Endometriosis and infertility

The Practice Committee of the American Society for Reproductive Medicine

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Women with endometriosis typically present with pelvic pain, infertility or an adnexal mass. Surgery for persistent adnexal masses may be indicated to remove an endometrioma or other pelvic pathology. Surgical or medical therapy is efficacious for pelvic pain due to endometriosis, but treatment of endometriosis in the female partner of an infertile couple raises a number of complex clinical questions that do not have simple answers. (Fertil Steril® 2006;86(Suppl 4):S156–60. ©2006 by American Society for Reproductive Medicine.)

Women with endometriosis typically present with pelvic pain, infertility or an adnexal mass. Surgery for persistent adnexal masses may be indicated to remove an endometrioma or other pelvic pathology. Surgical or medical therapy is efficacious for pelvic pain due to endometriosis, but treatment of endometriosis in the female partner of an infertile couple raises a number of complex clinical questions that do not have simple answers. There are few infertility problems requiring greater clinical acumen than those needed to plan therapy for an infertile woman with endometriosis.

FECUNDITY IN WOMEN WITH ENDOMETRIOSIS

Fecundity is defined as the probability of a woman achieving a live birth for any given month (1). In normal couples, fecundity is in the range of 0.15 to 0.20 per month and decreases with age (2). In untreated women with endometriosis and infertility, monthly fecundity is 0.02 to 0.10 (3). Early studies suggested that 25% to 50% of infertile women have endometriosis and that 30% to 50% of women with endometriosis are infertile (4). There is a higher prevalence of endometriosis in infertile women (48%) compared with fertile women undergoing tubal sterilization (5%) (5). Other reports have confirmed that infertile women are 6 to 8 times more likely to have endometriosis than fertile women (6).

ENDOMETRIOSIS AND INFERTILITY: CAUSE AND EFFECT

The hypothesis that endometriosis causes infertility or a decrease in fecundity remains controversial. Whereas there is a reasonable body of evidence to demonstrate an association between endometriosis and infertility, a cause and effect relationship has not been established. In a prospective study of women undergoing therapeutic donor insemination, fecundity was 0.12 in women without endometriosis and 0.036 in those with minimal endometriosis (7). The results of this study were at odds with two retrospective studies from the 1980s in which fecundity of women with minimal endometriosis was similar to that of other women undergoing donor insemination (8, 9). On the premise that endometriosis does cause infertility, then eradication of the disease should improve fecundity. Two randomized controlled trials (RCTs) have compared outcomes following laparoscopic ablation or expectant management of endometriosis. In the Canadian Collaborative Group on Endometriosis RCT involving 341 women with stage I/II disease followed for 36 weeks after laparoscopy, monthly fecundity was 0.047 and 0.024 in the ablated and untreated groups, respectively (10). In the Gruppo Italiano per lo Studio dell' Endometriosi RCT involving 101 women with stage I/II disease followed for 52 weeks after laparoscopy, fecundity was 0.016 and 0.019 in the ablated and untreated groups, respectively (11). Although fecundity was significantly improved only in the Canadian surgical trial, fecundity remained significantly lower than that observed in normal fertile women. Thus the visible lesions of endometriosis contribute only a small fraction of the reduced fecundity seen in women with endometriosis.

BIOLOGIC MECHANISMS THAT MAY LINK ENDOMETRIOSIS AND INFERTILITY

Several mechanisms have been proposed to clarify the association between endometriosis and infertility (12). It should be emphasized that none of these mechanisms has been proven to decrease fecundity in women. These mechanisms are briefly discussed below.

Distorted Pelvic Anatomy

Major pelvic adhesions, including those that result from endometriosis, can impair oocyte release from the ovary or inhibit ovum pickup or transport (13).

