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# Endometriosis: Still tough to diagnose and treat

## ■ ABSTRACT

Endometriosis is a chronic disease that may have life-altering implications such as chronic pelvic pain and infertility. The following review will familiarize the practicing physician with available therapies to maintain and enhance reproductive potential and control pelvic pain in women with endometriosis.

## ■ KEY POINTS

Medical treatments for endometriosis include oral contraceptives, progesterone, testosterone derivatives, and gonadotropin-releasing hormone (GnRH) agonists.

The antiestrogenic side effects of GnRH agonists (eg, bone loss, hot flashes, vaginal dryness) can be mitigated by giving back estrogen in replacement doses, making long-term GnRH therapy possible.

Laparoscopic surgical resection of endometriotic lesions is as effective as open surgery, but recurrence is common with either method.

Endometriosis is the most common cause of chronic pelvic pain in adolescents.

Medical and surgical treatments for endometriosis do not restore normal fertility rates, although surgery can improve the patient's chances of fertility.

**D**ESPITE ADVANCES, endometriosis is still tough to diagnose, tough to treat, and tough to live with.

Defined as the presence of endometrial glands and stroma outside the uterine cavity, endometriosis can only be diagnosed definitively by seeing the endometriotic lesions on laparoscopy or laparotomy. Medical therapy is far from ideal. Despite surgical ablation, many patients experience recurring pelvic pain and infertility.

In this article we explore the management of chronic pelvic pain in adult women and adolescents and infertility due to endometriosis.

## ■ PATHOGENESIS IS UNCLEAR

Various theories have been proposed to explain the pathogenesis of endometriosis.

In the 1920s, Sampson<sup>1</sup> proposed that in endometriosis, the pelvic peritoneum is “seeded” by retrograde menstruation. However, 90% of women have been shown to have retrograde menstruation; therefore, some authors propose that women with endometriosis have an immune deficiency that leads to inappropriate clearance of endometrial cells from the pelvic peritoneum.

Endometriosis in distant sites has been explained by metastasis of endometrial cells through lymphatic or blood vessels. In addition, some believe in the existence of totipotent cells that can transform into endometrial cells.

## ■ CHRONIC PELVIC PAIN

The most common clinical manifestation of endometriosis is chronic pelvic pain. (Pelvic pain is usually deemed chronic if it persists for



### PATIENT INFORMATION

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TABLE 1

### Medical therapies for pelvic pain due to endometriosis

MEDICATION	DOSAGE	SIDE EFFECTS
<b>Nonsteroidal anti-inflammatory drugs (NSAIDs)</b>	Variable	Gastrointestinal irritation
<b>Oral contraceptives</b>	20–35 µg ethinyl estradiol (cyclic or noncyclic)	Breakthrough bleeding, nausea, fluid retention
<b>Progestational agents</b>		Breakthrough bleeding, fluid retention, acne, weight gain
Medroxyprogesterone acetate (oral)	30–50 mg/day	
(depot injection)	150 mg/3 months	
Megestrol acetate	40 mg/day	
<b>Testosterone derivatives</b>		
Methyltestosterone	5–10 mg/day	Masculinization, fluid retention, irregular menses
Danazol	800 mg/day	Weight gain, hirsutism, acne, irregular menses, abnormal lipid profile
<b>GnRH agonists</b>		Hot flushes, vaginal dryness, decreased bone density
Leuprolide (depot suspension)	3.75 mg/4 weeks	
Nafarelin	1 puff twice daily	
<b>GnRH agonist plus “add-back” therapy</b>	A GnRH agonist, as above plus (a) conjugated equine estrogens 0.625 mg/day and medroxyprogesterone 2.5 mg/day or (b) an oral contraceptive	Possible decreased bone density

more than 6 months.) Some patients with endometriosis may suffer from a concomitant pain syndrome, which is defined as pain that:

- Does not respond to over-the-counter analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs)
- Disrupts the patient’s life, preventing her from functioning in the family or on the job
- Is accompanied by depression or other psychological disorder
- Is out of proportion to any identifiable abnormality found on examination or imaging studies.

