile women.³ Infertility could be explained by functional alterations of the peritoneal environment affecting gamete, embryo, or fallopian tube function or by anatomical abnormalities of genital organs.^{4,5}

Several mechanisms have been suggested to clarify-explain the association between endometriosis and infertility.. Jansen et al reported that fecundity was 0.12 in women without endometriosis and 0.036 in those with minimal endometriosis in women undergoing therapeutic donor insemination.⁶ Reduced endometrial expression of the $\alpha\beta$ integrin (a cell adhesion molecule) during the time of implantation has been described in some women with endometriosis.⁷ On the other hand, very low levels of an enzyme involved in the synthesis of the endometrial ligand for L-section (a protein that coats the trophoblast on the surface of the blastocyst)⁸ have been observed in infertile women with endometriosis.⁹ IgG

and IgA antibodies may be increased in the endometrium of women with endometriosis. These abnormalities may alter endometrial receptivity and embryo implantation. Autoantibodies to endometrial antigens are reported to be increased in some women with endometriosis.¹⁰

The Impact of Endometriosis on The Outcome of in Vitro Fertilization Outcome

The impact of endometriosis on in vitro fertilization (IVF) outcomes is controversial. Xu et al compared the amount of regulated upon activation, normal T cell expressed and secreted (RANTES) and monocyte chemotactic protein 1 (MCP-1) in follicular fluid of women with and without endometriosis and determined their oocyte fertilization and pregnancy rates. RANTES is a selective and very potent monocyte, macrophage, T lymphocyte, and eosinophil chemoattractant in vivo and in vitro. MCP-1 is a potent chemotactic and activating factor specific for monocytes. The levels of RANTES in follicular fluid from women with endometriosis were significantly higher compared with concentrations in women with tubal infertility. In contrast, MCP-1 concentrations in follicular fluid from women with endometriosis were lower than in women with tubal infertility. Oocyte fertilization rates in the endometriosis group (54%) were significantly lower than those of the tubal infertility group (73%), were the pregnancy rates (19% vs. 35%, respectively). They concluded that women with endometriosis-associated infertility have a poor IVF outcome. Immune cell recruitment into the ovary might affect follicular function and lead to impaired oocyte quality.¹¹ On the other hand, Bukulmez et al investigated the impact of endometriosis on the outcome of intracytoplasmic sperm injection (ICSI) outcome. There were no differences in cycle

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and (embryo transfere) ET cancellation rates between control and endometriosis groups. The number of oocytes retrieved, fertilization and cleavage rates and the number and quality of embryos developed and transferred were similar among the groups. The implantation and clinical pregnancy rates were also comparable. They concluded that the presence and extent of endometriosis do not affect implantation and clinical pregnancy rates in patients undergoing ICSI.¹²

Endometriomas and Responsiveness to Ovarian Stimulation

Endometriomas usually contain thick fluid like tar; such cysts are often densely adherent to the peritoneum of the ovarian fossa and the surrounding fibrosis may involve the tubes and bowel.¹³ It is a common pathology among women with endometriosis and affects 17%-44% of patients with endometriosis.¹⁴ It is generally unilateral (72%-81%) (15). Dede et al evaluated the management of incidental adnexal masses observed at the time of cesarean section. The pathologic diagnosis of the masses were endometrioma 4.4%.¹⁶

The impact of endometriomas on IVF outcomes has been studied in some studies. Gupta et al evaluated the ovarian reserve and ovarian responsiveness to ovarian stimulation and assisted reproduction outcomes in patients with ovarian endometrioma in a meta-analysis. The odds for clinical pregnancy were not affected significantly in patients with ovarian endometrioma compared with controls, with an overall odds ratio of 1.07 from three studies. The overall pregnancy rate was similar with an estimated odds ratio of 1.17. Decreased ovarian responsiveness to ovarian stimulation in patients with ovarian endometrioma may be due to a reduced number of follicles in these patients compared with controls ($P=0.002$).¹⁷ Suzuki et al investigated the effect of endometriosis and the presence of an ovarian endometrioma on outcomes of IVF. Endometriosis affects oocyte number but not embryo quality or pregnancy outcome, irrespective of the presence of an ovarian endometrioma.¹⁸ dos Reis et al showed that the presence of endometrioma during IVF causes a worsening of oocyte fertilization and embryo cleavage but does not affect the pregnancy rate per transfer.¹⁹ Al-Azemi et al characterized reduced ovarian response, which required higher doses of gonadotropin treatment in women with endometriomas.²⁰ Somigliana et al reported that the presence of ovarian endometriomas is associated with a reduced responsiveness to gonadotropins. In their study, the numbers of codominant follicles in the intact and affected ovaries were 4.0 ± 2.2 and 3.0 ± 1.7 , respectively ($p=.01$). This difference corresponded to a mean reduction of 25%.²¹ Dlugi et al suggested that the presence of an ovarian endometrioma has an adverse effect on IVF outcome and suggested that patients with ovarian endometriomas should have them removed prior to undergoing IVF.²²

