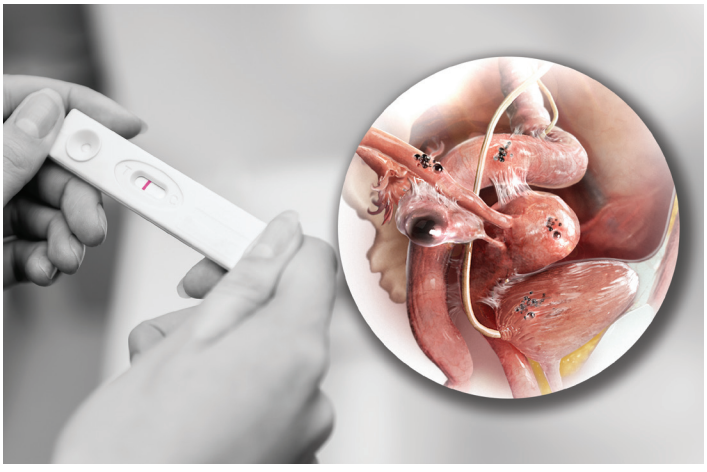
LAST OF 3-PART SERIES

Endometriosis and infertility: Expert answers to 6 questions to help pinpoint the best route to pregnancy



Which patients are likely to benefit from medical therapy? When is surgery indicated? And when is it best to proceed to IVF? Our experts answer these and other questions.

Janelle Yates, Senior Editor

IN THIS ARTICLE

Although endometriosis and infertility are clearly linked—in life as well as the medical literature—no causal relationship has been established. Nevertheless, data suggest that 25% to 50% of infertile women have endometriosis, and that as many as 30% to 50% of women who have endometriosis are infertile.[1]

Among the mechanisms that have been proposed to explain this link are:

- distorted pelvic anatomy
- endocrine and ovulatory abnormalities
- impaired implantation
- impaired quality of the oocyte and embryo
- altered peritoneal function
- altered hormonal and cell-mediated function
- abnormal uterotubal transport.[2]

Recent studies by Kao and colleagues and Giudice and colleagues have led to new findings in regard to endometriosis and infertility, says Ceana Nezhat, MD.[3,4] Dr. Nezhat is Director of the Nezhat Medical Center in Atlanta, Georgia, and Medical Director of Training and Education at Northside Hospital in Atlanta. "These researchers have discovered that endometriosis causes changes to the endometrium that contribute to infertility."

"There are no studies that have specifically assessed whether one anatomic site is associated with increased infertility over another," says Tommaso Falcone, MD. "However, it is assumed that disease that involves the tubes and ovaries would impede fertility the most. Adhesive disease and endometriomas around the tubes and ovaries are associated with a worsening prognosis. Although peritoneal disease probably influences fertility solely on the basis of inflammation, disease around the tubes and ovaries is thought to have a mechanical effect as well." Dr. Falcone is Professor and Chair of Obstetrics and Gynecology at the Cleveland Clinic in Cleveland, Ohio.

"Endometriosis is a chronic and heterogeneous disease process," says Stephanie J. Estes, MD, Director of Robotic Surgical Services and Associate Professor, Division of Reproductive Endocrinology and Infertility,

ILLUSTRATION: JOE GORMAN FOR OBG MANAGEMENT

Department of Obstetrics and Gynecology, at Penn State Hershey Medical Center in Hershey, Pennsylvania.

"It is likely that no single site is the causative factor," Dr. Estes says. "Endometriosis alters prostaglandins, cytokines, and proteases that may adversely affect eggs, sperm, or embryo development. In addition, altered endometrial receptivity may play a role. It has been shown that, when donor oocytes from women with endometriosis are transferred to women without endometriosis, there are lower implantation rates and poorer embryo quality."[5]

Does it follow, then, that eradication of endometriosis improves fertility?

The answer is not clear. Rather, it depends on a number of variables, including the stage of the disease, its location, the presence of symptoms, and more.

"The approach for endometiosis-associated infertility is completely different from the approach for pain," says Dr. Nezhat. "In a patient with pain, complete eradication of endometriosis is necessary. However, when addressing infertility, a surgeon must be cautious in the vicinity of the reproductive organs, even if a multistage approach is required. Fertility preservation is the goal.[6,7] However, thorough treatment of endometriosis improves fertility rates even in cases of failed in vitro fertilization" (IVF).[8]

In this article, the focus is on 6 critical questions concerning endometriosis and infertility, including the role of medical therapy, when surgery is indicated, and whether an endometrioma warrants removal or referral for IVF.

In Part 1 of this 3-part series, which appeared in the April 2015 issue of OBG Management, the subject was diagnosis of endometriosis. In Part 2, which appeared in May 2015, the focus was endometriosis and pain.

