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REVIEW ARTICLE

Clinical management of endometriosis-associated infertility

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Abstract Endometriosis is a common chronic benign disease that affects reproductive age women and causes chronic pelvic pain and infertility. Despite its prevalence, the exact mechanisms of the pathogenesis of endometriosis-associated infertility are unknown, and precise standards of management have not yet been established. Medical and surgical treatments for endometriosis have different effects on the chance of conception, either spontaneously or via assisted reproductive technologies (ART). In this manuscript, we review the literature from years 1979 to 2015 to report on the proposed mechanism of endometriosis-associated infertility, the staging system of endometriosis for pregnancy outcomes and the current management of patients with endometriosis-associated infertility.

Keywords Assisted reproductive technologies ·
Endometrioma · In vitro fertilization · Staging · Treatment

Introduction

Endometriosis, a common estrogen-dependent gynecological disorder, affects 10 % of reproductive aged women and causes pelvic pain and infertility. It is defined as the presence of endometrial-like tissue (glands and stroma) outside the uterus [1]. The ovary, the most common site of endometriosis, may have unilateral or bilateral involvement [2].

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Prevalence of endometriosis has increased up to 50 % in women with infertility [3]. Women with endometriosis have a low monthly fecundity rate (MFR) compared with the MFR in fertile controls. Monthly fecundity is 0.02–0.10 in infertile women with endometriosis, while fecundity ranges from 0.15 to 0.20 per month in normal couples [4]. The presence of endometriosis may negatively affect both the spontaneous chance of conception [5, 6] and in vitro fertilization (IVF) pregnancy rates when compared with those of women with unexplained infertility or tubal factor controls [7]. The hypothesis that endometriosis causes infertility is not fully understood. Several mechanisms have been proposed to link the association between endometriosis and infertility. (Table 1)

Pathophysiology of endometriosis-associated infertility

Ovarian-tubal dysfunction

Anatomical distortion of ovary and tube

In patients with moderate to severe endometriosis, pelvic adhesion involving ovaries and tubes may impair oocyte release from the ovary, inhibit tubal ovum pick up or ovum transport, and/or block sperm transfer into the fallopian tube [8]. By using hysterosalpingoscintography (HSSG), patients with endometriosis showed a significant reduction in physiologic utero-tubal transport capacity compared with controls [9].

Ovulation failure

Mechanisms that facilitate normal ovulation are impaired in women with endometriosis. Prolactin (PRL) levels were

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Table 1 Pathophysiology of endometriosis-associated infertility

1. Ovarian-tubal dysfunction
Anatomical distortion of ovary and tube
Ovulation failure
Hyperprolactinemia
LUF (luteinized un-ruptured follicle)
Abnormal follicle development
Reduced follicle development
Decreased estrogen production
Increased apoptosis of granulosa cells
2. Immunological disorder
Anti-endometrial antibody
3. Abnormal peritoneal environment
Increased peritoneal fluids and high concentrations of cytokines
Activated macrophage
4. Dysregulated endometrial function

significantly higher in infertile women with endometriosis when compared with those of women without endometriosis [10]. An elevated level of PRL prevents luteinizing hormone (LH) pulsatility and interferes with hypothalamic function by blocking estrogen receptors, thus producing anovulation [11]. Another cause of ovulation failure is luteinized unruptured follicle syndrome (LUFs). LUF occurs when oocytes become trapped in a luteinizing corpus hemorrhagicum, which is common in patients with mild or minimal endometriosis. This may be one of the causes of endometriosis-associated infertility [12].

Abnormal follicle development

The number of preovulatory follicles, follicular growth, dominant follicle size, and follicular estradiol concentrations are reduced in the ovaries of endometriosis patients [13–16]. Further, interleukin-6 (IL-6) and its soluble receptor, which are present in the peritoneal fluid of women with endometriosis [17], significantly decreased aromatase gene expression as well as estrogen production via the MAPK signal pathway in human granulosa cells. This may lead to a suboptimum follicular environment [18]. Women with endometriosis also have a higher incidence of apoptotic cells in their granulosa cells, indicating poor oocyte quality [19]. Collectively, these data provide evidence of mechanisms that may cause altered follicular development and ovulatory dysfunction in endometriosis.

Immunological disorder

Aberrant immunological mechanism including production of autoantibodies might be a potent pathophysiological mechanism of endometriosis-associated infertility.

