

Endometriosis and infertility: a committee opinion

The Practice Committee of the American Society for Reproductive Medicine

American Society for Reproductive Medicine, Birmingham, Alabama

Women with endometriosis typically present with pelvic pain, infertility, or an adnexal mass, and may require surgery. Treatment of endometriosis in the setting of infertility raises a number of complex clinical questions that do not have simple answers. This document replaces the 2006 ASRM Practice Committee document of the same name. (*Fertil Steril*® 2012;98:591–8. ©2012 by American Society for Reproductive Medicine.)

Earn online CME credit related to this document at www.asrm.org/elearn

Discuss: You can discuss this article with its authors and with other ASRM members at <http://fertstertforum.com/goldsteinj-endometriosis-and-infertility-a-committee-opinion/>



Use your smartphone to scan this QR code and connect to the discussion forum for this article now.*

* Download a free QR code scanner by searching for "QR scanner" in your smartphone's app store or app marketplace.

Endometriosis is a common, chronic disease. Although women may be asymptomatic, most women typically present with pelvic pain, infertility, or an adnexal mass. Treatment of endometriosis in the setting of infertility raises a number of complex clinical questions. The purpose of this document is to review the current literature regarding the implications of endometriosis and its management on reproduction.

Classical studies suggested that 25% to 50% of infertile women have endometriosis and that 30% to 50% of women with endometriosis are infertile (1). The true prevalence of endometriosis is difficult to quantify as very wide ranges have been reported in the literature. One study suggested the prevalence of endometriosis in women who undergo tubal sterilization is 1% to 7%, while the prevalence of endometriosis in women undergoing a laparoscopy for evaluation of infertility is 9% to 50% (1, 2). Among women with pelvic pain the prevalence of endometriosis ranges from 30% to 80% (1). Other studies

have not reported prevalence but have confirmed that infertile women are 6 to 8 times more likely to have endometriosis than fertile women (2). Apparent risk factors for endometriosis also include a low body mass index (BMI), alcohol use, and smoking (1). African-American women are less likely than Caucasian women to have endometriosis (odds ratio [OR] 0.6, 95% confidence interval [CI] 0.4–0.9) (1).

ENDOMETRIOSIS AND INFERTILITY

The hypothesis that endometriosis causes infertility or a decrease in fecundity remains controversial. Whereas a reasonable body of evidence demonstrates an association between endometriosis and infertility, a causal relationship has not been clearly established. However, endometriosis can result in adhesions or distorted pelvic anatomy that precludes fertility. The fecundity rate in normal couples is in the range of 15% to 20% per month and decreases with age of the female partner (3, 4). The fecundity rate of

untreated women with endometriosis is difficult to quantify, given the wide range reported in the literature (2% to 10%) (5). If endometriosis does cause infertility, then eradication of the disease should improve fecundity. Unfortunately, suppressive medical therapy for endometriosis has not been shown to improve fecundity rates and may only result in a delay in the use of more effective treatments to achieve pregnancy. Surgery for stage III or IV endometriosis can be useful to treat pelvic adhesions that may impact reproductive function.

BIOLOGIC MECHANISMS THAT MAY LINK ENDOMETRIOSIS AND INFERTILITY

No mechanism has been identified to explain the link between endometriosis and subfertility; however, several mechanisms have been proposed (6–8). It should be emphasized that none of these mechanisms has been proven to decrease fecundity in women with endometriosis. These mechanisms are briefly discussed below.

Distorted Pelvic Anatomy

Major pelvic adhesions, including those that result from endometriosis, can

Received May 15, 2012; accepted May 22, 2012; published online June 15, 2012.

No reprints will be available.

Correspondence: Practice Committee, American Society for Reproductive Medicine, 1209 Montgomery Hwy., Birmingham, AL 35216 (E-mail: jgoldstein@asrm.org).

Fertility and Sterility® Vol. 98, No. 3, September 2012 0015-0282/\$36.00

Copyright ©2012 American Society for Reproductive Medicine, Published by Elsevier Inc.

doi:10.1016/j.fertnstert.2012.05.031

impair oocyte release from the ovary or inhibit ovum capture or transport (9).

Altered Peritoneal Function

Many studies demonstrate that women with endometriosis have an increased volume of peritoneal fluid, as well as increased peritoneal fluid concentrations of prostaglandins, proteases, and cytokines including inflammatory cytokines such as IL-1, IL-6, and TNF α , and angiogenic cytokines, such as IL-8 and VEGF produced by macrophages (10, 11). Several studies have also demonstrated elevated concentrations of inflammatory cytokines in the serum of women with endometriosis, implying that endometriosis may lead to systemic inflammation. It is unknown if inflammation predisposes to, or results from, endometriosis. An ovum capture inhibitor that prevents normal cumulus-fimbria interaction has been reported in the peritoneal fluid of hamsters with induced endometriosis (12). These alterations may have adverse effects on oocyte, sperm, embryo, or fallopian tube function (13).

Altered Hormonal and Cell-Mediated Function

IgG and IgA antibodies and lymphocytes 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 (13).