#### Consider other causes of chronic pain

Even if a patient has been diagnosed with endometriosis, it is important to consider other causes of chronic pain. Endometriosis is a common finding on laparoscopy performed for indications other than pelvic pain. Often,

physicians simply assume that any pelvic pain in a patient with endometriosis is related to the endometriosis itself and do not consider alternative diagnoses, treating the patient with medication or surgery—with significant side effects and very little relief.

Many disorders can cause chronic pelvic pain: irritable bowel syndrome, interstitial cystitis, musculoskeletal problems, and others. Think about consulting a gastroenterologist if the symptoms are focused in the gastrointestinal system, or a urologist if the symptoms are in the urinary system.

#### ■ DIAGNOSIS

Symptoms that suggest endometriosis are menstrual cycle-related pain (eg, midcycle pain or dysmenorrhea) and deep dyspareunia (pain during sexual intercourse). However, women with endometriosis do not have a



higher prevalence of menstrual dysfunction. The pain can be diffuse or localized.

Areas of tenderness can be better identified by performing a physical examination during a menstrual period. Nodularity of the cul-de-sac can be felt in patients with deeply infiltrating disease.

Imaging studies, such as ultrasonography or magnetic resonance imaging, will not show peritoneal disease or adhesions unless there are large endometriomas.<sup>2</sup> Serum markers such as cancer antigen (CA) 125 are not sensitive enough to be used for screening.<sup>3</sup> The definitive diagnosis of endometriosis can only be made by laparoscopy or laparotomy.

#### ■ FOUR STAGES OF ENDOMETRIOSIS

In the classification system developed by the American Society of Reproductive Medicine,<sup>4</sup> endometriosis has four stages, based on the location and extent of disease: stage 1 (minimal), 2 (mild), 3 (moderate), and 4 (severe).

Perception of pain is related to both somatic and psychologic components. Patients with deeply infiltrating disease of the cul-de-sac often have significantly higher pain scores; however, the stage of disease often does not correlate with the severity of the pain.

#### ■ MEDICAL TREATMENT OF ENDOMETRIOSIS ASSOCIATED WITH PELVIC PAIN

A variety of medical therapies are available for patients with recurring pelvic pain due to endometriosis (TABLE 1). With recurrence of dysmenorrhea, a trial of NSAIDs may be all that is necessary to control the symptoms.

**Oral contraceptives** are the most common form of medical treatment. No specific formulation is superior.

In an open-label, randomized clinical trial,<sup>5</sup> a cyclic low-dose oral contraceptive was inferior to the gonadotropin-releasing hormone (GnRH) agonist goserelin in relieving deep dyspareunia but similar in relieving non-menstrual pain. (The women in the goserelin group had no menstrual pain because the drug suppressed the menses completely.) Pain scores fell significantly from baseline in the oral contraceptive group, but some patients still had dysmenorrhea. Six months after stop-

ping treatment, pain scores did not differ between the two groups.

Patients who still have significant dysmenorrhea while on cyclic oral contraceptives may take it continuously to prevent menstruation and its associated pain.

**Danazol** is a derivative of 17-alpha ethinyltestosterone that inhibits the midcycle gonadotropin surge and ovarian steroidogenesis. The net effect is a hypoestrogenic, hyperandrogenic environment. Danazol is as effective as the GnRH agonists,<sup>6</sup> but has side effects related to hypoestrogenemia and hyperandrogenemia. Irreversible hepatocellular damage has been reported.

**Progestins.** Medroxyprogesterone acetate was as effective as danazol in relieving pain symptoms in a placebo-controlled trial.<sup>7</sup>

**Gonadotropin-releasing hormone (GnRH) agonists,** after a brief stimulatory phase, suppress estradiol levels to castrate levels. Subcutaneous and inhalational forms may be taken on a daily basis; intramuscular preparations can be given once a month or once every 3 months.

