

Treating Deep Endometriosis in Infertile Patients before Assisted Reproductive Technology

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Abstract

Deep endometriosis (DE) causes infertility and pelvic pain. Surgical management of DE has become a topic of increasing interest in gynecological surgery. In women desirous of pregnancy, optimal management such as surgery versus first-line assisted reproductive technology (ART) for patients with severe endometriosis is strongly debated. Current guidelines and literature including retrospective and prospective studies in English available on DE surgery, infertility, and pregnancy outcomes following surgery were searched in Cochrane Library with DE, DIE, Infertility, “DE surgery and pregnancy outcomes,” and “Deep infiltrating endometriosis and assisted reproduction” as keywords. The purpose was to find evidence to answer the following clinical questions: How does DE affect fertility and pregnancy? What are the possible benefits of primary surgery for DIE before *in vitro* fertilization (IVF)? Several studies have recently concluded that surgical removal of DE nodules might actually have a favorable impact on IVF outcomes. This is in contradiction to European Society of Human Reproduction and Embryology statement which stated that there was no evidence supporting surgical management of DE prior to ART to improve pregnancy rate; several studies have suggested that the surgical removal of DE nodules might actually have a favorable impact on IVF outcomes. Treatment of DE affecting the rectovaginal septum or bowel requires complex surgery with considerable risk of complications. This review article tries to analyze the rationale of surgical treatment of DE before ART. A balance must be struck between exposing the patient to surgical risk and improvement in pain and fertility potential. Decisions should be tailored according to the individual needs of each woman and most importantly on the ability of the surgeons.

Keywords: Deep endometriosis, deep endometriosis excision, deep infiltrating endometriosis, infertility with deep endometriosis

INTRODUCTION

Endometriosis is a heterogeneous, complex, pathobiological benign gynecological disease affecting 10% of women of reproductive age group. It is defined as presence and growth of the endometrium gland and stromal tissue in sites outside the uterine cavity, primarily on the pelvic peritoneum and ovaries.^[1] As surgical intervention is required along with histological evidence to diagnose endometriosis, its true prevalence remains uncertain. The prevalence ranges from 2% to 11% among asymptomatic women, 5%–21% among women hospitalized for pelvic pain, and 5%–50% among infertile women.^[2] The incidence among

Southeast Asian and Japanese women was found to be 15%, which is higher compared to the Western population.^[3]

The umbrella term endometriosis encompasses the entities: superficial endometriosis, ovarian cystic endometriomas, and deep infiltrating endometriosis or deep endometriosis (DE).^[4] DE was described in the early nineties as adenomyosis externa with endometrial glands and stroma in fibromuscular tissue. Because the glandular activity was more in phase with the menstrual cycle at depths >5 mm, DE was defined as

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lesions >5 mm in the peritoneum.^[5] The pathophysiology of DE is however still unclear. With the discovery of the old European literature on uterine bleeding in 5%–10% of the neonates and histologic evidence that the bleeding represents decidual shedding, it is hypothesized that endometrial progenitor cells, implanted in the pelvic cavity after birth, may be at the origin of adolescent and even the occasionally premenarcheal pelvic endometriosis. Endometriosis in the adolescent is characterized by angiogenic and hemorrhagic peritoneal and ovarian lesions. The development of DE at a later age suggests that deep infiltrating endometriosis is a delayed stage of endometriosis. Another hypothesis is that the endometriotic cell has undergone genetic or epigenetic changes and those specific changes determine the development into DE. This is compatible with the hereditary aspects, and with the clonality of deep and cystic ovarian endometriosis. It explains the predisposition and an eventual causal effect by dioxin or radiation. Specific epigenetic changes could explain the various expressions and thus typical, cystic, and DE become three different diseases. Subtle lesions are not a disease until epigenetic changes occur.^[6]

Patients with DE may present with dysmenorrhea, deep dyspareunia, infertility, dyschezia, and chronic pelvic pain. The association of DE with infertility has been debated for the past few decades. But theoretically, it can cause infertility by changing the pelvic milieu due to pelvic adhesions, thus affecting the gamete migration. The distortion of pelvic anatomy and alteration of uterine endometrial receptivity further contributes to infertility.^[7] The diagnosis and management of DE is surgical. Laparoscopy remains the gold standard for diagnosis by visual confirmation of lesions and retrieval of tissue for histological verification. Surgical excision of lesions for pain relief and for women with failed medical management of symptoms remains an established indication.^[8] The controversy however fringes around the need for DE excision to improve fertility outcomes. The recommendation by the European Society of Human Reproduction and Embryology (ESHRE) and European Society of Gynaecological Endoscopy (ESGE) working group in 2014 stated that excision of deep nodules of endometriosis does not improve fertility outcomes.^[9] While the recommendation was based on low evidence resources of few retrospective studies and case series, it began the debate on the futility of such surgeries.