Gleicher et al. (1987) [20] reported the presence of IgG, IgM, and IgA autoantibodies directed against cell-derived antigens in women with endometriosis. In a study by Gajbhiye et al. (2008), both IgG and IgM anti-endometrial antibodies (AEA) could be detected in almost 60 % of patients with endometriosis, and it has been suggested that AEAs might be partially responsible for failure of implantation and decreased endometrial receptivity leading to infertility [21].

Abnormal peritoneal environment

Increased peritoneal fluids and high concentration of cytokines

The volume of peritoneal fluid (PF) is significantly elevated in infertile women with endometriosis compared with those without endometriosis [22]. It has been demonstrated that incubation with PF from women with moderate or severe endometriosis caused approximately 40, 50, and 80 % declines in sperm motility [23]. Moreover, PF in patients with endometriosis has a detrimental action on the sperm acrosome reaction [24], mouse embryo growth [25], sperm binding to the zona pellucida [26], and ciliary action in the human Fallopian tube [27]. Studies demonstrated that endometriotic implants secrete estradiol and progesterone, which attract macrophages, vascular endothelial growth factor (VEGF), and interleukin-8 (IL-8) [28, 29]. An increased number of activated macrophages also secrete various local products, such as growth factors, and inflammatory cytokines, such as IL-1, IL-6, and tumor necrosis factor alpha (TNFα), and angiogenic cytokines, such as IL-8 and VEGF, which are increased in concentration in PF of patients with endometriosis. We also reported that endometriotic stromal cells produced a significant amount of cytokines [30], such as IL-6 and IL-8 [31]. Adding IL-6 into the culture media reduced mouse embryo development [22, 24] and sperm motility [32]. Thus, an inflammatory state exists, impairing fertility by having a toxic effect on gametes and embryos and impairing tubal motility [17, 30–32]. Increased IL-6 associated with endometriosis may not only reduce sperm motility, but may also affect the metaphase-II oocyte spindle by impairing the microtubule and chromosomal structure, contributing to infertility [33] (Fig. 1).

Activated macrophage

Activated macrophages may contribute to an unfavorable milieu by producing various kinds of inflammatory cytokines. In the meantime, the increased number of macrophages and their sperm phagocytosis can disturb ovum fertilization by causing damage to oocytes or zygotes and

Fig. 1 Association of
Interleukin-6 and infertility
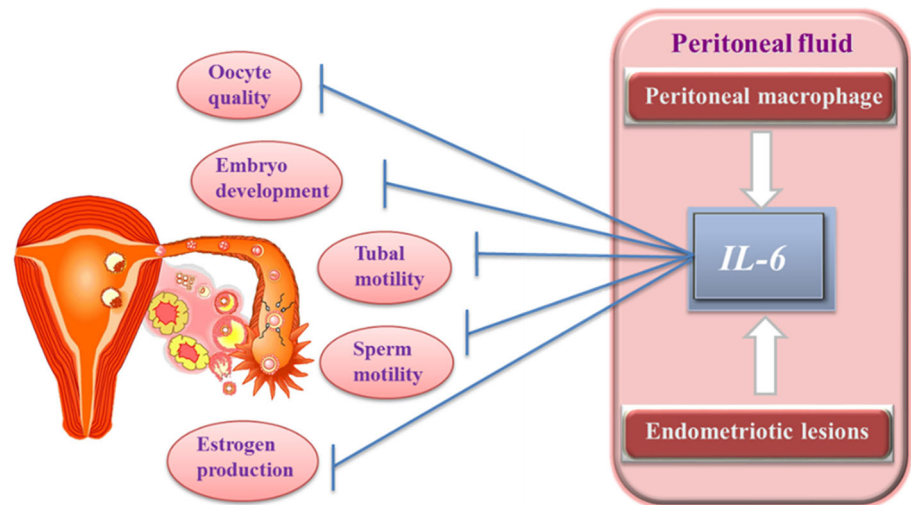
inducing infertility [34]. Interestingly, it has been found that both endometriotic cells and macrophages are responsible for the high concentration of reactive oxygen species in PF of women with endometriosis [35]. These reactive oxygen and nitrogen species may negatively affect embryo implantation and sperm viability in the peritoneal microenvironment. The effects of free radicals on oocytes, sperm, and embryos have also been implicated in poor reproductive outcomes in assisted reproductive technologies (ART) [36].

Dysregulated endometrial function

Several studies have suggested that implantation is not affected in patients with endometriosis. The presence of severe endometriosis [37] or bilateral ovarian endometrioma [36] does not lower implantation or pregnancy rates. Infertility in these patients is not related to an endometrial environment affecting endometrial receptivity [37, 38].