1. Is there a role for medical therapy?

In women who have endometriosis-related infertility, medical therapy does not appear to produce any benefit. In its committee opinion on the subject, the American Society for Reproductive Medicine (ASRM) states as much: "There is no evidence that medical treatment of endometriosis improves fertility."[2]

In fact, observes Dr. Estes, trials of medical treatment, involving such medications as combined estrogen-progestin therapy, danazol, progestins, or gonadotropin-releasing hormone (GnRH) agonists, may cause an unnecessary "delay in the use of more effective treatments that could result in pregnancy."

Dr. Nezhat believes that medical therapy is effective in patients who have adenomyosis in addition to endometriosis. "Three months of treatment with a GnRH agonist will improve fertility rates in these patients," he says.

"Medical treatments inhibit ovulation," notes Dr. Estes. "These therapies have no role in pretreatment of patients with endometriosis prior to infertility treatment. On the other hand, medical therapy with GnRH agonists for 3 to 6 months prior to an IVF cycle does result in increased pregnancy rates."[9]

Experts featured in this article

Stephanie J. Estes, MD, is Director of Robotic Surgical Services and Associate Professor, Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, at Penn State Hershey Medical Center in Hershey, Pennsylvania.

Tommaso Falcone, MD, is Professor and Chair of Obstetrics and Gynecology at the Cleveland Clinic in Cleveland, Ohio.

Ceana Nezhat, MD, is Director of the Nezhat Medical Center in Atlanta, Georgia, and Medical Director of Training and Education at Northside Hospital in Atlanta.

Dr. Nezhat reports that he is a consultant to Karl Storz Endoscopy, a scientific advisor to Plasma Surgical, and serves on the medical advisory board for SurgiQuest. Dr. Estes and Dr. Falcone report no financial relationships relevant to this article.

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Medical therapy may be effective in women who have adenomyosis in addition to endometriosis

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2. What is the role of clomiphene and intrauterine insemination?

Should women who have endometriosis, open fallopian tubes, and infertility be treated with clomiphene and intrauterine insemination (IUI) prior to a cycle of IVF?

"This is a complex question," says Dr. Estes, "as clinical parameters such as age, symptoms, duration of infertility, and the ability to proceed with IVF are important, as well as stage of disease."

"Overall, in patients younger than 35 years, clomiphene-IUI is an option and has an increased pregnancy rate over timed intercourse" (9% vs 3%), she says.[10] "However, clearly IVF is much more successful and is the most effective treatment, with pregnancy rates of approximately 46% for women younger than 35 years (3% of whom have a 'diagnosis' of endometriosis, and 13% of whom have an 'unknown' infertility factor).[11] Women who are older than 35 or who have additional infertility factors, such as male factor, should consider IVF first."

FAST TRACK

Women who have significant pain associated with their infertility will benefit from surgery, which offers both pain relief and improvement in the spontaneous pregnancy rate

3. When is surgery indicated?

"Patients who have significant pain associated with their infertility will benefit from surgery, which offers both pain relief and an improvement in the spontaneous pregnancy rate," says Dr. Falcone. "Patients who are infertile and desire spontaneous pregnancy without pharmacologic intervention or assisted reproductive technology (ART) also benefit from surgery."

The benefit of surgery in asymptomatic women with minimal to mild endometriosis is unclear. In a randomized controlled trial of 341 women (aged 20–39 years) with infertility and minimal to mild endometriosis, laparoscopic resection or ablation of visible lesions resulted in pregnancy in 30.7% of women, compared with 17.7% of women who underwent diagnostic laparoscopy only.[12]

Another randomized study of 96 women with minimal to mild endometriosis who underwent resection/ablation or diagnostic laparoscopy found no difference in the birth rate at 1 year.[13]

When the results of these 2 studies are combined, the number needed to treat is 12 laparoscopies in women with endometriosis, says Dr. Falcone. "So 1 additional pregnancy would be gained from performing endometriosis surgery in 12 patients. If we assume a prevalence of 30% in asymptomatic women with infertility, then you need to perform 40 diagnostic laparoscopies to achieve an extra pregnancy."

For women with infertility and severe endometriosis, a nonrandomized study found cumulative pregnancy rates of 45% and 63% after laparoscopy and laparotomy, respectively, in 216 women followed for up to 2 years.[14] The difference in rates was not statistically significant.