METHODS

We reviewed current literature available on DE surgery, infertility, and pregnancy outcomes following surgery. Retrospective and prospective studies in English were searched in Cochrane Library with DE, DIE, Infertility, “DE surgery and pregnancy outcomes,” and “Deep infiltrating

endometriosis and assisted reproduction” as keywords. Various guidelines on DE including ESHRE, The National Institute for Health and Care Excellence (NICE), and American Society of Reproductive Medicine (ASRM) were also studied by the authors along with various systematic reviews and books. The purpose was to find evidence to answer the following clinical questions: How does DE affect fertility and pregnancy? What are the possible benefits of primary surgery for DE before *in vitro* fertilization (IVF)?

Effect of deep endometriosis on fertility

Endometriosis impairs fertility. There is a reduced monthly fecundity rate (2%–10%) compared with fertile couples (15%–20%).^[10] Endometriosis also impacts assisted reproductive technology (ART) outcomes. In Stage I/II endometriosis there is a 7% reduction in fertilization rates. Implantation rates and clinical pregnancy rates have shown 21% reduction in Stage III/IV endometriosis along with lower oocyte retrieval rate.^[11]

Although DE has been frequently associated with infertility, there is little evidence connecting the disease and infertility. Studies suggest that infertility in women with DE is probably related to the strong association between DE and adhesions, superficial endometriotic implants, ovarian endometriomas, and adenomyosis.^[12] Several anomalies too are presumed to contribute to DE-related infertility such as hormonal function (estrogen and progesterone receptors) and immunological factors, such as peritoneal macrophages, lymphocytes, and natural killer cells. Clinicians would benefit from remembering that a variety of confounding factors interfere with the interpretation of studies when considering the association between infertility and DE. First, there can be an association with other types of endometriotic lesions such as peritoneal and ovarian, which may accompany DE and affect fertility on their own. Stand-alone DE lesions are seldom encountered. Compared to that, connotations with other forms of endometriosis are more frequent. Second, production of inflammatory cytokines and chemokines from superficial peritoneal lesions results in an altered hormonal milieu, increased oxidative stress, and impaired sperm and tubal function.^[13] Endometriomas are also known additionally to interfere with folliculogenesis and result in poor oocyte and embryo quality causing impaired ovarian response and pregnancy rates in IVF.^[14] Adenomyosis, which has a more frequent association with women with DE, than other forms of endometriosis, significantly reduces (68%) the likelihood of pregnancy in women attempting conception after colorectal or rectovaginal surgery for endometriosis.^[15,16] Finally, published data point out that in women with endometriosis, the endometrium itself harbors several anomalies which results in reduced endometrial receptivity and decreased implantation rates.^[13,17] Unfortunately, the relationship between DE and

infertility is rather complex and a final conclusion on the matter yet to be produced.

Surgery for deep endometriosis

The aim of surgery in endometriosis should not only be to remove macroscopic endometriotic implants to prevent disease exacerbation but also to restore normal pelvic anatomy to improve chances of success of IVF. The surgeon should also do adequate intra-operative staging of the extent of the disease and obtain tissue for histopathological disease confirmation. According to the World Endometriosis Society Montpellier Consortium,^[18] strong evidence exists for laparoscopic surgical removal of endometriosis as an effective first-line approach for treating pain related to endometriosis. Laparoscopic surgery for endometriosis should always be undertaken in preference to laparotomy, where possible (strong Good Practice Principles (GPP)). Furthermore, laparoscopic excision (cystectomy) for ovarian endometriomas is preferred where possible to minimize symptom recurrence and endometrioma recurrence (strong).^[19] The consortium also states that with regard to surgery for infertility in women with endometriosis, there exists strong evidence that laparoscopic surgical removal of endometriosis improves fertility in Stage I and II endometriosis. Laparoscopic excision (cystectomy) where possible for endometriomas is preferred to laparoscopic ablation (drainage and coagulation) to enhance fertility (strong). Medical adjunct therapy in conjunction with laparoscopic surgery has not been shown to have fertility benefit (strong).^[18,19]

For DE, indications for surgical intervention include severe pelvic pain unamenable to medical management, obstructive uropathy, symptomatic bowel stenosis, adnexal mass of doubtful nature, and fertility desire. In infertile women with AFS/ASRM Stage III/IV endometriosis, clinicians can consider operative laparoscopy, instead of expectant management, to increase spontaneous pregnancy rates.^[9] This however does not apply for women planning for ART. There are many nonrandomized uncontrolled studies with results varying from a postoperative pregnancy rate of 30%–67% in women having undergone operative laparoscopic treatment for endometriosis. Three high-quality prospective cohort studies showed crude spontaneous pregnancy rates of 57%–69% (moderate endometriosis) and 52%–68% (severe endometriosis) after laparoscopic surgery, which are much higher than the crude spontaneous pregnancy rates of 33% (moderate) and 0% (severe) after expectant management.^[20]