Endocrine and Ovulatory Abnormalities

It has been proposed that women with endometriosis may have endocrine and ovulatory disorders, including luteinized unruptured follicle syndrome, luteal phase dysfunction, abnormal follicular growth, and premature as well as multiple luteinizing hormone (LH) surges (9). There is some evidence to suggest that endometriosis may be associated with a longer follicular phase with possibly lower serum estradiol levels and lower LH-dependent progesterone secretion during the luteal phase of the cycle (14, 15). However, endocrine disturbances have not been linked to the outcome of pregnancy.

Impaired Implantation

Some evidence suggests that disorders of endometrial function may contribute to the decreased fecundity observed in women with endometriosis. Reduced endometrial expression of $\alpha v \beta 3$ integrin (a cell adhesion molecule) during the time of implantation has been described in some women with endometriosis (16), but this finding has not been replicated. More recently, 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) have been observed in infertile women with endometriosis (17–21).

Oocyte and Embryo Quality

Infertility in women with endometriosis may be related to alterations within the follicle, poor oocyte quality and subse-

quent embryogenesis, or decreased endometrial receptivity. This theory is supported by findings of altered progesterone and cytokine concentrations in follicular fluid from women with endometriosis (22). Abnormalities of oocyte and embryo quality have been described in women with endometriosis. Embryos derived from women with endometriosis appear to develop more slowly compared to those embryos derived from women with tubal disease (23). Also, in oocyte donation cycles, women with moderate to severe endometriosis who receive oocytes from disease-free women appear to have normal endometrial receptivity and pregnancy rates. Conversely, when donor oocytes from women with endometriosis are transferred into women without endometriosis, implantation rates are lower and embryo quality is reduced (24). Further studies are needed to determine whether pregnancy rates are lower in recipients who receive oocytes from donors with or without endometriosis (24).

Abnormal Uterotubal Transport

It has been suggested that women with endometriosis demonstrate a reduction in physiologic uterotubal transport capacity compared to control subjects. In women with patent fallopian tubes and endometriosis, further investigation using hysterosalpingoscintigraphy (HSSG) suggested abnormal transport (contralateral to the dominant follicle or a complete failure of transport) in 64% of patients compared to 32% of patients in a control group with the diagnosis of male infertility (25). These findings must be confirmed by others.

DIAGNOSIS AND STAGING

In current clinical practice, a surgical procedure such as laparoscopy is required for a definitive diagnosis of endometriosis. Histologic evaluation is warranted whenever the diagnosis is not apparent on visual inspection at surgery. When addressing whether or not to perform a laparoscopy on a woman presenting with a complaint of infertility, one should consider both the likelihood of the diagnosis of endometriosis as well as potential benefit of treatment. A history and physical examination can yield a number of significant findings suggestive of endometriosis including: cyclic or chronic pelvic pain, dysmenorrhea, dyspareunia, a fixed retroverted uterus, an adnexal mass, and uterosacral ligament nodularity, thickening, or tenderness. Additionally, ultrasound can help the clinician establish a presumptive diagnosis of an ovarian endometrioma but cannot reliably image peritoneal implants of disease.

A laparoscopic diagnosis of asymptomatic endometriosis in a woman without signs or symptoms of the disease can sometimes be made. However, laparoscopic confirmation of asymptomatic endometriosis is almost always limited to uncovering minimal or mild disease. The therapeutic benefit of laparoscopy to increase fecundity in a woman with mild disease is minimal. The combination of these factors renders laparoscopy of asymptomatic women with infertility, simply to rule out or confirm disease, unwarranted (26, 27).

Endometriosis is a heterogeneous disease with typical and atypical peritoneal lesions ranging from a single 1 mm peritoneal implant to ≥ 10 cm endometriomas and cul-de-sac

TABLE 1

Cycle fecundity in women with stage I or II endometriosis, according to treatment (reported as percentage).

Treatment	Group				
	Unexplained infertility	Endometriosis-associated infertility			
Reference	Guzick et al. (55)	Deaton et al. (41)	Chaffkin et al. (57)	Fedele et al. (42)	Kemmann et al. (43)
No treatment or intracervical insemination	2	3.3	–	4.5	2.8
IUI	5 ^a	–	–	–	–
Clomiphene	–	–	–	–	6.6
Clomiphene/IUI	–	9.5 ^a	–	–	–
Gonadotropins	4 ^a	–	6.6	–	7.3 ^a
Gonadotropins/IUI	9 ^a	–	12.9 ^a	15 ^a	–
IVF	–	–	–	–	22.2 ^a

Note: Data presented as percent.

^a $P < .05$ for treatment vs. no treatment.Practice Committee. Endometriosis and infertility. *Fertil Steril* 2012.

obliteration (28). Consequently, a staging system has been proposed to allow clinicians to communicate the extent of disease and to permit standardization and comparisons of outcomes for clinical trials. The American Society for Reproductive Medicine classification system for endometriosis (ASRM 1996) is the most widely accepted staging system (28). Unfortunately, no staging system correlates well with the chance of conception following therapy. This poor predictive ability is related to the arbitrary assignment of point scores for the observed pathology and the arbitrary cut-off points chosen to establish the stage of disease. The ASRM 1996 classification system might be enhanced by including a description of the morphologic subtype of disease or other biological markers (29). A more accurate staging system is unlikely until there is a better understanding of the pathophysiology of endometriosis-associated infertility. However, new staging systems have been proposed (30).