Altered Peritoneal Function

Many studies demonstrate that women with endometriosis have an increased volume of peritoneal fluid, increased concentration of activated macrophages and increased peritoneal fluid concentrations of prostaglandins, interleukin-1, tumor necrosis factor and proteases. Peritoneal fluid from women with endometriosis reportedly contains an ovum capture

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inhibitor that prevents normal cumulus-fimbria interaction (14). These alterations may have adverse effects on the oocyte, sperm, embryo or fallopian tube function (15).

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 (15).

Endocrine and Ovulatory Abnormalities

It has been proposed that women with endometriosis may have endocrine and ovulatory disorders, including the luteinized unruptured follicle syndrome, luteal phase dysfunction, abnormal follicular growth and premature as well as multiple luteinizing hormone (LH) surges (13). Whereas these hypotheses have been proposed, there is no evidence to validate them.

Impaired Implantation

Mounting evidence suggests that disorders of endometrial function may contribute to the deceased fecundity observed in women with endometriosis. Reduced endometrial expression of the $\alpha v\beta$ integrin (a cell adhesion molecule) during the time of implantation has been described in some women with endometriosis (16). More recently, very low levels of an enzyme involved in the synthesis of the endometrial ligand for L-section (a protein that coats the trophoblast on the surface of the blastocyst) (17) have been observed in infertile women with endometriosis (18). These data lend credence to the hypothesis that functional disorders of the endometrium may both predispose to the development of endometriosis and impair implantation mechanisms in affected women.

DIAGNOSIS AND STAGING

The current clinical opinion is that a surgical procedure such as laparoscopy is required for definitive diagnosis of endometriosis. Given this state of clinical practice, an important question is when to perform laparoscopy to determine if endometriosis is present. A history and physical examination can yield a number of significant findings, including affected first degree relatives, chronic pelvic pain and dysmenorrhea, retroverted uterus, adnexal masses, cul de sac nodularity and uterosacral ligament thickening and tenderness, but none is diagnostic. Ultrasound can help the clinician establish a presumptive diagnosis of ovarian involvement with endometriosis, but laparoscopy is necessary to confirm the diagnosis. Endometriosis is a heterogeneous disease with typical and atypical morphology and spanning a spectrum from a single 1-mm peritoneal implant to 10-cm endometriomas with cul-de-sac obliteration (19). Consequently, a clinical staging system is necessary to allow clinicians to communicate effectively regarding prognosis and treatment. The American Society for Reproductive Medicine revised classification system for endometriosis (ASRM 1996) is the most widely accepted staging system (19). Unfortunately, the staging system does not correlate well with a woman's chance of conception following therapy. This poor predictive ability is related to the arbitrary assignment of a point score 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 (20). It is unlikely that any accurate staging system will be introduced until we have a better understanding of the pathophysiology of endometriosis-associated infertility.

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 fecundity. Several options have been suggested for treatment: danazol, gonadotropin-releasing hormone agonists (GnRH-a) and antagonists, progestins and combined estrogen-progestin therapy. Several RCTs demonstrate that danazol, other progestins or GnRH-a are not effective treatments for infertility associated with minimal to mild endometriosis (21, 22). In two RCTs involving 105 infertile women with minimal to mild endometriosis, pregnancy rates were no better with danazol than expectant management (21, 23). 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-a treatment (6 months) or expectant management (22). 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 (24). Also, in a small RCT involving 31 women, pregnancy rates with progestins and expectant management were 41% and 43%, respectively (25). In a meta-analysis that included seven studies comparing medical treatment to no treatment or placebo, the common odds ratio for pregnancy was 0.85 (95% CI 0.95, 1.22) (3). Thus hormonal treatment does not improve the fecundity of infertile women with Stage I/II endometriosis.