Randomized clinical trials have shown excellent short-term results. Leuprolide, a GnRH agonist, was shown in a placebo-controlled trial to be effective in treating endometriosis-associated pain.<sup>8</sup>

The main side effects of GnRH agonists are due to low estrogen levels. Patients lose trabecular bone density, which can take up to 2 years to restore after 6 months of treatment.<sup>9</sup> In addition, they notice symptoms such as hot flashes and vaginal dryness.

These side effects initially precluded long-term use of GnRH agonists, until "add-back" therapy was developed in which the patient is given enough estrogen to relieve the flushes and prevent bone loss. A combination of conjugated estrogens 0.625 mg and medroxyprogesterone 2.5 mg daily has been shown to be effective in preventing the hypoestrogenic side effects of GnRH agonists and maintaining their efficacy. Other agents such as bisphosphonates have been used successfully to prevent bone loss.

These add-back regimens have introduced the possibility of long-term therapy in some patients. Long-term results of therapy with GnRH agonists showed a 5-year recurrence rate of 37% with minimal disease and 74%

**Even if the patient has endometriosis, consider other causes of chronic pain**

with severe disease.<sup>10</sup> In another retrospective review,<sup>11</sup> the median time to recurrence of symptoms after medical therapy (danazol or a GnRH agonist) was 6 months.

GnRH agonist therapy has also been used to prevent postoperative recurrence of symptoms, although the results have been contradictory. Hornstein et al,<sup>12</sup> in a placebo-controlled trial, found that a GnRH agonist increased the median time to initiation of alternative treatment (24 months with the GnRH agonist nafarelin vs 11 months with placebo). However, at 6 months, the two groups did not differ in their pain scores.

### ■ SURGICAL TREATMENT OF ENDOMETRIOSIS ASSOCIATED WITH PELVIC PAIN

Conservative surgical treatment of endometriosis entails removing or destroying the lesions.

**Laparoscopic surgery.** Several observational studies found laparoscopy to be just as effective as laparotomy in treating endometriosis, regardless of severity.<sup>13</sup>

Sutton et al<sup>14</sup> performed one of the few randomized double-blind clinical trials to evaluate the results of surgery for endometriosis. Patients were randomized to undergo either diagnostic laparoscopy or laparoscopy with treatment. Pain scores improved in 22% of the patients in the control group (owing to a placebo effect), compared with 63% of the treated women, of whom 90% continued to report pain relief 1 year later.<sup>15</sup>

**Nerve ablation.** If pain persists, other surgical options include denervation procedures such as uterosacral nerve ablation (“LUNA” if performed laparoscopically) or presacral neurectomy.

The LUNA procedure involves transecting nerves near the cervix. A recent review by the International Cochrane Collaboration concluded there is no evidence that the LUNA procedure adds benefit to surgery for endometriosis ablation.<sup>16</sup>

Presacral neurectomy involves transecting nerves below the bifurcation of the aorta. A randomized clinical trial found that this procedure did show some benefit in relieving midline pelvic pain.<sup>17</sup>

Depending on the extent of disease and

completeness of resection, patients may be started on medical therapy immediately after surgery.

### ■ ENDOMETRIOSIS IN ADOLESCENTS

Endometriosis is the most common cause of chronic pelvic pain in adolescents,<sup>18</sup> accounting for up to 70% of cases.<sup>19</sup> The likelihood of finding endometriosis in an adolescent with pelvic pain increases with age.<sup>20</sup> Unlike in adult women, definitive therapy (removal of all reproductive organs) to manage endometriosis pain is not an option for adolescents.

#### Endometriotic lesions are different in adolescents

Endometriotic lesions in adolescents do not have the typical “powder-burn” appearance found in adults. Therefore, the surgeon must maintain a high level of suspicion when perusing the pelvis. Lesions may be clear, vesicular, white, or hemorrhagic. With time, they are believed to progress to the typical powder-burn lesions seen in adults.<sup>20</sup> Redwine<sup>21</sup> showed that black lesions are usually noted 10 years later than red and clear lesions.