MEDICAL THERAPY FOR ENDOMETRIOSIS

Whereas medical therapy is effective for relieving pain associated with endometriosis, there is no evidence that medical treatment of endometriosis improves fertility. In actuality, fertility is essentially eliminated during treatment because all medical treatments for endometriosis inhibit ovulation. Several options have been suggested for medical treatment: progestins and combined estrogen-progestin therapy, gonadotropin-releasing hormone agonists and antagonists, danazol, and, most recently, aromatase inhibitors. Several randomized clinical trials (RCTs) have demonstrated that progestins or gonadotropin-releasing hormone (GnRH) agonists are not effective treatments for infertility associated with minimal to mild endometriosis (31–33). In two RCTs involving 105 infertile women with minimal to mild endometriosis, pregnancy rates were no better with danazol than with expectant management (31, 34). In an RCT involving 71 infertile women with minimal to mild endometriosis, the one- and two-year cumulative pregnancy rates were similar in the groups receiving GnRH-agonist treatment (6 months) or expectant management (32). In a small RCT involving 37 infertile women with minimal to

mild endometriosis treated with progestins or expectant management, pregnancy rates were similar at one year in both groups (35). Also, in a small RCT involving 31 women, pregnancy rates with progestins or expectant management were 41% and 43%, respectively (36). In one randomized trial, medical therapy with gestrinone was not superior to placebo even in women in whom the endometriosis disappeared. The 12-month conception rate was 25% (5/20) with gestrinone and 24% (4/17) with placebo. The conception rate was 25% (4/16) in all women with no visible endometriosis at the second laparoscopy and 30% (6/20) when residual disease was present. These rates compare with 23% (6/26) among patients with unexplained infertility. None of these rates differ significantly from each other (35). In a meta-analysis that included seven studies comparing medical treatment to no treatment or placebo, the common OR for pregnancy was 0.85 (95% CI 0.95, 1.22) (5). A review of 13 RCTs that included nearly 800 infertile women with endometriosis reported no evidence that ovulation suppression was superior to placebo in women who wished to conceive (33). Thus, hormonal treatment does not improve the fecundity of infertile women with Stage I/II endometriosis.

At present, there are insufficient data to evaluate the efficacy of aromatase inhibitors, selective estrogen receptor modulators (SERMs), progesterone antagonists, or selective progesterone receptor modulators (SPRMs) in the medical management of endometriosis for fertility.

SURGERY FOR ENDOMETRIOSIS

In stage I/II endometriosis, laparoscopic ablation of endometrial implants has been associated with a small but significant improvement in live birth rates. Two RCTs have evaluated effectiveness of laparoscopic surgery for Stage I or II endometriosis associated with infertility, with only one study demonstrating benefit (26, 27). Both studies permitted surgical discretion in the intervention regarding excision or ablation. The primary outcomes were slightly different: the Italian study analyzed pregnancies that occurred within one year after laparoscopy and proceeded to live births (27); the Canadian study analyzed pregnancies that occurred within

36 weeks after laparoscopy and proceeded to gestation of 20 weeks, an end-point which is nearly identical to the live birth rate (26). In the Italian study, 10/51 (20%) and 10/45 (22%) of the treated and untreated patients, respectively, were successful. In the Canadian study, 50/172 (29%) and 29/169 (17%) of the treated and untreated patients, respectively, were successful. The baseline untreated pregnancy rates were 22% in 52 weeks and 17% in 36 weeks, respectively, in the Italian and Canadian studies, indicating that the patient populations were similar. The main difference was the lower power of the Italian study, which was planned to detect a 2.7-fold higher live birth rate with ablation/resection (27). When the results are combined, there is no significant statistical heterogeneity, and the overall absolute difference is 8.6% in favor of therapy (95% CI 2.1, 15) (37). The number needed to treat is 12 (95% CI 7, 49). Thus, for every 12 patients having Stage I/II endometriosis diagnosed at laparoscopy, there will be one additional successful pregnancy if ablation/resection of visible endometriosis is performed compared to no treatment. However, this benefit would apply only to those who have endometriosis. Given the conservative estimate that approximately 30% of asymptomatic patients with otherwise unexplained infertility will be diagnosed with endometriosis, the number of laparoscopies that need to be performed to gain one additional pregnancy is actually 40. There is no evidence that the outcome is affected by the method of ablation, either electrosurgery or laser delivery systems (26).

With respect to severe endometriosis, a non-randomized study demonstrated that the cumulative pregnancy rates in 216 infertile patients followed for up to two years after laparoscopy or laparotomy were 45% and 63%, respectively (37). Laparoscopic cystectomy for ovarian endometriomas greater than 4 cm improved fertility compared to cyst drainage and coagulation, which is associated with a high risk of cyst recurrence (38). While these and other observational studies suggest that, in women with Stage III/IV endometriosis who have no other identifiable infertility factors, conservative surgical treatment with laparoscopy and possible laparotomy may increase fertility (29), a possible adverse consequence is the loss of viable ovarian cortex (39). After the first infertility operation, additional surgery has only rarely increased fecundability, and these patients may be better served by using assisted reproductive technology (ART) (40).