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 reported on the effectiveness of laparoscopic surgery for Stage I or II endometriosis associated with infertility (10, 11). Both studies permitted surgical discretion in the intervention regarding excision or ablation. The primary outcomes were slightly different: the Italian study analyzed pregnancies which occurred within one year after laparoscopy and proceeded to live births; the Canadian study analyzed pregnancies which occurred within 36 weeks after laparoscopy and proceeded to 20 weeks gestation, an end- point which is nearly identical to the live birth rate. In the Italian study, 10/51 (20%) and 10/45

(22%) of the ablation/ resection and no treatment patients, respectively, were successful. In the Canadian study, 50/172 (29%) and 29/169 (17%) of the ablation/resection and no treatment patients, respectively, were successful. The baseline untreated rates were 22% in 52 weeks and 17% in 36 weeks, respectively, in the Italian and Canadian patients, 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 (11). 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) (26). 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. There is no evidence that the outcome is affected by the method of ablation, by electro-surgery or laser delivery systems (10).

A nonrandomized study demonstrated that the cumulative probability of pregnancy in 216 infertile patients with severe endometriosis, followed for up to 2 years after laparoscopy or laparotomy, was significantly increased, 45% and 63%, respectively (26). These and other observational studies, that are not free from bias, suggest that in women with Stage III/IV endometriosis, without other identifiable infertility factors, conservative surgical treatment with laparoscopy and possible laparotomy may increase fertility (20).

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. Postoperative medical therapy has been advocated as a means to eradicate residual endometriotic implants in patients with extensive disease in whom resection of all implants is impossible or inadvisable. Postoperative hormonal therapy may also treat "microscopic disease"; however, none of these treatments has been proven to enhance fertility.

SUPEROVULATION AND INTRAUTERINE INSEMINATION (COH/IUI)

Superovulation (SO) with gonadotropins and intrauterine insemination (IUI) are frequently used to treat women with infertility (27). An NIH Reproductive Medicine Network study of 932 infertile couples with Stage I/II endometriosis or otherwise unexplained infertility randomized patients to intracervical insemination (IC), IUI, gonadotropin/IC or gonadotropin/IUI. In this large RTC the monthly fecundity in the gonadotropin/IUI group (0.09) was significantly higher than the monthly fecundity in the IUI group (0.05), the gonadotropin/IC group (0.04) and the IC group (0.02) (27).

Several studies also report success with SO/IUI in the treatment of endometriosis-associated infertility. In an RCT comparing clomiphene citrate and IUI with preovulatory intercourse in patients with unexplained infertility or surgically corrected endometriosis, a statistically significant increase in cycle fecundity was seen with four cycles of clomiphene citrate/IUI compared with controls (0.095 versus 0.033, respectively) (28). Another study randomized patients to receive either gonadotropins with intercourse or gonadotropins with IUI (29). All patients had endometriosis previously treated with laser laparoscopy. The fecundity was greater in the gonadotropin/IUI group (0.129; n = 109) than in the intercourse group (0.066; n = 76). A randomized trial of 40 women with stage I/II endometriosis and infertility studied the effect of either three cycles of gonadotropin/IUI or no treatment (expectant management) (30). The fecundity was 0.15 in the gonadotropin/IUI group and 0.045 in the untreated group ($P<.05$). Another study reported on the effects of expectant management, clomiphene citrate, gonadotropins or in vitro fertilization-embryo transfer (IVF-ET) on fecundity in women with infertility and minimal or mild endometriosis (31). The observed cycle fecundity with gonadotropin treatment alone (0.073) was significantly higher than with no treatment (0.028; Table 1).

ASSISTED REPRODUCTIVE TECHNOLOGY

The most 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 is 29.4% (32).

There are no large RCTs which definitely demonstrate that IVF-ET is more effective than expectant management in the treatment of stage-specific infertility associated with endometriosis. In one small RCT, 21 women with endometriosis and infertility were randomized to receive either IVF (n = 15) or expectant management (n = 6) (33). None of the women in the expectant management group became pregnant compared to five of the 15 women who received IVF-ET (33%, P=NS) (33).