Impact of surgery on the fertility of women with deep endometriosis

DE is a heterogeneous disease. Analysis of the anatomical location of the lesions revealed a multifocal pattern, as 61%

of the women with DE had more than one site simultaneously affected. This makes it more difficult to study possible relationships between pain and anatomical location, or to establish the role of DE on fertility. Furthermore, there is a paucity of data from randomized controlled trials, as the available published studies are case series or uncontrolled studies with many confounding factors such as use of ART and presence of other infertility factors. Natural fecundity in women with endometriosis is rarely evaluated, and except for peritoneal disease, no randomized trials have been carried out to assess the effect of surgery in this setting.^[11]

Douay-Hauser *et al.* published a retrospective case-control study in 2011 comparing fertility outcomes in women undergoing intraperitoneal surgery (Group 1) with extensive surgery (Group 2) for DE.^[21] Among the 34 women in Group 1, 6 became pregnant, compared with 8 of the 41 women who had extensive surgery (12-month cumulative probabilities, 24.8% and 11.4%, respectively, and 24-month cumulative probabilities, 24.8% and 23.2%, respectively; $P = 0.82$). The perioperative surgical complication rate was higher in Group 2 (6/41 vs. 0/34; $P = 0.02$). The study concluded that extensive surgery for intraperitoneal and DE in infertile women does not modify global fertility outcome but is associated with a higher complication rate.

Meanwhile, Brown and Farquhar collected evidence from 17 Cochrane systematic reviews on treatment options for women with pain or subfertility associated with endometriosis using live birth, clinical pregnancy, ongoing pregnancy, miscarriage, and adverse events as primary outcomes.^[22] Out of the seven reviews related to infertility, five described spontaneous pregnancy and two presented ART-related outcomes.^[23,24] Postsurgical medical therapy resulted in no benefits in terms of pregnancy rates, but 3 months of adjuvant treatment with GnRH agonists improved pregnancy rates in women with endometriosis undergoing IVF. Laparoscopic surgery improved live birth and pregnancy rates when compared to diagnostic laparoscopy alone. Excisional surgery resulted in better spontaneous pregnancy rates in the 9–12-month period postsurgery when compared to ablative surgery. Medical treatment apparently did not improve clinical pregnancy rates. A skillful surgeon remained the key factor.

In a retrospective study, Centini *et al.* studied the impact of laparoscopic excision of lesions on DE-related infertility in 115 women. All the surgeries were performed by a single skilled surgeon at a tertiary center.^[25] Evaluation of fertility outcome after laparoscopic treatment of DE by spontaneous conception and by ART correlated with lesion number, size, and location (anterior, posterolateral, pouch of Douglas, and multiple locations). After a mean follow-up of 22 months, the overall pregnancy rate was 54.78%, with a live birth

rate of 42.6%. Among those patients given the chance to conceive spontaneously, the overall pregnancy rate was 60%: 38.5% spontaneously and 21.4% by ART. The removal of multiple lesions was associated with a higher pregnancy rate after surgery. When comparing isolated lesion size and disease location, there was no difference in pregnancy rate. Furthermore, those patients who underwent surgical eradication of the disease for the first time had a higher pregnancy rate (odds ratio, 4.18).

Duffy *et al.* found that laparoscopic surgery was associated with an increased live birth or ongoing pregnancy and clinical pregnancy rates in comparison to diagnostic laparoscopy. However, no conclusions on safety were drawn, as there was insufficient evidence on adverse events.^[26] Varying other studies advocate complete surgical removal of endometriotic lesions to improve fertility,^[27,28] while a few others affirm that extensive surgery for peritoneal endometriosis and DE in infertile women does not improve global fertility outcomes and may be associated with higher complication rates.^[21,29]

Vercellini *et al.*, in their literature review, highlighted that women should be carefully counseled on the real chances of getting pregnant after surgery.^[29,30] They found that pregnancy rates decreased by 15% in individuals who sought spontaneous conception after surgery versus women offered IVF (39% vs. 24%). The time to conception after surgery also plays an important factor which should be considered, as delays have been associated with lower pregnancy and higher relapse rates.

Thus, the effect of surgery on the fertility of women with DE remains unanswered due to the heterogeneous nature of the disease and the lack of adequate trials with enough power and follow-up to study the matter. Decisions should be tailored according to the individual needs of each woman after they are provided with information on the potential benefits, harm, and costs of each treatment alternative.