COMBINATION MEDICAL AND SURGICAL THERAPY

Combination medical and surgical therapy for endometriosis consists of either preoperative or postoperative medical therapy. Although theoretically advantageous, there is no evidence in the literature that combination medical-surgical treatment significantly enhances fertility, and it may unnecessarily delay further fertility therapy. Preoperative therapy is reported to reduce pelvic vascularity and the size of endometriotic implants, thus reducing intraoperative blood loss and decreasing the amount of surgical resection needed. It is unknown if preoperative therapy will make it more difficult to identify and therefore treat lesions at the time of surgery.

Postoperative medical therapy has been advocated as a means of eradicating residual endometriotic implants in patients with extensive disease in whom resection of all implants is impossible or inadvisable. Postoperative hormonal therapy also may treat “microscopic disease”; however, none of these treatments has been proven to enhance fertility. Based on biological plausibility and expert opinion, but not on evidence from clinical trials, these therapies are sometimes advocated to reduce pain.

SUPEROVULATION AND INTRAUTERINE INSEMINATION

Several studies report success with superovulation (SO)/intrauterine insemination (IUI) in the treatment of endometriosis-associated infertility. Review of this subject is complicated as most studies have included women whose endometriosis was “treated” prior to SO/IUI or have included women with unexplained infertility (some of whom are presumed to have minimal endometriosis). In a cross-over RCT among patients with unexplained infertility or surgically corrected endometriosis, the pregnancy rate per cycle was significantly higher with four cycles of clomiphene citrate/IUI than with four cycles of timed intercourse (9.5% versus 3.3%, respectively) (41). A randomized trial among 49 women with stage I/II endometriosis and infertility compared three cycles of gonadotropin/IUI with six months of expectant management (42). The pregnancy rate per cycle was 15% in the gonadotropin/IUI group and 4.5% in the untreated group ($P < 0.05$). Another study reported increased fecundity with gonadotropin therapy compared to no treatment (7.3% vs. 2.8% respectively) in women with infertility and minimal or mild endometriosis (43) (Table 1).

Other studies have shown that the clinical pregnancy rate using SO/IUI shortly after laparoscopic excision of minimal or mild endometriosis was comparable in women with unexplained infertility (some of whom likely had untreated endometriosis). The per-cycle pregnancy rates in women with minimal endometriosis, mild endometriosis, or unexplained infertility were 21%, 18.9%, and 20.5%, respectively. Cumulative live-birth rates following 4 cycles were also comparable among the three groups (70.2%, 68.2%, and 66.5%, respectively) (44). Thus, Level II evidence and one small trial suggest that SO/IUI may be a viable treatment option for women who have had a surgical diagnosis and treatment of stage I or II endometriosis as an alternative to in vitro fertilization (IVF) or further surgical therapy. There is insufficient evidence to determine if SO/IUI is more successful after endometriosis is diagnosed and treated compared to minimal or mild endometriosis left undiagnosed or untreated.

ASSISTED REPRODUCTIVE TECHNOLOGY

A recent report on in vitro fertilization-embryo transfer (IVF-ET) outcomes in the United States indicates that the overall delivery rate per retrieval in infertile women ranges from 44.6% in those under 35 years of age to 14.9% in those 41–42 years of age. The average delivery rate per retrieval for all diagnoses was 33.2%, compared with 39.1% for women with endometriosis (45). This is in contrast to a meta-analysis

of observational studies which found that women with endometriosis-associated infertility had lower pregnancy rates with IVF than those with tubal factor infertility (OR 0.56; 95% CI, 0.44 to 0.70) (46). In addition, pregnancy rates in those with severe endometriosis were lower than in those with mild disease (OR, 0.60; 95% CI, 0.42 to 0.87). This same study showed that there were significant decreases in fertilization and implantation rates and in the number of oocytes retrieved in patients with endometriosis. The discrepancy between the results from the meta-analysis and the Society for Assisted Reproductive Technology (SART) data may be due to confounding variables from unadjusted analyses (for example, women with endometriosis that undergo IVF may be younger than women that undergo IVF for other reasons) and bias resulting from use of non-adjudicated data collected in a registry (45).

While endometriosis may affect IVF results, IVF likely maximizes cycle fecundity for those with endometriosis, especially in those with distortion of pelvic anatomy due to moderate or severe disease. There are few studies comparing the use of IVF in women with endometriosis to expectant management. In one RCT, a sub-group of 21 women with endometriosis and infertility had IVF ($n = 15$) or expectant management ($n = 6$) (47). None of the women in the expectant management group became pregnant compared to five of the 15 women who received IVF-ET (33%, $P = \text{not significant}$) (47).

The impact of ovarian endometriomas on ART outcomes remains controversial. There are no randomized trials comparing laparoscopic excision to expectant management before IVF/intracytoplasmic sperm injection (ICSI) cycles. One case-control study involving 189 patients found that laparoscopic cystectomy before commencing an IVF cycle did not improve fertility outcomes (48). A second retrospective comparison of 171 subjects with an endometrioma or tubal factors also concluded that aspiration of endometriomas before controlled ovarian stimulation (COS) did not increase the number of follicles >17 mm, the number of metaphase II oocytes retrieved, or the clinical pregnancy rates. At the same time, conservative surgical treatment in symptomatic patients did not impair the success rates of IVF or ICSI. Thus, to date, evidence suggests that surgery does not benefit asymptomatic women with an endometrioma prior to scheduled IVF/ICSI. However, there are no studies evaluating impact of size of the endometrioma on outcome. In each case the benefits and risks should be balanced by clinicians (49). Possible benefits of surgical treatment prior to IVF, especially for large endometriomas, include prevention of possible ruptured endometriomas, facilitation of oocyte retrieval, detection of occult malignancy (particularly in view of a large study confirming an association between endometriosis and certain ovarian cancers [50]), avoidance of contamination of follicular fluid with endometrioma content, and prevention of progression of endometriosis. Disadvantages of surgery include surgical trauma, surgical complications, economic costs, potential decreased ovarian response, and lack of evidence for improved IVF pregnancy rates (51).