Treatment of Endometrioma in Infertile Women

Various approaches have been used to achieve conception in infertile women, including expectant management, cystectomy, medical therapy, controlled ovarian hyperstimulation (COH), and assisted reproductive technologies (ART). In a randomized controlled study, infertile women with endometriosis were randomized to receive either IVF or expectant management. None of the women in the expectant management group became pregnant. Pregnancy rate was 33% in the IVF group.²³ Ovarian endometriomas do not respond well to medical treatment with danazol or LH-releasing hormone agonists.²⁴ Therefore, surgical therapy is most frequently chosen for endometrioma because medical therapy alone is insufficient.²⁵ Kennedy et al recommend that histology should be obtained to exclude malignancy in cases of endometrioma of more than 3 cm diameter and cystectomy is generally used for endometriomas of more than 3 cm in diameter before ART.²⁶

Ovarian Cystectomy and Ovarian Reserve

The impact of cystectomy, the most common surgical procedure used in the treatment of endometrioma, on IVF outcome and ovarian reserve are debatable. Loo et al evaluated the effect of laparoscopic ovarian cystectomy for endometrioma on the clinical outcome of IVF treatment. They concluded that women who received ovarian cystectomy for endometriomas have fewer oocytes harvested during IVF treatment. However, their chance of pregnancy was comparable to patients with tubal problems who underwent IVF treatment.²⁷ Marconi et al reported that laparoscopic cystectomy for endometriomas is an appropriate treatment since it did not negatively affect the ovarian response for IVF-ET.²⁸ Loh et al investigated the follicular response of ovaries after laparoscopic ovarian cystectomy for endometriotic cysts. Postcystectomy ovaries showed reduced follicular response in natural and clomiphene citrate-stimulated cycles for women < 35 years of age. Postcystectomy ovaries produced a comparable number of follicles as normal ovaries when stimulated with gonadotropins.²⁹ Yazbeck et al investigated the follicular response to COH in IVF-ET cycles after laparoscopic ovarian cystectomy for large endometriomas. Ovarian response was reduced during IVF-ET cycles in patients with a history of severe endometriosis and laparoscopic excision of endometriomas compared to women with mild or minimal endometriosis without ovarian surgery.³⁰ In a retrospective study, ovarian response during IVF cycles after laparoscopic ovarian cystectomy for endometriotic cysts >3 cm was investigated. The number of oocytes and embryos obtained was not significantly decreased by laparoscopic cystectomy, suggesting that in experienced hands this procedure may be a valuable surgical tool for the treatment of large ovarian endometriomas.³¹ Esinler et al studied the impact of prior unilateral or bilateral endometrioma cystectomy on COH and ICSI outcome. The mean number of oocytes, metaphase II oocytes, and two-

pronucleated oocytes were significantly lower in the bilateral cystectomy group compared to the unilateral cystectomy and control groups. However, all other parameters, including fertilization rate, the mean number of embryos transferred, the mean number of grade 1 embryos transferred, the clinical pregnancy rate per embryo transfer, and implantation rate, were comparable among the groups. They reported that laparoscopic endometrioma cystectomy reduced the ovarian reserve. However, diminished ovarian reserve does not translate into impaired pregnancy outcome.³² Demiroglu et al investigated the effect of conservative surgery of ovarian endometriomas before an ICSI cycle. The patients were prospectively randomized into two groups; group I underwent conservative ovarian surgery before the ICSI cycle and group II underwent the ICSI cycle directly. They reported that ovarian surgery resulted in longer stimulation, higher FSH requirement and lower oocyte number, but fertilization, pregnancy and implantation rates did not differ between the groups.³³ Ho et al reported that surgery for ovarian endometrioma may damage ovarian reserve. It potentially results in poor ovarian response to COH, compared to the response of the contralateral normal ovary in the same individual.³⁴ Garcia-Velasco et al investigated whether conservative surgery on ovarian endometriomas before an IVF cycle improves fertility outcomes. Conservative surgical treatment of ovarian endometriomas in symptomatic women did not impair IVF or intracytoplasmic sperm injection success rates. They concluded that proceeding directly to COH in women with asymptomatic ovarian endometriomas might reduce the time to pregnancy, the costs of treatment, and the hypothetical complications of laparoscopic surgery.³⁵ In the other study, the implantation and clinical pregnancy rates, COH with both GnRH antagonist and GnRH-a protocols may be equally effective in patients with mild-to-moderate endometriosis and endometrioma who did and did not undergo ovarian surgery.³⁶