However, endometrial receptivity, which allows the developing embryo to implant, is a complex process involving regulation by hormones, cytokines, adhesion molecules, and other factors [39]. Defective ''window of implantation'' due to the inadequate expression of various endometrial receptivity molecules may occur in the endometrium of women with endometriosis [40]. Integrins were proposed to be sensitive indicators of the endometrial receptive state. The expression of αvβ3 integrin occurs during the window of implantation in healthy controls and the absence of it is associated with poor reproductive outcomes [41]. Reduced endometrial expression of the αvβ integrin, which may interfere with embryo attachment during the time of implantation, has been described in some women with endometriosis [42, 43] and with unexplained infertility [44]. Moreover, decreased expression of four biomarkers of implantation, such as glycodelin A,

osteopontin, lysophosphatidic acid receptor 3, and HOXA10, indicate impaired endometrial receptivity in patients with endometriosis [45]. Some women with endometriosis also exhibit very low levels of an enzyme involved in the synthesis of the endometrial ligand for L-selectin (a protein that coats the trophoblast on the surface of the blastocyst) [46].

New scoring system for infertility

The American Fertility Society (AFS) (now the American Society for Reproductive Medicine, or ASRM) proposed a classification system in 1979 [47], which was modified in 1985 [48]; it classifies the disease as minimal (Stage I), mild (Stage II), moderate (Stage III) or severe (Stage IV). Currently, revised American Society of Reproductive Medicine Classification (r-ASRM classification) is the most widely used staging system of endometriosis. Unfortunately, it has a limited predictive ability for pregnancy outcome after surgery [49, 50]. In 2002, Fujishita et al. modified the r-AFS classification by adding TOP score (fallopian tubes, ovaries, peritoneum and other factors) and assessed the fertility rate. According to TOP classification, the pregnancy rate was mostly affected by tubal condition, and they suggested that individual tubal condition may have a clinically predictive value in assessing the reproductive outcome of women with endometriosis. However, they did not consider the factors affecting pregnancy, e.g., patient age [50].

The new staging system, endometriosis fertility index (EFI), was developed by Adamson and Pasta in 2010 to predict fecundity after endometriosis surgery. EFI is a scoring system that not only assesses the historical factors at the time of surgery (age, duration of infertility, and pregnancy history), but also evaluates least-function (LF)

score (functional score of fallopian tubes, fimbriae, and ovaries bilaterally) and extent of endometriosis (r-ASRM endometriosis lesion score and total r-ASRM score) [51]. Tomassetti C et al. [52] also suggested that EFI could be useful as a clinical tool for counseling patients with endometriosis after surgery about their fertility prognosis and eventual need for fertility treatment.

Wang et al. [53] were the first to compare the predictive value of the EFI score with the r-ASRM classification in the same population of women with endometriosis who had received IVF treatment. They suggested that neither the future of pregnancy nor IVF outcome could be predicted by r-ASRM classification. Unlike r-ASRM classification, EFI may have more predictive power, since it includes the assessment of reproductive factors such as age, duration of infertility, pregnancy history, and reproductive potential of pelvic organs by LF score. The clinical pregnancy rate was higher in patients with EFI ≥ 6 score than in those with EFI ≤ 5 score, providing a valuable reference to predict pregnancy outcome after surgery in women with endometriosis.

Evidence of infertility treatment of endometriosis-associated infertility

COH–IUI

Some randomized, controlled trials have shown that ovulation induction and superovulation (SO) with and without intrauterine insemination (IUI) increases fertility rates in patients without distorted anatomy [54, 55]. There is evidence that controlled ovarian hyperstimulation (COH)–IUI seems to be better than expected management in infertile women with endometriosis. In a study by Tummon et al., treatment with COH–IUI had a better outcome than no treatment for infertility associated with minimal or mild endometriosis. Live births followed 14 of 127 (11 %) superovulation and IUI cycles and four of 184 (2 %) no-treatment cycles [55].

Notably, most of the studies were assessed in patients with minimal-mild endometriosis, and there is insufficient evidence to support SO/IUI in patients with severe endometriosis. Gandhi et al. [56] demonstrated that COH+IUI cumulative fertility rate was threefold lower in patients with surgically treated stage III/IV endometriosis. However, according to the European Society of Human Reproduction and Embryology (ESHRE) recommended guideline (2014) [57], IUI is only recommended in sub-fertile women with minimal-to-mild endometriosis, and IUI with controlled ovarian stimulation should be considered within 6 months following surgery in the treatment of infertile women with AFS/ASRM stage I/II endometriosis.