A summary of three randomized controlled trials that included a total of 165 women concluded that administration

of GnRH agonists for a period of 3–6 months prior to IVF or ICSI in women with endometriosis increases the odds of clinical pregnancy (OR 4.28, 95% CI, 2.00 to 9.15) (52). However, the very high reported clinical pregnancy rates of 75% and 80% in the treatment arms of two of these studies makes these studies difficult to extrapolate to other populations (53, 54). It is also unclear whether this therapy is equally beneficial for mild and severe stages of the disease and what the mechanism might be.

PREGNANCY OUTCOMES IN WOMEN WITH ENDOMETRIOSIS

Women with endometriosis have been shown to have adverse obstetrical outcomes compared to those without endometriosis. A Swedish cohort study evaluated 8,922 women diagnosed with endometriosis who delivered 13,090 singleton infants from the national medical birth registry of over 1.4 million singleton births (55). Compared to women without endometriosis, the risk of preterm birth associated with endometriosis among women with ART was 1.24 (95% CI, 0.99–1.57), and among women without ART, 1.37 (95% CI, 1.25–1.50). In addition, women with endometriosis had higher risk of pre-eclampsia (OR 1.13, 95% CI, 1.02–1.26), antepartum bleeding/placental complications (OR 1.76, 95% CI, 1.56–1.99) and cesarean section (OR 1.47, 95% CI, 1.40–1.54). There was no association between endometriosis and small for gestational age-birth or stillbirth. It is not clear if these associations are related to the endometriosis, the resulting infertility, or the ART treatment therapy.

DECISIONS AMONG INFERTILE WOMEN WITH ENDOMETRIOSIS

Clinical decisions in the management of infertility associated with endometriosis are difficult because many clinical decision points have not been evaluated in RCTs. Moreover, the observational data are conflicting and prevent confident conclusions.

For infertile women with suspected stage I/II endometriosis, a decision must be made whether to perform laparoscopy before offering treatment with clomiphene, gonadotropins, or IVF-ET. Clearly, factors such as the woman's age, duration of infertility, ability to undergo IVF-ET, family history, and pelvic pain must be taken into consideration. Because it is uncommon to find advanced stage endometriosis in an asymptomatic woman (with a normal ultrasound), there is low utility in performing laparoscopy in asymptomatic women. When laparoscopy is performed, ablation or excision of visible endometriosis should be considered based on Level I evidence. This should be discussed openly with the patient when planning her treatment. Expectant management after laparoscopy is an option for younger women. Alternatively, superovulation with IUI may be offered, although the evidence indicates that the number of cycles needed to achieve an additional pregnancy is 14 (56).

Female age is an important factor in designing therapy. After age 35 years, there is a significant decrease in fecundity and an increase in the spontaneous miscarriage rate. Fecundity may be decreased due to the additive adverse effects of

endometriosis and increasing age. Consequently, in the older infertile woman with endometriosis, a more aggressive therapeutic plan with either SO/IUI or IVF-ET may be reasonable. The patient with endometriosis should be informed that she may have a decreased success rate after IVF compared to a woman undergoing IVF for another indication, for example, tubal factor infertility.

For infertile women with ASRM stage III/IV endometriosis and no other identifiable infertility factor, conservative surgery with laparoscopy and/or possible laparotomy or IVF are recommended (28). Although not evaluated with RCTs, observational studies suggest that surgical therapy increases fertility in women with advanced endometriosis, thus discouraging expectant management.

For women who are found to have an asymptomatic endometrioma and who are planning to undergo IVF/ICSI, there is insufficient evidence to suggest that removal of the endometrioma will improve IVF success rates. However, if the endometrioma is large (>4 cm), surgery should be considered to confirm the diagnosis histologically, to improve access to follicles during oocyte retrieval, and possibly to improve ovarian response. The patient should be made aware that extensive ovarian surgery could compromise ovarian function and diminish the response to ovarian stimulation.

For infertile women who have stage III/IV endometriosis and have previously had one or more infertility operations, IVF-ET is often a better therapeutic option than another surgical intervention, though this is another question that has not been addressed in any randomized trial. In one retrospective study, 23 women with stage III/IV endometriosis underwent IVF-ET and 18 women underwent repeat surgery (43). The pregnancy rate after two cycles of IVF-ET was 70%, whereas the cumulative pregnancy rate was 24% within 9 months of a repeat operation. If initial surgery fails to restore fertility in patients with moderate to severe endometriosis, IVF-ET is an effective alternative. Current data are insufficient to estimate the effect of surgical treatment in addition to IVF-ET on the outcome of pregnancy in endometriosis-associated infertility.