Benefits of surgery for deep endometriosis before *in vitro* fertilization

According to the guidelines of the ESHRE,^[9] there is limited evidence for performing surgery with the sole objective of increasing live birth rates. The established causes for IVF in cases of infertility associated with endometriosis are distorted pelvic anatomy and impaired tubal function, or in cases of male factor infertility and when other treatments have failed. The main purpose of surgery for women suffering from endometriosis-related infertility ideally revolves around the restoration of normal pelvic anatomical relationships and preservation of the function of pelvic organs.

In the only prospective study available to date, Bianchi *et al.* compared IVF results in women with DE-associated

infertility who underwent extensive laparoscopic excision of endometriosis before IVF to subjects not operated on before IVF. This prospective cohort study included 179 women divided into IVF-only group ($n = 105$) and surgical resection of DIE lesions before IVF group ($n = 64$). In the group where surgical excision before IVF was performed, the odds of attaining pregnancy were 2.45 times higher.^[31]

DE has also been impugned for lowering the pregnancy rates of IVF cycles. The results of the study by Centini *et al.* that the surgical removal of multiple lesions increased pregnancy and live birth rates in both spontaneous and IVF conceptions has already been previously discussed.^[25] A retrospective study by Ballester *et al.* examined 103 women with endometriomas ($n = 30$) and with endometriomas associated with DE ($n = 73$). DE, when associated with endometrioma, adversely affected cumulative pregnancy rates (82.5% vs. 69.4%). In the study, the authors recommended surgery when pregnancy was not achieved after three attempts at IVF.^[32] On the other hand, Capelle *et al.* considered that surgery for DE before IVF did not result in improved pregnancy and birth rates.^[33]

Interestingly, a study demonstrated that infertile women with DE trying to conceive a second child and who had had surgery, had 78% higher live birth rates and a spontaneous pregnancy rate of 54%.^[34] Thus, the literature is replete with studies discussing the impact of surgery on IVF, while the results remain controversial. While women with advanced-stage endometriosis submitted to surgery before IVF did not respond as well to gonadotropins when compared to women with tubal factor infertility, the implantation, pregnancy, and delivery rates were nonetheless similar.^[33] Some authors recommend a combination of surgery with IVF as a more effective approach in endometriosis-associated infertility.^[31]

Hence, who is right and what should be the approach when encountered with an infertile woman with DE? The answer lies with the skills of the surgeon. A reproductive endocrinologist may not be as skilled as a reproductive surgeon in tackling extensive pelvic pathology and doing justice to the excision of DE in such patients. A high index of suspicion of DE symptomatology during history taking and initial clinical examination should be the thrust for an inexperienced pelvic surgeon to refer the case to a skilled surgeon at a tertiary center with a multidisciplinary team available to handle bowel and urinary complications associated with radical surgery.^[35]

The authors agree that the available published studies are observational and are not large enough to allow for any definitive conclusions. Except for peritoneal disease, no

randomized trials have been published to determine the effect of surgery in subfertile women with DE. Thus, to define the absolute benefit of surgery for ovarian and rectovaginal lesions remains a challenge.^[36] However, the decision to undergo surgery must be individually tailored as per the requirement of the patient. The patient must be informed in detail about the risks and benefits, and other variables, such as presence of pain, large or complex adnexal masses, bowel or ureteral stenosis, and coexisting infertility factors, must be discussed. Specifically, in cases of recurrent endometriosis, IVF should generally be the first option.^[37,38]

CONCLUSION

The role of surgery in the treatment of infertile women with DE has remained a matter of intense debate over the past decade. Available evidence is poor, as it amounts mostly from case series, which may probably be the cause of bias in the conclusions in previous studies. With changing surgical practices and expertise in pelvic surgery improving, it is judicious to recommend DE surgery for infertile women. Women with DE should be counseled individually, and surgery tailored taking into consideration several factors. This not only includes the surgeons experience, but also presence of pelvic pain and other symptoms, age, lesion location, previous treatments (surgery and ART), as well as possible pregnancy complications. In this scenario, management by a skilled laparoscopic pelvic surgeon along with a multidisciplinary endometriosis team is a key factor in achieving successful outcomes. The surgeon should aim at one-stop surgery with the resolve to do complete excision of all lesions. Excision of diseased tissue restores normal anatomy, significantly increasing the chance of spontaneous conception, enabling patients to avoid ART treatment. Laparoscopic excision thus alleviates painful symptoms, improves sexual function, strengthens couple's relationships, and positively impacts a women's quality of life, further illustrating the benefits of surgical treatment for endometriosis-related infertility. However, in asymptomatic infertile women or in those in whom the pain symptoms can be effectively managed with medical treatment, surgery without excision of deep lesions or straight IVF may be considered.

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