In vitro fertilization (IVF)

IVF is currently the most effective treatment of endometriosis-associated infertility [58]. It is still uncertain as to how much endometriosis influences IVF success rates. A meta-analysis by Barnhart et al. (2002), including publications from 1983 to 1998, concluded that women with endometriosis have lower pregnancy rates with IVF than those with tubal infertility (OR 0.56; 95 % CI, 0.44 to 0.70) [59]. However, the limitation in their meta-analysis is that they did not distinguish between women who had received previous medical and surgical interventions, limiting the applicability of their findings. Similarly, another review by Harb et al. [60] addressing this issue demonstrated that the presence of stage III/IV endometriosis is associated with poor implantation and clinical pregnancy rates in women undergoing IVF treatment.

Interestingly, in contrast to these studies, The Society of Assisted Reproductive Technology reported that over 1400 live births resulted from 5600 IVF cycles in patients with endometriosis. Average delivery rate per retrieval of patients undergoing IVF was 39.1 % in women with endometriosis, compared with 33.2 % in women with all causes of infertility [58]. Barbosa et al. [61] also concluded that women with endometriosis undergoing ART have the same chance of achieving clinical pregnancy and live birth as do women with other causes of infertility. They observed the ART outcomes (live birth [LB], clinical pregnancy [CP], miscarriage and number of oocytes retrieved) in women with endometriosis in different stages and those without endometriosis. In this review, the probability of achieving LB and CP were not relevantly different between women with endometriosis and without endometriosis [LB, RR = 0.99 (95 % CI, 0.92–1.06); CP, RR = 0.95 (95 % CI, 0.89–1.02); miscarriage, RR = 1.31 (95 % CI, 1.07–1.59); number of oocytes retrieved, MD = –1.56 (95 % CI, –2.05 to –1.08)]. In addition, women with stage I/II or III/IV endometriosis had comparable LB and CP rates compared with women with other causes of infertility. No relevant difference was observed in the chance of achieving LB and CP following ART when comparing stage III/IV with Stage I/II endometriosis. [LB, RR = 0.94 (95 % CI, 0.80–1.11); CP, RR = 0.90 (95 % CI, 0.82–1.00); miscarriage, RR = 0.99 (95 % CI, 0.73–1.36); number of oocytes retrieved, MD = –1.03 (95 % CI, –1.67 to –0.39).

A recent study by Hamdan et al. (2015) [62] also evaluated whether the presence and/or severity of endometriosis affects the main ART outcomes, by searching the published articles from 1980 to 2014 in MEDLINE, PubMed, ClinicalTrials.gov, and Cochrane databases. According to the following results, women with endometriosis who underwent ART were found to have the
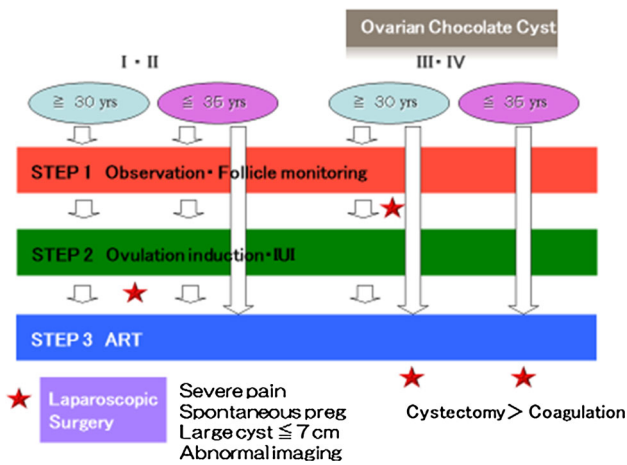
Fig. 2 Treatment strategies for women with endometriosis-associated infertility

same chance of achieving LB and CP as women without endometriosis. Compared with women with no endometriosis, women with endometriosis undertaking IVF/ICSI have a similar LB rate per woman (OR 0.94, 95 % CI 0.84–1.06), a lower CP rate per woman (OR 0.78, 95 % CI 0.65–0.94), a lower mean number of oocyte retrieved per cycle (MD −1.98, 95 % CI −2.87 to −1.09) and a similar miscarriage rate per woman (OR 1.26, 95 % CI 0.92–1.70). However, in this review, following ART, women with severe endometriosis showed lower LB, CP rates, and lower mean number of oocytes retrieved when compared with women without endometriosis, suggesting that their ovarian reserve may be diminished before IVF/ICSI. On the basis of these findings, patients with endometriosis can be referred for early infertility treatment, including IVF, to increase the chances of conception. Direct IVF should be considered if the women's age is more than 35 years and duration of infertility is long (Fig. 2).