SUMMARY

- There is insufficient evidence to indicate that resection of endometriomas prior to IVF improves outcomes.
- IVF success rates in women with endometriosis appear to be diminished compared to women with tubal factor infertility; however, IVF likely maximizes cycle fecundity for those with endometriosis.
- Women with endometriosis have higher incidences of preterm delivery, pre-eclampsia, antepartum bleeding/placental complications, and cesarean section when compared to women without endometriosis.

CONCLUSIONS

- Female age, duration of infertility, pelvic pain, and stage of endometriosis should be considered when formulating a management plan.

- The benefit of laparoscopic treatment of minimal or mild endometriosis is insufficient to recommend laparoscopy solely to increase the likelihood of pregnancy.
- When laparoscopy is performed for other indications, the surgeon may consider safely ablating or excising visible lesions of endometriosis.
- In younger women (under age 35 years) with stage I/II endometriosis-associated infertility, expectant management or SO/IUI can be considered as first-line therapy.
- For women 35 years of age or older, more aggressive treatment, such as SO/IUI or IVF may be considered.
- In women with stage III/IV endometriosis-associated infertility, conservative surgical therapy with laparoscopy or possible laparotomy may be beneficial.
- Surgical management of an endometrioma should include resection or ablation, rather than drainage, with resection preferred.
- For women with stage III/IV endometriosis who fail to conceive following conservative surgery or because of advancing reproductive age, IVF-ET is an effective alternative.

Acknowledgments: This report was developed under the direction of the Practice Committee of the American Society for Reproductive Medicine as a service to its members and other practicing clinicians. Although this document reflects appropriate management of a problem encountered in the practice of reproductive medicine, it is not intended to be the only approved standard of practice or to dictate an exclusive course of treatment. Other plans of management may be appropriate, taking into account the needs of the individual patient, available resources, and institutional or clinical practice limitations. The Practice Committee and the Board of Directors of the American Society for Reproductive Medicine have approved this report.

The Practice Committee acknowledges the special contribution of Beata Seeber, MD in the preparation of this document. The following members of the ASRM Practice Committee participated in the development of this document. All Committee members disclosed commercial and financial relationships with manufacturers or distributors of goods or services used to treat patients. Members of the Committee who were found to have conflicts of interest based on the relationships disclosed did not participate in the discussion or development of this document. Samantha Pfeifer, M.D.; Marc Fritz, M.D.; Jeffrey Goldberg, M.D.; R. Dale McClure, M.D.; Roger Lobo, M.D.; Michael Thomas, M.D.; Eric Widra, M.D.; Glenn Schattman, M.D.; Mark Licht, M.D.; John Collins, M.D.; Marcelle Cedars, M.D.; Catherine Racowsky, Ph.D.; Michael Vernon, Ph.D.; Owen Davis, M.D.; Kurt Barnhart, M.D., MSCE; Clarisa Gracia, M.D., MSCE; William Catherino, M.D., Ph.D.; Robert Rebar, M.D.; and Andrew La Barbera, Ph.D.

REFERENCES

1. Missmer SA, Hankinson SE, Spiegelman D, Barbieri RL, Marshall LM, Hunter DJ. Incidence of laparoscopically confirmed endometriosis by demographic, anthropometric, and lifestyle factors. *Am J Epidemiol* 2004;160:784-96.
2. Verkauf BS. Incidence, symptoms, and signs of endometriosis in fertile and infertile women. *J Fla Med Assoc* 1987;74:671-5.