Alternative Surgical Approaches For Endometriomas

The effects of a few surgical techniques to treat endometriomas on fertility and recurrence were compared. The absence of a thickened capsule around the endometrioma makes it difficult to excise the wall of the endometrioma and may result in the loss of viable ovarian cortex during ovarian cystectomy. Therefore, laparoscopic fenestration of the endometrioma (removal of at least 2 cm of the cyst wall) followed by destruction with coagulation of the lining of the endometrioma appears to be the ideal surgical method of treatment. Hemmings et al reported that the laparoscopic fenestration and coagulation with bipolar cautery of ovarian endometriomas was associated with faster conception and did not have a higher recurrence rate compared with ovarian cystectomy over a 3-year follow-up period.³⁷ Wyns et al reported that the theoretical risk of loss of ovarian cortex when treating endometriotic cysts can be eliminated by the technique of vaporization of the

internal wall of the endometrioma.³⁸ Fedele et al compared the functional ovarian damage associated with the use of bipolar coagulation versus ovarian suture after laparoscopic excision of ovarian endometriomas in patients with a solitary ovary. Their results suggested that bipolar electrocoagulation of the ovarian parenchyma after laparoscopic stripping of an endometriotic ovarian cyst adversely affects ovarian function.³⁹ Donnez et al investigated the management of large endometriomas in a series of 814 patients. Combined therapy using gonadotrophin-releasing hormone agonist (GnRHa) and carbon dioxide laser laparoscopy was proposed. Drainage and GnRHa for 12 weeks provoked a reduction of the endometrioma size up to 50% of the initial value. After vaporization of the internal wall, a cumulative pregnancy of 51% after 1 year was achieved. A recurrence rate of 8% was observed for a follow-up of 2-11 years.⁴⁰ Alborzi et al determined the difference between two laparoscopic methods for the management of endometriomas with regard to recurrence of signs, symptoms and pregnancy rate. Patients were randomly divided into two groups; one group underwent cystectomy (group 1), and fenestration and coagulation were performed for the other (group 2). The recurrence of symptoms, such as pelvic pain and dysmenorrhea, was 15.8% in group 1 and 56.7% in group 2 after 2 years. The rate of reoperation was 5.8% in group 1 and 22.9% in group 2 and these differences were statistically significant. The cumulative pregnancy rate was significantly higher in group 1 (59.4%) than in group 2 (23.3%) at 1-year follow-up. They concluded that laparoscopic cystectomy of endometriomas is a better choice than fenestration and coagulation.⁴¹ Beretta et al reported that for the treatment of ovarian endometriomas, a better outcome with a similar rate of complications is achieved with laparoscopic cystectomy than with drainage and coagulation.⁴² Saleh et al found that the laparoscopic excision of ovarian endometriomas is associated with a lower reoperation rate than that of fenestration. The reoperation rate after fenestration is independent of the size of the endometrioma and the age of the patient. However, after excision, the reoperation rate is higher in those with larger cysts.⁴³ Takuma et al attempted to identify the optimal laparoscopic procedures in laparoscopic treatment of ovarian-endometrioma-associated infertility. Among cases in which patients received no IVF-ET after the laparoscopic treatment, the pregnancy rate after complete cystectomy of endometriomas was statistically lower than that after fenestration with electrocoagulation of the cyst wall. Among cases in which patients received IVF-ET, there was no difference in ovarian response between patients that had complete cystectomy and fenestration with electrocoagulation of the cyst wall. However, the pregnancy rate in patients who had aspiration alone was statistically lower than that in patients who had aspiration followed by ethanol fixation. Thus, it appears that for patients who do not require follow-up IVF-ET, fenestration with elec-

trocoagulation of the cyst wall is suitable, whereas for patients who need follow-up IVF-ET, ethanol fixation may be a better choice.⁴⁴ In the other study, a similar IVF-ET outcome was observed in patients with endometriosis after ablation of endometriomas compared to women with tubal factors. Endometrioma surgery by internal wall vaporization did not impair IVF outcome. The clinical pregnancy rate was respectively 37.4% and 34.6% in the endometriosis group and the control group.⁴⁵