Most adolescents with endometriosis present with stage 1 disease.<sup>18</sup> Indeed, in most series, none of the adolescent patients had stage 3 or 4 disease.

The degree of pain and discomfort in these patients does not correlate with the amount or location of endometriosis.<sup>22</sup> One study<sup>23</sup> showed that a higher amount of prostaglandin F<sub>2</sub>-alpha is released from hemorrhagic lesions, possibly explaining the increased dysmenorrhea in adolescents.

#### Müllerian anomalies

Patients with obstructive müllerian anomalies such as imperforate hymen, transverse vaginal septum, cervical agenesis, or a non-communicating uterine horn have a higher incidence of endometriosis. An obstruction in the outflow tract will lead to increased backflow of blood into the peritoneal cavity, which is likely to increase the probability of endometriosis.<sup>24</sup>

These adolescents are more likely to present with stage 3 or 4 endometriosis as compared with adolescents without müllerian

**The stage of disease often does not correlate with the severity of the pain**



anomalies who have endometriosis. Müllerian anomalies are likely to be first detected in adolescence, when, at menarche, the patient is likely to begin experiencing symptoms. Initially she may complain of cyclic pain, which gradually progresses to pain throughout the cycle.

The physician's index of suspicion must be very high to diagnose these patients appropriately. An adolescent presenting with pelvic pain or amenorrhea or menstrual irregularities should have an evaluation of her reproductive organs. Early diagnosis is mandatory, since relief of the müllerian obstruction leads to resolution of endometriosis and pain.<sup>24</sup> In addition, the earlier the abnormality is detected, the greater the chance that damage to reproductive organs can be minimized and fertility potential maintained.

### Therapy for adolescent endometriosis

A combination of medical and surgical therapy is used to manage adolescent endometriosis. The goal is to control pain, minimize the number of surgical procedures, and preserve all reproductive organs.

**Surgery.** At the time of diagnosis during laparoscopy, all endometriotic lesions should be destroyed through excision, endocoagulation, or laser vaporization. Women managed with laser laparoscopy vs expectant management have significant relief of pain.<sup>14</sup> However, results are poorest for stage 1 patients.<sup>14</sup>

Since adolescents are more likely to have low-stage endometriosis, they are less likely to experience complete resolution of symptoms with surgical destruction of lesions. Concomitant diagnoses such as irritable bowel syndrome and lactose intolerance must be considered. Also, a thorough sexual history must be obtained, since girls with a history of sexual abuse are more likely to have pelvic pain.

**Medical treatment** of pelvic pain due to endometriosis in adolescents is similar to its management in adults (TABLE 1). However, danazol and methyltestosterone are rarely used in adolescents, owing to their unacceptable side effects.

**Education.** Some adolescents may need to be seen by a pediatric psychologist, not only

to detect any psychologic issues that may be contributing to lack of pain control, but also to teach methods of pain control.

It is imperative to spend additional time with adolescents to explain endometriosis and its possible clinical implications. Multiple visits should be scheduled to answer questions and concerns that arise as the adolescent attempts to understand her disease.

### ■ ENDOMETRIOSIS AND INFERTILITY

From 25% to 40% of women undergoing diagnostic laparoscopy because of infertility are found to have endometriosis, compared with 2% to 5% of women undergoing laparoscopic tubal ligation.<sup>25</sup> In addition, the disease is more severe in the infertile group.

#### How does endometriosis impair fertility?

In advanced endometriosis, large endometriomas and extensive pelvic adhesions can disrupt the normal anatomic relationship between the fallopian tubes and the ovaries, creating an obvious impediment to conception. However, in minimal or mild disease it is unclear how a few superficial lesions can reduce the monthly fecundity rate from a normal of about 20% down to 2% to 3%.

A possible mechanism of infertility is that endometriosis generates a local peritoneal inflammatory response, leading to immune dysfunction and altered levels of prostaglandins, growth factors, and cytokines.<sup>26</sup> Increased numbers of peritoneal macrophages may phagocytose sperm and reduce their fertility potential.