Surgical or medical management of endometriosis-associated infertility

Several studies assessed whether ovulation suppression agents, such as danazol, progestins, and oral contraceptives, could be affective to improve pregnancy outcomes in subfertile women with endometriosis [63]. However, no evidence was found that suppressing ovarian function with hormone therapy improves fertility in the treatment of endometriosis [57, 63]. In addition, there was insufficient evidence to support that the use of hormonal suppression therapy for endometriosis before or after surgery is more effective than surgery alone [64]. In 2010, Matsuzaki et al. [65] identified the risk factors for the removal of normal

ovarian tissue during laparoscopic cystectomy for endometriosis, and suggested that pre-operative medical treatment might predispose to the risk of removing normal ovarian tissue.

In patients with endometriosis-related infertility, the objective of the surgery is to restore the anatomical relationship and preserve the function of pelvic organs. To establish a favorable pelvic environment, a skilled surgeon must perform a surgical procedure [66]. Duffy et al. (2014) reviewed the effectiveness of laparoscopic surgery in subfertility associated with endometriosis [67]. Laparoscopic removal of minimal-mild stage endometriosis not only reduces pain, but also increases spontaneous pregnancy rate when compared with diagnostic laparoscopy alone. In infertile women with ovarian endometrioma, operative laparoscopy instead of expectant management may increase spontaneous pregnancy rates [68]. There are various conservative surgical treatments, such as cyst wall ablation, cystectomy, or USG-guided aspiration for ovarian chocolate cyst. Currently, laparoscopic excision remains as a favored surgical approach to the management of ovarian endometrioma. A Cochrane review concluded that excisional surgery for the endometrioma capsule should be done instead of drainage and electrocoagulation of the endometrioma wall to increase post-operative spontaneous pregnancy rate [69]. However, inadvertent removal of normal ovarian tissues and recurrence became clinical problems in the surgical management of ovarian endometriosis, as recurrence rate of ovarian endometrioma was significantly increased in women with previous surgery for endometriosis during follow-up [70–74]. It is important to note that the ESHRE (2014) [57] guideline recommended that clinicians carefully consider whether to perform surgery if the woman has had previous ovarian surgery, because of the significant damage to ovarian function after repeated surgery.

Regarding medical or surgical treatment prior to ART, the role of medical treatment before IVF was studied by Sallam et al. [75]. They reported that pre-treatment with gonadotrophin-releasing hormone (GnRH) agonists at least 3 months prior to IVF increased the pregnancy rate. Moreover, pregnancy outcomes after IVF-ET using either GnRH agonist or GnRH antagonist were found to be equally effective [76]. With respect to the effectiveness of surgery in women with minimal to mild endometriosis who underwent laparoscopic surgery prior to ART, surgical eradication of endometriosis and associated adhesion improved the result of ART outcome, including live birth rate [77]. Therefore, in infertile women with AFS/ASRM stage I/II endometriosis, complete surgical removal of endometriosis may be considered before treatment with ART. However, in infertile women with endometrioma larger than 3 cm, there was insufficient evidence that

Table 2 Guidelines for surgery of endometriosis associated infertility

	ESHRE 2014	ASRM 2012
Stage I/II	Recommended A	Recommended
	Better than diagnostic laproscopy	Small effect
Stage III/IV	Recommended B	Recommended
	Better than expected management	May be beneficial
Post-op medical therapy	Not recommended A	Not recommended
	Not recommended prior to surgery GPP	
Prior to IVF	I/II may be considered C	No evidence of improved pregnancy rate by cystectomy
	No evidence of improvement (3 cm or larger endometrioma) A	
	Only for pain or oocyte PU GPP	
Cases with recurrence	Not described	Not recommended

A meta analysis or multiple RTs (of high quality), *B* meta analysis or multiple RTs (of moderate quality), *C* single randomized trial, large non-randomized trial(s) or case control/cohort studies (of moderate quality), *GPP* (good practice point) based on experts opinion

cystectomy prior to ART treatment improves pregnancy rate [57, 69, 78, 79]. Thus, the effect of surgery before ART in these women is unclear. Recently, excisional surgery for a cyst has been concerned with damage to ovarian reserve [80]. While some reproductive specialists have advised that endometrioma > 3 cm should be treated by cystectomy before ART, others have suggested the damaging effect of surgery on ovarian reserve. Some studies have demonstrated the possible association between the laparoscopic cystectomy and loss of follicles [81, 82]. Damage to the ovary is more severe when an endometrioma > 4 cm in diameter is excised [83].