Several studies suggest that in women with advanced endometriosis, long-term treatment with GnRH-a before initiation of a cycle may improve fecundity. Among patients with severe endometriosis, 6 months of hormonal suppression with GnRH-a resulted in higher numbers of oocytes retrieved, embryos transferred, and pregnancies (34). The investigators concluded that long-term GnRH-a therapy might reduce preclinical abortions in patients with severe endometriosis who are undergoing IVF-ET (34). A recent study demonstrated the benefits of prolonged down-regulation with GnRH-a before initiation of IVF-ET in patients with endometriosis (35). In this RCT, the overall experience with 51 patients undergoing IVF-ET demonstrated significantly higher ongoing

TABLE 1

Cycle fecundity in women with stage I or II endometriosis, according to treatment.

Group	Unexplained infertility	Endometriosis-associated infertility			
Treatment	Guzick et al. (27)	Deaton et al. (28)	Chaffkin et al. (29)	Fedele et al. (30)	Kemmann et al. (31)
No treatment or intracervical insemination	0.02	0.033	—	0.045	0.028
IUI	0.05[a]	—	—	—	—
Clomiphene	—	—	—	—	0.066
Clomiphene/IUI	—	0.095[a]	—	—	—
Gonadotropins	0.04[a]	—	0.066	—	0.073[a]
Gonadotropin/IUI	0.09[a]	—	0.129[a]	0.15[a]	—
IVF	—	—	—	—	0.222[a]

[a] $P<.05$ for treatment vs. no treatment.

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pregnancy rates with prolonged dura- tion of GnRH-a use before IVF-ET (35). Although these studies suggest that longer periods of pretreatment with GnRH-a will improve implantation rates in patients, with endometriosis who undertake IVF-ET, support for this treatment strategy is not unanimous (36).

CLINICAL APPROACH TO INFERTILE WOMEN WITH ENDOMETRIOSIS

Clinical decisions in the management of infertility associated with endometriosis are difficult because few RCTs have been conducted to evaluate and compare the effectiveness of the various forms of treatment. Moreover, the available 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, the factors such as the patient's age, duration of infertility, family history and pelvic pain must be taken into consideration. When laparoscopy is performed, the safe ablation or excision of visible endometriosis should be considered based on observations from RTC. This should be discussed openly with the patient when planning her treatment. Of course, if pain were also a concern, laparoscopy and surgical treatment would be appropriate. Expectant management after laparoscopy is an option for younger women. Alternatively, superovulation with IUI may be offered. Female age is an important factor in designing therapy. After age 35, there is a significant decrease in fecundity and an increase in the spontaneous abortion rate. The decrease in fecundity due to the two variables of endometriosis and age may be additive. Consequently, in the older infertile woman with endometriosis, a more aggressive therapeutic plan with SO/IUI or IVF-ET may be reasonable rather than expectant management.

For infertile women with ASRM 1996 stage III/IV endometriosis and no other identifiable infertility factor the conservative surgery with laparoscopy and possible laparotomy are recommended. Several studies suggest that surgical therapy increases fertility in women with advanced endometriosis (19). These studies indicate that expectant management is not a good option for women with infertility and severe endometriosis. However, it should be pointed out that there are no RCTs to define results of surgical treatment for stage III/IV disease.

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 infertility operation. There is no sufficiently powered prospective randomized trial evaluating the effect on pregnancy outcome of surgical treatment followed by IVF-ET versus IVF-ET alone. In one retrospective study, 23 women with stage III/IV endometriosis underwent IVF-ET and 18 women underwent repeat surgery (31). 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. In summary, there are limited data available to estimate the effect of surgical treatment in addition to IVF-ET on the outcome of pregnancy in endometriosis-associated infertility.

SUMMARY AND RECOMMENDATIONS

- There are few RCTs on the treatment of endometriosis-associated infertility.
- Female age, duration of infertility, family history, pelvic pain and stage of endometriosis should be taken into account when formulating a management plan.
- When laparoscopy is performed, the surgeon should consider safely ablating or excising visible lesions of endometriosis.
- In women with stage I/II endometriosis-associated infertility, expectant management or superovulation/IUI after laparoscopy can be considered for younger patients.