Other possible mechanisms:

- Endometriosis may interfere with ovulation and oocyte pickup by its association with the luteinized unruptured follicle syndrome and a factor that inhibits capture of the ovulated oocyte by the fimbria of the fallopian tube, although the evidence for this is very weak.<sup>26</sup>
- Endometriosis may impair fertilization and embryo quality.
- It may also reduce implantation of the embryo by reducing endometrial alpha-v-beta-3 integrin (an adhesion molecule necessary for implantation of the fertilized egg) and leukemia inhibitory factor.<sup>27</sup>

**Without estrogen replacement, patients lose bone density and have hot flashes on GnRH agonists**

### Treatments to enhance fertility

Infertile patients have three options short of in vitro fertilization: medical, surgical, and superovulation with intrauterine insemination.

**Medical and surgical treatment.** Although minimal and mild endometriosis reduces monthly fecundity rates, medical and surgical treatments have not been shown to restore normal fertility. In fact, placebo-controlled trials have not shown suppressive therapy with GnRH agonists, danazol, or progestins to enhance fertility for any stage of endometriosis.<sup>28,29</sup>

A meta-analysis of pregnancy rates with endometriosis treatment found that surgical treatment with laparotomy or laparoscopy resulted in significantly higher pregnancy rates than medical treatment or expectant management.<sup>30,31</sup> However, the improvement was limited to patients with moderate to severe disease.

Two randomized studies—one from Italy and the other from Canada—compared surgical treatment with no treatment at the time of diagnostic laparoscopy for minimal to mild endometriosis. The Canadian study<sup>32</sup> followed patients for 36 weeks postoperatively. The control group had a monthly fecundity rate of 2.4% compared with 4.7% for the treatment group. Although this difference was statistically significant, 4.7% is still a long way from the normal 20%.

The pregnancy rates at 1 year in the Italian study were 24% in the control group vs 29% in the treatment group; the difference was not statistically significant.<sup>33</sup>

**Superovulation with intrauterine insemination.** Tummon et al<sup>34</sup> randomized patients with minimal to mild endometriosis to undergo superovulation with intrauterine insemination

or no treatment. The live birth rate per cycle was significantly better with treatment: 11% vs 2%.


A similar study<sup>35</sup> compared three cycles of superovulation with intrauterine insemination to six cycles of expectant management and found that the monthly fecundity rate was significantly higher with treatment (15% vs 4.5%), but the cumulative pregnancy rate was not (37.5% vs 24%).

### Does endometriosis affect in vitro fertilization success rates?

Studies comparing pregnancy rates with in vitro fertilization between patients with endometriosis vs tubal infertility yielded inconsistent results. Several noted reduced pregnancy and implantation rates in women with endometriosis,<sup>36–38</sup> while others showed no difference.<sup>39,40</sup> The stage of disease does not seem to affect pregnancy rates.<sup>40,41</sup> The presence of endometriomas also did not impair pregnancy rates.

Lower fertilization rates were reported in some studies.<sup>38</sup> One study<sup>36</sup> also observed that embryos from women with endometriosis contained fewer blastomeres and that more embryos arrested in culture.

The same study also noted no difference in pregnancy rates between women with or without endometriosis who received oocytes donated from women without endometriosis. On the other hand, oocytes donated from women with endometriosis yielded lower pregnancy rates than oocytes from donors without the disease.<sup>36</sup> Another study confirmed that oocyte recipients with and without endometriosis had the same pregnancy rates.<sup>41</sup>

These findings suggest that endometriosis impairs oocyte and subsequent embryo quality but not endometrial receptivity. 