3. Chandra A, Mosher WD. The demography of infertility and the use of medical care for infertility. *Infertil Reprod Med Clin North Am* 1994;5: 283–96.
4. Schwartz D, Mayaux MJ. Female fecundity as a function of age: results of artificial insemination in 2193 nulliparous women with azoospermic husbands. *Federation CECOS. N Engl J Med* 1982;306:404–6.
5. Hughes EG, Fedorkow DM, Collins JA. A quantitative overview of controlled trials in endometriosis-associated infertility. *Fertil Steril* 1993;59:963–70.
6. Schenken RS. Treatment of human infertility: the special case of endometriosis. In: Adashi EY, Rock JA, Rosenwaks Z, editors. *Reproductive endocrinology, surgery and technology*. Philadelphia, PA: Lippincott-Raven; 1996: 2122–39.
7. Bulun SE. Endometriosis. *N Engl J Med* 2009;360:268–79.
8. Giudice LC. Clinical practice. Endometriosis. *N Engl J Med* 2010;362:2389–98.
9. Schenken RS, Asch RH, Williams RF, Hodgen GD. Etiology of infertility in monkeys with endometriosis: luteinized unruptured follicles, luteal phase defects, pelvic adhesions, and spontaneous abortions. *Fertil Steril* 1984; 41:122–30.
10. Bedaiwy MA, Falcone T, Sharma RK, Goldberg JM, Attaran M, Nelson DR, et al. Prediction of endometriosis with serum and peritoneal fluid markers: a prospective controlled trial. *Hum Reprod* 2002;17:426–31.
11. Pizzo A, Salmeri FM, Ardita FV, Sofo V, Tripepi M, Marsico S. Behaviour of cytokine levels in serum and peritoneal fluid of women with endometriosis. In: *Gynecol Obstet Invest*. Vol. 54. Switzerland: 2003. S. Karger AG, Basel; 2002:82–7.
12. Suginami H, Yano K. An ovum capture inhibitor (OCI) in endometriosis peritoneal fluid: an OCI-related membrane responsible for fimbrial failure of ovum capture. *Fertil Steril* 1988;50:648–53.
13. Lebovic DI, Mueller MD, Taylor RN. Immunobiology of endometriosis. *Fertil Steril* 2001;75:1–10.
14. Cahill DJ, Wardle PG, Maile LA, Harlow CR, Hull MG. Ovarian dysfunction in endometriosis-associated and unexplained infertility. *J Assist Reprod Genet* 1997;14:554–7.
15. Cunha-Filho JS, Gross JL, Bastos de Souza CA, Lemos NA, Giugliani C, Freitas F, et al. Physiopathological aspects of corpus luteum defect in infertile patients with mild/minimal endometriosis. *J Assist Reprod Genet* 2003;20: 117–21.
16. Lessey BA, Castelbaum AJ, Sawin SW, Buck CA, Schinnar R, Bilker W, et al. Aberrant integrin expression in the endometrium of women with endometriosis. *J Clin Endocrinol Metab* 1994;79:643–9.
17. Genbacev OD, Prakobphol A, Foulk RA, Krtolica AR, Ilic D, Singer MS, et al. Trophoblast L-selectin-mediated adhesion at the maternal-fetal interface. *Science* 2003;299:405–8.
18. Kao LC, Germeyer A, Tulac S, Lobo S, Yang JP, Taylor RN, et al. Expression profiling of endometrium from women with endometriosis reveals candidate genes for disease-based implantation failure and infertility. *Endocrinology* 2003;144:2870–81.
19. Burney RO, Talbi S, Hamilton AE, Vo KC, Nyegaard M, Nezhat CR, Lessey BA, Giudice LC. Gene expression analysis of endometrium reveals progesterone resistance and candidate susceptibility genes in women with endometriosis. *Endocrinology* 2007;48:3814–26.
20. Cakmak H, Taylor HS. Molecular mechanisms of treatment resistance in endometriosis: the role of progesterone-hox gene interactions. *Semin Reprod Med* 2010;28:69–74.
21. Taylor HS, Bagot C, Kardana A, Olive D, Arici A. HOX gene expression is altered in the endometrium of women with endometriosis. *Hum Reprod* 1999;14:1328–31.
22. Garrido N, Navarro J, Remohi J, Simon C, Pellicer A. Follicular hormonal environment and embryo quality in women with endometriosis. *Hum Reprod Update* 2000;6:67–74.
23. Pellicer A, Oliveira N, Ruiz A, Remohi J, Simon C. Exploring the mechanism(s) of endometriosis-related infertility: an analysis of embryo development and implantation in assisted reproduction. *Hum Reprod* 1995; 10(Suppl 2):91–7.
24. Garrido N, Navarro J, Garcia-Velasco J, Remohi J, Pellice A, Simon C. The endometrium versus embryonic quality in endometriosis-related infertility. *Hum Reprod Update* 2002;8:95–103.
25. Kissler S, Hamscho N, Zangos S, Gatje R, Muller A, Rody A, et al. Diminished pregnancy rates in endometriosis due to impaired uterotubal transport assessed by hysterosalpingoscintigraphy. *BJOG* 2005;112:1391–6.
26. Marcoux S, Maheux R, Berube S. Laparoscopic surgery in infertile women with minimal or mild endometriosis. Canadian Collaborative Group on Endometriosis. *N Engl J Med* 1997;337:217–22.
27. Parazzini F. Ablation of lesions or no treatment in minimal-mild endometriosis in infertile women: a randomized trial. Gruppo Italiano per lo Studio dell' Endometriosi. *Hum Reprod* 1999;14:1332–4.
28. American Society for Reproductive Medicine. Revised American Society for Reproductive Medicine classification of endometriosis: 1996. *Fertil Steril* 1997;67:817–21.
29. Schenken RS. Modern concepts of endometriosis. Classification and its consequences for therapy. *J Reprod Med* 1998;43:269–75.
30. Adamson GD, Pasta DJ. Endometriosis fertility index: the new, validated endometriosis staging system. *Fertil Steril* 2010;94:1609–15.
31. Bayer SR, Seibel MM, Saffan DS, Berger MJ, Taymor ML. Efficacy of danazol treatment for minimal endometriosis in infertile women. A prospective, randomized study. *J Reprod Med* 1988;33:179–83.
32. Fedele L, Parazzini F, Radici E, Bocciolone L, Bianchi S, Bianchi C, et al. Buserelin acetate versus expectant management in the treatment of infertility associated with minimal or mild endometriosis: a randomized clinical trial. *Am J Obstet Gynecol* 1992;166:1345–50.
33. Hughes E, Brown J, Collins JJ, Farquhar C, Fedorkow DM, Vandekerckhove P. Ovulation suppression for endometriosis. *Cochrane Database Syst Rev* 2007;CD000155.
34. Telimaa S. Danazol and medroxyprogesterone acetate inefficacious in the treatment of infertility in endometriosis. *Fertil Steril* 1988;50:872–5.
35. Thomas EJ, Cooke ID. Successful treatment of asymptomatic endometriosis: does it benefit infertile women? *Br Med J* 1987;294:1117–9.
36. Hull ME, Moghissi KS, Magyar DF, Hayes MF. Comparison of different treatment modalities of endometriosis in infertile women. *Fertil Steril* 1987;47: 40–4.
37. Crosignani PG, Vercellini P, Biffignandi F, Costantini W, Cortesi I, Imperato E. Laparoscopy versus laparotomy in conservative surgical treatment for severe endometriosis. *Fertil Steril* 1996;66:706–11.
38. Chapron C, Vercellini P, Barakat H, Vieira M, Dubuisson JB. Management of ovarian endometriomas. *Hum Reprod Update* 2002;8:591–7.
39. Donnez J, Nisolle M, Gillet N, Smets M, Bassil S, Casanas-Roux F. Large ovarian endometriomas. *Hum Reprod* 1996;11:641–6.
40. Pagidas K, Falcone T, Hemmings R, Miron P. Comparison of reoperation for moderate (stage III) and severe (stage IV) endometriosis-related infertility with in vitro fertilization-embryo transfer. *Fertil Steril* 1996; 65:791–5.
41. Deaton JL, Gibson M, Blackmer KM, Nakajima ST, Badger GJ, Brumsted JR. A randomized, controlled trial of clomiphene citrate and intrauterine insemination in couples with unexplained infertility or surgically corrected endometriosis. *Fertil Steril* 1990;54:1083–8.
42. Fedele L, Bianchi S, Marchini M, Villa L, Brioschi D, Parazzini F. Superovulation with human menopausal gonadotropins in the treatment of infertility associated with minimal or mild endometriosis: a controlled randomized study. *Fertil Steril* 1992;58:28–31.
43. Kemmann E, Ghazi D, Corsan G, Bohrer MK. Does ovulation stimulation improve fertility in women with minimal/mild endometriosis after laser laparoscopy? *Int J Fertil Menopausal Stud* 1993;38:16–21.
44. Werbrouck E, Spiessens C, Meuleman C, D'Hooghe T. No difference in cycle pregnancy rate and in cumulative live-birth rate between women with surgically treated minimal to mild endometriosis and women with unexplained infertility after controlled ovarian hyperstimulation and intrauterine insemination. *Fertil Steril* 2006;86:566–71.
45. Society for Assisted Reproductive Technology, the American Society for Reproductive Medicine. Assisted reproductive technology in the United States: 2010 results generated from the American Society for Reproductive Medicine/Society for Assisted Reproduction registry. Available at: www.sart.org. Last accessed May 24, 2012.
46. Barnhart K, Dunsmoor-Su R, Coutifaris C. Effect of endometriosis on in vitro fertilization. *Fertil Steril* 2002;77:1148–55.