In a prospective, randomized study by Demirol et al. (2006) [84], ovarian endometrioma cystectomy before IVF even resulted in decreased ovarian response in the ICSI cycle. In the cystectomy group, the total recombinant follicle-stimulating hormone (FSH) dose was significantly higher and the mean number of mature oocytes retrieved was significantly lower, although there was no difference in pregnancy outcomes. A meta-analysis by Benschop et al. [78] also compared the surgery (aspiration or cystectomy) with expectant management in patients with ovarian endometrioma and demonstrated that there were no significant differences in terms of clinical pregnancy, although these reports were conducted in patients with unilateral endometrioma. In a recent report by Streuli et al. [85], findings also suggest that endometrioma per se do not diminish the ovarian response reflected by Anti-Müllerian hormone (AMH) levels, but that alterations seen in women with endometriosis are a deleterious consequence of endometrioma surgery. According to the results of these studies, cystectomy before ART is not recommended in recent guidelines (Table 2).

In contrast to the data on unilateral ovarian endometrioma, despite the use of higher doses of gonadotrophins, the number of follicles, oocytes retrieved, embryos obtained and pregnancy rates were significantly lower in women operated on for bilateral endometrioma [86]. Furthermore, Busacca et al. [87] reported that patients who had been operated on for bilateral endometrioma have a low (2.4 %) but definite risk of premature ovarian failure occurring immediately after surgery. These findings should be taken into account in the decision to operate on endometrioma in women with a desire for future pregnancy.

Treatment strategies for women with endometriosis-associated infertility

Endometriosis among infertile women is increasingly being detected. The decision about which is the most appropriate treatment for women suffering from endometriosis-associated infertility is still controversial. Currently, laparoscopic excisional surgery for ovarian endometrioma remains the gold standard. [57]. However, recurrent endometrioma surgery may be more harmful to the ovarian reserve if compared with endomeriomas operated on for the first time [88], and may have the risk of premature ovarian failure occurring immediately after surgery for bilateral endometriomas [89]. Additionally, AMH level was reduced in women with previous endometrioma surgery, not in women suffering from current ovarian endometrioma who had never had previous endometrioma surgery [85], especially in older patients and in the case of bilateral cysts [89]. High cost and post-operative complications (1.4–7.5 %) are other unfavorable outcomes following surgery [57, 90]. The advantages of surgical treatment include reduction of pain, prevention of the risk of cystic rupture, transvaginal assessment of ovarian follicles, and elimination of the difficulty of ovum pick up (OPU) in ART. Pathological examination also reveals a malignancy rate of 0.7 % [91]. Surgery allows the

assessment of the relationship of the fallopian tube with surrounding adhesion.

However, surgical indications for young patients should be limited if pelvic pain is not severe, and they should be counseled about the potential risks of reduced ovarian function after surgery [57]. For young women who have had previous ovarian surgery and a desire for pregnancy, ovarian reserve should be assessed first, and, if the estimated probability of spontaneous conception is low, immediate ART should be considered [92] since there is a lack of evidence that cystectomy prior to ART treatment improves pregnancy rate in infertile women with endometrioma larger than 3 cm [57] (Fig. 2).

Conclusion

Endometriosis, an enigmatic gynecological disease with poorly understood pathogenesis, can affect fertility at different levels. In endometriosis patients, EFI may have more power to predict the IVF outcome than ASRM classification. However, the dilemma in regard to the best approach to manage endometriosis-associated infertility remains partially unresolved. Before choosing the most appropriate treatment, it is critical for clinicians to consider the severity of clinical symptoms, stage of the disease, age of the patient, infertility duration, and possibility of ART. Clinicians should perform a thorough assessment of ovarian reserve, tubal patency, sperm function, and the uterine cavity before initiating therapy. Indication for surgery for endometrioma should be chosen with caution.

Compliance with ethical standards

Conflict of interest Yin Mon Khine, Fuminori Taniguchi, and Tasuku Harada declare that they have no conflict of interest.

Human/Animal studies This article does not contain any studies with human or animal subjects performed by any of the authors.

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