Medical treatment of endometriosis does not improve fertility

## REFERENCES

1. Sampson JA. Benign and malignant endometrial implants in the peritoneal cavity and their relationship to certain ovarian tumors. *Surg Gynecol Obstet* 1924; 38:287–311.
2. Alcazar JL, Laparte C, Jurado M, Lopez-Garzia G. The role of transvaginal ultrasonography combined with color velocity imaging and pulsed Doppler in the diagnosis of endometrioma. *Fertil Steril* 1997; 67:487–491.
3. Franssen AMHW, van der Heijden PFM, Thomas CMG, et al. On the origin and significance of serum CA-125 concentrations in 97 patients with endometriosis before, during, and after buserelin acetate, nafarelin, or danazol. *Fertil Steril* 1992; 57:974–979.
4. The American Fertility Society. Revised American Fertility Society classification of endometriosis. *Fertil Steril* 1985; 43:351–352.
5. Vercellini P, Trespidi L, Colombo A, et al. A gonadotropin-releasing hormone agonist versus a low dose oral contraceptive for pelvic pain associated with endometriosis. *Fertil Steril* 1993; 60:75–79.
6. Henzl MR, Corson SL, Moghissi K, Buttram VC, Berqvist C, Jacobson J. Administration of nasal nafarelin as compared with oral danazol for endometriosis. A multicenter double-blind comparative clinical trial. *N Engl J Med* 1998; 318:485–489.
7. Telimaa S, Puolakka J, Ronnberg L, Kaupilla A. Placebo controlled comparison of danazol and high-dose medroxyprogesterone acetate in the treatment of endometriosis. *Gynecol Endocrinol* 1987; 1:13–25.
8. Dlugi AM, Miller JD, Knittle J. Lupron depot in the treatment of endometriosis: a randomized, placebo-controlled, double blind study.