47. Soliman S, Daya S, Collins J, Jarrell J. A randomized trial of in vitro fertilization versus conventional treatment for infertility. *Fertil Steril* 1993;59:1239–44.
48. Garcia-Velasco JA, Mahutte NG, Corona J, Zuniga V, Giles J, Arici A, et al. Removal of endometriomas before in vitro fertilization does not improve fertility outcomes: a matched, case-control study. *Fertil Steril* 2004;81:1194–7.
49. Garcia-Velasco JA, Somigliana E. Management of endometriomas in women requiring IVF: to touch or not to touch. *Hum Reprod* 2009;24:496–501.
50. Pearce CL, Templeman C, Rossing MA, Lee A, Near AM, Webb PM, et al. Association between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case-control studies. *Lancet Oncol* 2012;13:285–94.
51. Somigliana E, Vercellini P, Vigano P, Ragni G, Crosignani PG. Should endometriomas be treated before IVF-ICSI cycles? *Hum Reprod Update* 2006;12:57–64.
52. Sallam HN, Garcia-Velasco JA, Dias S, Arici A. Long-term pituitary down-regulation before in vitro fertilization (IVF) for women with endometriosis. *Cochrane Database Syst Rev* 2006:CD004635.
53. Dicker D, Goldman JA, Levy T, Feldberg D, Ashkenazi J. The impact of long-term gonadotropin-releasing hormone analogue treatment on preclinical abortions in patients with severe endometriosis undergoing in vitro fertilization-embryo transfer. *Fertil Steril* 1992;57:597–600.
54. Surrey ES, Silverberg KM, Surrey MW, Schoolcraft WB. Effect of prolonged gonadotropin-releasing hormone agonist therapy on the outcome of in vitro fertilization-embryo transfer in patients with endometriosis. *Fertil Steril* 2002;78:699–704.
55. Stephansson O, Kieler H, Granath F, Falconer H. Endometriosis, assisted reproduction technology, and risk of adverse pregnancy outcome. *Hum Reprod* 2009;24:2341–7.
56. Guzick DS, Carson SA, Coutifaris C, Overstreet JW, Factor-Litvak P, Steinkampf MP, et al. Efficacy of superovulation and intrauterine insemination in the treatment of infertility. *N Engl J Med* 1999;340:177–83.
57. Chaffkin LM, Nulsen JC, Luciano AA, Metzger DA. A comparative analysis of the cycle fecundity rates associated with combined human menopausal gonadotropin (hMG) and intrauterine insemination (IUI) versus either hMG or IUI alone. *Fertil Steril* 1991;55:252–7.