Simple drainage of endometriomas has been shown to be inadequate because of the high incidence of recurrence.⁴⁶ Pabuccu et al investigated whether aspiration of ovarian endometriomas before COH improves ICSI outcomes. In their study, all patients with endometriomas had significantly lower numbers of MII oocytes compared with those in patients with tubal factor infertility. They proposed that aspiration of endometriomas before COH neither reduces the amount of gonadotropins nor increases the number of follicles >17 mm, the number of MII oocytes retrieved, the implantation rates, or the clinical pregnancy rates.⁴⁷ In a retrospective study, Isaacs et al reported that the aspiration of an endometrioma at the time of oocyte retrieval has no adverse effect on IVF outcome.⁴⁸ Sukanuma et al investigated that to determine what pretreatment should be performed for ovarian endometrial cyst before IVF-ET, they analyzed IVF outcomes with or without pretreatment in patients with endometrioma. Infertile women with endometrioma who underwent IVF-ET were divided into 3 groups, including patients who had received laparotomy or laparoscopy, patients for whom the endometrioma content had been aspirated and treated with or without alcohol fixation, and patients who did not undergo pretreatment. The results showed that pretreatment for endometrioma reduces the number of retrieved oocytes. Although oocyte quality as a rate of mature oocytes was not affected by the presence of an ovarian endometrial cyst, the fertilization rate was improved by cyst aspiration. They proposed that surgical pretreatment is not necessary for ovarian endometrial cyst before IVF-ET, but cyst aspiration may be beneficial after several failed attempts of IVF.⁴⁹ Fisch et al demonstrated sclerotherapy with 5% tetracycline after aspiration of endometrioma. Complete resolution was observed in 75% of patients. An ongoing gestation was identified in 57% patients after IVF treatment.⁵⁰

Endometrioma and Recurrence

Postoperative recurrence is an important concern for women with endometriosis. Tinkanen et al investigated whether operative treatment of recurrent ovarian endometriosis improves the prognosis of IVF. In their retrospective analysis of one hundred endometriosis patients admitted for IVF treatment, forty-five patients had an ovarian endometrioma during IVF treatment, 36 of the cases being recurrences after

a previous operation. Fifty-five patients had ovarian endometriomas operated without recurrence. The patients with ovarian endometriosis had more embryos (mean 3.9) than women without endometriomas (mean 2.8) ($p < 0.05$) and the respective pregnancy rates per IVF cycle were 38% and 22%. Patients with endometriomas had a live birth rate of 27% compared with 20% in women with no endometriomas. They concluded that the presence of a small endometrioma does not reduce the success of IVF treatment.⁵¹ Fedele et al indicated that 60 months after laparoscopic excision of ovarian endometriomas, the cumulative recurrence rate of moderate to severe pain symptoms and the recurrence rate of endometriotic cysts in the same ovary as assessed by transvaginal sonography are about 20%.⁵² Kikuchi et al observed the clinical course of patients who underwent laparoscopic cystectomy using transvaginal ultrasonography. They reported that young age and severe endometriosis appeared to be the factors associated with high recurrence risk. They suggested that recurring ovarian endometriomas probably include cysts occurring spontaneously and those recurring from the cyst residues in the lesions where cystectomy has been performed.⁵³ Koga et al analysed risk factors that influence the recurrence of endometrioma after laparoscopic excision. Recurrence was defined as the presence of endometrioma more than 2 cm in size, detected by ultrasonography within 2 years of surgery. The overall rate of recurrence was 30.4%. Significant factors that were independently associated with higher recurrence were previous medical treatment of endometriosis [odds ratio (OR) = 2.324] and larger diameter of the largest cyst (OR = 1.182). Post-operative pregnancy was associated with lower recurrence (OR = 0.292). They concluded that previous medical treatment of endometriosis or large cyst size was a significant factor that was associated with higher recurrence of the disease. Post-operative pregnancy was a favourable prognostic factor.⁵⁴ Exacoustos et al evaluated the role of transvaginal sonography (TVS) in the management of recurrent endometriomas and wanted to establish ultrasonographic criteria that would direct the therapy toward additional surgery versus medical or expectant management. They concluded that recurrent endometriomas, as detected by TVS, can remain asymptomatic and do not necessarily progress in size with or without medical treatment. The decision to reoperate depends less on the endometrioma's size than on symptoms, in particular severe pain, and failure of medical treatment.⁵⁵