"Although surgery is indicated to diagnose endometriosis, multiple repeat procedures are not an effective treatment for infertility," says Dr. Estes. "Plus, especially for stage I and II endometriosis [according to the ASRM classification system], approximately 12 patients will need surgery for 1 additional pregnancy—and many more will have needed the procedure to even get to those who have endometriosis. While patients often want us to 'do something'—often a covered service such as surgery—we need to consider that surgery for early disease does not provide a significant or long-lasting enhancement to women's ability to conceive."

In the absence of male-factor infertility, surgical diagnosis with conservative and precise treatment of endometriosis at the same time is better than going directly to IVF, says Dr. Nezhat. Younger patients who undergo surgical treatment have a better chance of achieving more than 1 spontaneous pregnancy than they do with IVF. And older patients also will have an improved conception rate with ART when they are treated surgically, he says.[8]

4. Surgery or IVF for endometriomas?

When an endometrioma is present, should it

be surgically treated or should the patient go straight to IVF? And does the optimal approach depend on the size of the endometrioma?

"The answer to this question ultimately depends on the skill and experience of the surgeon and the type of endometrioma," says Dr. Nezhat, "because improper removal of an endometrioma may compromise the function of the ovary."

"I recommend removal of the endometrioma by a skilled surgeon experienced in the management of ovarian cysts and preservation of ovarian function, especially in patients who have failed IVF," he says.[6,15]

According to the ASRM committee opinion on endometriosis and infertility, laparoscopic cystectomy for endometriomas larger than 4 cm improves fertility, compared with cyst drainage and coagulation, which is associated with a high risk of cyst recurrence.[2] However, no randomized trials have compared laparoscopic excision of an endometrioma to expectant management prior to IVF/intracytoplasmic sperm injection (ICSI). One case-control study found that laparoscopic cystectomy prior to IVF had no effect on fertility outcomes.[16] At the same time, however, "conservative surgical treatment in symptomatic patients did not impair the success rates of IVF or ICSI," notes the ASRM.[2] Therefore, "evidence suggests that surgery does not benefit asymptomatic women with an endometrioma prior to scheduled IVF/ICSI," the ASRM concludes.[2]

Dr. Nezhat cautions against the practice of indiscriminate IVF in the setting of ovarian endometriomas because he has seen patients who developed tubo-ovarian abscess and infected endometriomas after transvaginal egg retrieval. He notes that there are additional case reports of similar findings from other surgeons.

As far as excision versus ablation is concerned, all studies have shown some effect on ovarian function after excision, says Dr. Falcone. "The studies assessed this parameter using several endpoints, such as the number of oocytes retrieved at IVF. Recently, anti-Müllerian hormone has been used and has confirmed this observation. The decreased ovarian reserve is especially problematic with bilateral ovarian disease. The extent of the decreased ovarian function is dependent on several parameters, especially how much energy is used to achieve hemostasis. Several techniques have been proposed to reduce damage, including less

Coding and reimbursement

For endometriosis, the correct diagnostic code helps establish the medical necessity of later treatments

Several diagnostic codes are available to describe the location of endometriotic implants, but the fact remains that these codes can be reported only after a definitive diagnosis is made, which generally comes after confirmatory surgery has been performed. When the patient is in the diagnostic phase, she may present with complaints of pelvic pain, dyspareunia, dysmenorrhea, or infertility. Knowing which codes to use at the time of evaluation goes a long way toward establishing medical necessity for any later surgery or medical treatment.

In the **TABLE** on page 34, you will find common diagnostic codes that can be reported during evaluation of endometriosis, including both *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) and ICD-10-CM equivalents. Note that, with ICD-10-CM, payers are looking for a more specific type of dysmenorrhea in the documentation. In the case of painful menstruation suspected to arise from endometriosis, the code for secondary dysmenorrhea should be reported.

Diagnostic coding in cases in which the patient first presents with a complaint of infertility in the absence of other symptoms can be problematic, as many insurers still do not cover the treatment of infertility. However, in the diagnostic stage, codes for fertility testing can be reported instead of codes that confirm infertility when no other symptoms are present. Once the clinician has verified that endometriosis is the source of the infertility and begins treatment, the primary code for the type of endometriosis would be reported, not a diagnosis of infertility.

The procedure performed to diagnose endometriosis would be diagnostic laparoscopy (Current Procedure Terminology [CPT] code **49320,** *Laparoscopy, abdomen, peritoneum, and omentum, diagnostic, with or without collection of specimen[s] by brushing or washing [separate procedure]*) if medical treatment is being pursued. If the plan is to confirm and then immediately remove the implants, the CPT codes would be either **58662,** *Laparoscopy, surgical; with fulguration or excision of lesions of the ovary, pelvic viscera, or peritoneal surface by any method*, or **49203–49205,** *Excision or destruction, open, intra-abdominal tumors, cysts or endometriomas, 1 or more peritoneal, mesenteric, or retroperitoneal primary or secondary tumors*, based on the largest tumor diameter, if they are removed via an abdominal incision.