- Fertil Steril 1990; 54:419–427.
9. **Paoletti AM, Serra GG, Cagnacci A, et al.** Spontaneous reversibility of bone loss induced by gonadotropin-releasing hormone analog treatment. *Fertil Steril* 1996; 65:707–710.
  10. **Waller KG, Shaw RW.** Gonadotropin-releasing hormone analogues for the treatment of endometriosis: long-term follow-up. *Fertil Steril* 1993; 59:511–515.
  11. **Miller J, Shaw RW, Casper R, et al.** Historical prospective cohort study of the recurrence rate of pain after discontinuation of treatment with danazol or a gonadotropin-releasing hormone agonist. *Fertil Steril* 1998; 70:293–296.
  12. **Hornstein MD, Hemmings R, Yuzpe AA, Heinrichs WL.** Use of nafarelin versus placebo after reductive laparoscopic surgery for endometriosis. *Fertil Steril* 1997; 68:860–864.
  13. **Adamson GD, Subak LL, Pasta DJ, et al.** Comparison of CO<sub>2</sub> laser laparoscopy with laparotomy for treatment of endometriomata. *Fertil Steril* 1992; 57:965–973.
  14. **Sutton CJG, Ewen SP, Whitelaw N, Haines P.** Prospective randomized, double blind, controlled trial of laser laparoscopy in the treatment of pelvic pain associated with minimal, mild, and moderate endometriosis. *Fertil Steril* 1994; 62:696–700.
  15. **Sutton CJ, Pooley AS, Ewen SP, Haines P.** Follow-up report on a randomized controlled trial of laser laparoscopy in the treatment of pelvic pain associated with minimal to moderate endometriosis. *Fertil Steril* 1997; 68:1070–1074.
  16. **Wilson ML, Farquhar CM, Sinclair OJ, Johnson NP.** Surgical interruption of pelvic nerve pathways for primary and secondary dysmenorrhea (Cochrane Review). In: *The Cochrane Library*, issue 1, 2001.
  17. **Tjaden B, Schlaff WD, Kimball A, Rock JA.** The efficacy of presacral neurectomy for the relief of midline dysmenorrhea. *Obstet Gynecol* 1990; 76:89–91.
  18. **Laufer MR, Goitein L, Bush M, Cramer DW, Emans SJ.** Prevalence of endometriosis in adolescent women with chronic pelvic pain not responding to conventional therapy. *J Pediatr Adolesc Gynecol* 1997; 10:199–202.
  19. **Martin DC, Hubert GD, Vander Zwaag R, el-Zekay FA.** Laparoscopic appearances of peritoneal endometriosis. *Fertil Steril* 1989; 51:63–67.
  20. **Reese KA, Reddy S, Rock JA.** Endometriosis in an adolescent population: the Emory experience. *J Pediatr Adolesc Gynecol* 1996; 9:125–128.
  21. **Redwine DB.** Age-related evolution in color appearance of endometriosis. *Fertil Steril* 1987; 48:1062–1063.
  22. **Fedel L, Parazzini F, Bianchi S, Arcaini L, Candiani GB.** Stage and localization of pelvic endometriosis and pain. *Fertil Steril* 1990; 53:155–158.
  23. **Vernon MW, Beard JS, Graves K, Wilson EA.** Classification of endometriotic implants by morphologic appearance and capacity to synthesize prostaglandin F. *Fertil Steril* 1986; 46:801–806.
  24. **Sanfilippo JS, Wakim N, Schikler KN, Yussman MA.** Endometriosis in association with uterine anomaly. *Am J Obstet Gynecol* 1986; 154:39–43.
  25. **Verkauf BS.** Incidence, symptoms and signs of endometriosis in fertile and infertile women. *J Fla Med Assoc* 1987; 74:671–675.
  26. **Burns WN, Schenken RS.** Pathophysiology of endometriosis-associated infertility. *Clin Obstet Gynecol* 1999; 42:586–610.
  27. **Illera MJ, Juan L, Stewart CL, Cullinan E, Ruman J, Lessey BA.** Effect of peritoneal fluid from women with endometriosis on implantation in the mouse model. *Fertil Steril* 2000; 74:41–48.
  28. **Thomas EJ, Cooke ID.** Successful treatment of asymptomatic endometriosis: does it benefit infertile women? *Br Med J* 1987; 294:1117–1119.
  29. **Overton CE, Lindsay PC, Johal B, et al.** A randomized, double blind, placebo controlled study of luteal phase dydrogesterone in women with minimal to mild endometriosis. *Fertil Steril* 1994; 62:701–707.
  30. **Hughes EG, Fedorkow DM, Collins JA.** A quantitative overview of controlled trials in endometriosis-associated infertility. *Fertil Steril* 1993; 59:963–970.
  31. **Adamson GD, Pasta DJ.** Surgical treatment of endometriosis-associated infertility: meta-analysis compared with survival analysis. *Am J Obstet Gynecol* 1994; 171:1488–1505.
  32. **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; 337:217–222.
  33. **Parazzini F, Gruppo Italiano per lo Studio dell'Endometriosi.** Ablation of lesions or no treatment in minimal-mild endometriosis in infertile women: a randomized trial. *Hum Reprod* 1999; 14:1332–1334.
  34. **Tummon IS, Asher LJ, Martin JS, Tulandi T.** Randomized controlled trial of superovulation and insemination for infertility associated with minimal or mild endometriosis. *Fertil Steril* 1997; 68:8–12.
  35. **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.
  36. **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):91–97.
  37. **Azem F, Lessing JB, Geva E, et al.** Patients with stages III and IV endometriosis have a poorer outcome of in vitro fertilization-embryo transfer than patients with tubal infertility. *Fertil Steril* 1999; 72:1107–1109.
  38. **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; 64:392–398.
  39. **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; 65:791–795.
  40. **Pal L, Shifren JL, Isaacson KB, Chang Y, Leykin L, Toth TL.** Impact of varying stages of endometriosis on the outcome of in vitro fertilization-embryo transfer. *J Assist Reprod Genetics* 1998; 15:27–31.
  41. **Sung L, Mukherjee T, Takeshige T, Bustillo M, Copperman AB.** Endometriosis is not detrimental to embryo implantation in oocyte recipients. *J Assist Reprod Genetics* 1997; 14:152–156.

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