Women 35 years of age or older should be treated with SO/IUI or IVF-ET.

- In women with stage III/IV endometriosis-associated infertility, conservative surgical therapy with laparoscopy and possible laparotomy are indicated.
- 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.

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REFERENCES

1. 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.
2. 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.
3. Hughes EG, Fedorkow DM, Collins JA. A quantitative overview of controlled trials in endometriosis-associated infertility. Fertil Steril 1993;59: 963–70.
4. Counsellor VS. Endometriosis. A clinical and surgical review. Am J Obstet Gynecol 1938;36:877.
5. Strathy JH, Molgaard CA, Coulam CB, Melton LJ 3rd. Endometriosis and infertility: a laparoscopic study of endometriosis among fertile and infertile women. Fertil Steril 1982;38:667–72.
6. Verkauf BS. The incidence, symptoms, and signs of endometriosis in fertile and infertile women. J Fla Med Assoc 1987;74:671–5.
7. Jansen RP. Minimal endometriosis and reduced fecundability: prospective evidence from an artificial insemination by donor program. Fertil Steril 1986;46:141–3.
8. Portuondo JA, Echanojauregui AD, Herran C, Alijarte I. Early conception in patients with untreated mild endometriosis. Fertil Steril 1983;39:22–5.
9. Rodriguez-Escudero FJ, Neyro JL, Corcostegui B, Benito JA. Does minimal endometriosis reduce fecundity? Fertil Steril 1988;50:522–4.
10. Marcoux S, Maheux R, Bérubé S. Laparoscopic surgery in infertile women with minimal or mild endometriosis. Canadian Collaborative Group on Endometriosis. N Engl J Med 1997;337:217–22.
11. 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.
12. Schenken RS. Treatment of human infertility: the special case of endometriosis. In: Adashi EY, Rock JA, Rosenwaks Z, eds. Reproductive endocrinology, surgery and technology. Philadelphia, PA: Lippincott-Raven, 1996:2122–39.
13. 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.
14. 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.
15. Lebovic DI, Mueller MD, Taylor RN. Immunobiology of endometriosis. Fertil Steril 2001;75:1–10.
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. American Society for Reproductive Medicine. Revised American Society for Reproductive Medicine classification of endometriosis: 1996. Fertil Steril 1997;67:817–21.
20. Schenken RS. Modern concepts of endometriosis. Classification and its consequences for therapy. J Reprod Med 1998;43:269–75.
21. 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.
22. 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.
23. Telimaa S. Danazol and medroxyprogesterone acetate inefficacious in the treatment of infertility in endometriosis. Fertil Steril 1988;50:872–5.
24. Thomas EJ, Cooke ID. Successful treatment of asymptomatic endometriosis: does it benefit infertile women? Br Med J 1987;294:1117–9.
25. Hull ME, Moghissi KS, Magyar DF, Hayes MF. Comparison of different treatment modalities of endometriosis in infertile women. Fertil Steril 1987;47:40–4.
26. Al-Inany HG, Crosignani PG, Vercellini P. Evidence may change with more trials: concepts to be kept in mind [letters]. Hum Reprod 2000; 15:2447–8.
27. 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.
28. 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.
29. 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.
30. 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.
31. 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.
32. Society for Assisted Reproduction, the American Society for Reproductive Medicine. Assisted reproductive technology in the United States: 1999 results generated from the American Society for Reproductive Medicine/ Society for Assisted Reproduction registry. Fertil Steril 2002;78:918–31.
33. 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.
34. 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.
35. 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.
36. Olivennes F, Feldberg D, Liu HC, Cohen J, Moy F, Rosenwaks Z. Endometriosis: a stage by stage analysis—the role of in vitro fertilization. Fertil Steril 1995;64:392–8.