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Ms. Witt is an independent coding and documentation consultant and former program manager, department of coding and nomenclature, American Congress of Obstetricians and Gynecologists.

Common endometriosis diagnostic codes

Description	ICD-9-CM	ICD-10-CM
Dyspareunia	625.0	N94.1
Dysmenorrhea	625.3	—
Primary dysmenorrhea	—	N94.4
Secondary dysmenorrhea	—	N94.5
Dysmenorrhea, unspecified	—	N94.6
Unspecified symptom associated with female genital organs	625.9	—
Pelvic and perineal pain	—	R10.2
Procreative management; fertility testing	V26.21	—
Encounter for fertility testing	—	Z31.41
Endometriosis of uterus	617.0	N80.0
Endometriosis of ovary	617.1	N80.1
Endometriosis of fallopian tube	617.2	N80.2
Endometriosis of pelvic peritoneum	617.3	N80.3
Endometriosis of rectovaginal septum and vagina	617.4	N80.4
Endometriosis of intestine	617.5	N80.5
Endometriosis in scar of skin	617.6	N80.6
Endometriosis of other specified sites	617.8	—
Other endometriosis	—	N80.8
Endometriosis, site unspecified	617.9	—
Endometriosis, unspecified	—	N80.9

FAST TRACK

Many patients cannot afford IVF, so surgery is their only option

traumatic ways of achieving hemostasis in the ovarian hilus."

"The dilemma is that, if we excise the disease, the pregnancy rates are better than with ablation, but if we excise, there is more damage to the ovary. In my practice, I excise if there is minimal associated disease, such as adhesions, because the pregnancy rate after surgery is good. If, however, there are extensive adhesions with a low chance of spontaneous pregnancy, I minimize excision," Dr. Falcone says.

As for going straight to IVF, "many patients cannot afford IVF; therefore, surgery is their only option. Furthermore, many patients have severe associated pain; therefore, surgery is required to improve quality of life. However, if the decision is made to proceed to IVF, there is no evidence that cystectomy prior to treatment with ART improves the pregnancy rate," Dr. Falcone says.

"Basically, if a woman has no pain and no endometrioma, and infertility alone is the issue, I treat her in the same manner as I would a patient with idiopathic infertility—no surgery," Dr. Falcone says. "If a patient has severe pain and infertility, I treat her surgically but conservatively, especially when an endometrioma is present. The patient will get pain relief but also derive fertility benefit. If a patient has had previous surgery for endometriosis-associated infertility, additional surgery is not the next step—as our study has shown that pregnancy rates are better with IVF than repeat surgery."[17]

5. Is surgery ever effective after failed IVF?

To answer this question, Dr. Nezhat points to a retrospective case series by Littman and colleagues in which 29 women with a history of failed IVF underwent laparoscopic evaluation and treatment of endometriosis (by the same

surgeon).[8] Of 29 patients, 22 conceived after laparoscopic treatment of endometriosis, including 15 "non-IVF" pregnancies and 7 IVF pregnancies, the study results show.[8]

"It is not unusual for patients and health care providers to perceive IVF as the final treatment for infertility," Littman and colleagues write. "When this definitive therapy fails repeatedly, clinicians and patients may be inclined to pursue oocyte donation or elect to forego further treatment altogether. This is especially true in women of advanced age and in patients with borderline embryo quality. Presently, as a result of our clinical observation in patients with failed IVF, before egg donation or adoption, we offer the option to have meticulous laparoscopic evaluation and treatment by a skilled surgeon. Furthermore, we would not classify an infertility condition as unexplained without confirming the absence of endometriosis by a thorough laparoscopy. In our experience, patients under 35 years old with unexplained infertility who are found to have endometriosis at the time of laparoscopy have an excellent chance of pregnancy following surgical treatment without ART."[8]

6. Is repeat surgery ever helpful?

In the treatment of endometriosis-associated infertility, repeat surgery should be avoided if no symptoms are present, says Dr. Estes. "In women with continued symptoms, the benefits of repeat surgery are small, with known risks, including the potential for adhesive disease and the iatrogenic detrimental effect on ovarian function—often in a setting of already-present decreased ovarian reserve."

Dr. Nezhat agrees that multiple surgeries carry the potential for harm. "However, there is one caveat," he says. "What was done at the previous surgery and how? The skill and experience of the surgeon and proper technique are of paramount importance to the surgical outcome."

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Although many patients and health care providers perceive IVF as the final treatment for infertility, surgical therapy may be beneficial in some women in whom IVF has failed