Endometrioma and Adjuvant Therapy

The effect of adjuvant therapy on the fertility and recurrence in women with endometriosis was studied. Lin et al determined whether postoperative adjuvant therapy for endometriosis is effective in improving reproductive outcome. The adjuvant therapies included danazol, gonadotropin releasing hormone analogues, progestins, oral contraceptives, and mixed treatment. Their results suggested that postoperative

adjuvant therapy is ineffective in improving reproductive outcome in patients with either early (minimal or mild) or advanced (moderate and severe) endometriosis.⁵⁶ Montanino et al investigated thirty-six women with ultrasonographic diagnosis of ovarian endometrioma (bilateral in nine of them), who have been treated laparoscopically. After the surgical procedure, the patients were assigned to one of the following regimes: Gn-RH-a for 3 months, oral contraceptives if they wanted to avoid pregnancy, or nothing. The follow-up consisted of 1-3-6-12 months ultrasound. The first recurrences were observed at the 6-month ultrasound with an overall recurrence rate after 12 months of 11%. Improvement of pain symptoms occurred in 87% of the patients and the fertility rate was 45%.⁵⁷ Muzii et al reported that postoperative administration of low-dose cyclic oral contraceptives does not significantly affect the long-term recurrence rate of endometriosis after surgical treatment.⁵⁸ Kim et al suggested that immunotherapy with corticosteroids could improve the clinical pregnancy rate in endometriosis patients undergoing IVF-ET and may be more effective in patients with positive autoantibodies.⁵⁹

Aspiration of Endometrioma and Increased Risk of Infection in Infertile Women

Endometriomas can be possible sources of infection in IVF treatments. During a 6-year period Moini et al studied 5958 transvaginal ultrasound-guided oocyte retrievals which resulted in 10 cases of acute pelvic inflammatory disease (0.12%). Eight of the 10 patients were diagnosed as infertile because of endometriosis. Two patients had mild ovarian, three had stage III, and two had stage IV endometriosis. One patient had a 3–4 cm ovarian endometrioma. Their observation supports that endometriosis can raise the risk of pelvic inflammatory disease after oocyte retrieval. They concluded that more vigorous antibiotic prophylaxis and better vaginal preparation are recommended when oocyte pickup is performed in patients with endometriosis.⁶⁰ Tsai et al suggested that vaginal douching with aqueous povidone iodine followed by normal saline irrigation immediately before oocyte retrieval is effective in preventing the pelvic infection without compromising the outcome of IVF treatment.⁶¹ Younis et al reported that severe endometriosis with ovarian endometrioma seems to be a significant risk factor for pelvic abscess development, following transvaginal oocyte pick-up for IVF-ET. Prophylactic IV cefazolin does not seem to prevent this complication. They concluded that late manifestation of pelvic abscess supports the notion that the presence of old blood in an endometrioma provides a culture medium for bacteria to grow slowly after transvaginal inoculation.⁶²

The Clinical Follow-up of Endometriomas

The clinical follow-up of endometriomas is a popular but complicated topic. Alcazar et al assessed whether a correlation

exists between angiogenesis in ovarian endometrioma with the presence of pelvic pain in a prospective study. They concluded that vascularization of ovarian endometriomas evaluated by transvaginal color Doppler and microvessel density is higher in patients who present with pelvic pain than in asymptomatic patients. This could be an indicator of the activity of endometriosis.⁶³ Yoshida et al evaluated the effects of laparoscopic surgery on the symptoms associated with ovarian endometrioma. They examined serum interleukin-6 (IL-6) concentrations in patients with endometrioma. Ninety-two patients who underwent laparoscopic surgery for ovarian endometrioma were enrolled in their study. The mean duration of follow-up was 27.6 months. Transvaginal ultrasound examinations revealed a recurrence of endometrioma in 13% of the cases. Follicular growth was preserved in 94%, and the pregnancy rate was 43%. IL-6 was significantly higher in patients with endometrioma than in those without endometriosis at the time of diagnosis. The mean serum IL-6 concentration significantly decreased after the operation. They concluded that laparoscopic surgery is effective for alleviating pain and preserving fertility in patients with endometrioma. Measurements of serum IL-6 concentrations may be useful for the management of endometrioma.⁶⁴ Vicino et al studied preoperative predictions of follicular loss after laparoscopic cystectomy of ovarian endometriomas. They concluded that serum levels of CA 125 represent a useful parameter to predict follicular loss before surgery.⁶⁵

In conclusion, cystectomy combined with ART seems to be an effective approach to treating women with endometriomas greater than 3 cm. However, the reduced ovarian reserve caused by the surgical excision of ovarian endometriomas is of great concern.^{27,29,30,32–34} A probability of malignant transformation of endometriomas must not be disregarded.^{66,67} Prospective randomized controlled trials are needed to assess whether surgical treatment versus no surgical treatment improves pregnancy outcomes in women with ovarian endometrioma undergoing IVF.

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