Chapter 22
Endometriosis

John S. Hesla

John A. Rock

DEFINITIONS

Adenomyoma—A manifestation of adenomyosis characterized as localized, encapsulated disease of the uterine wall, as compared with the more common diffuse pattern of extension of endometrial glands and stroma in the myometrium.

Adenomyosis—Heterotopic endometrial glands and stroma located deep within the myometrium, with glandular extension below the endometrial-myometrial interface of at least 2.5 mm.

American Society for Reproductive Medicine (ASRM) classification of endometriosis—A scoring system to quantify the location and extent of endometriosis with a scalar rather than numeric terminology. This documentation has been proposed to allow direct comparison of patient responses to medical and surgical treatments and to identify factors predictive of disease outcome.

Atypical peritoneal implants of endometriosis—Lesions of varying appearance, including vesicles, flat plaques, raised blebs, polypoid structures, areas of fibrosis and adhesion formation, and peritoneal defects. May be clear, yellow, brown, blue, or black in color, as compared with the readily recognized red or gray implants.

Cancer antigen 125 (CA-125)—A high molecular weight glycoprotein expressed on the cell surface of some derivatives of embryonic coelomic epithelium. CA-125 is often elevated in cases of mild-to-severe endometriosis, as well as other conditions, including acute pelvic inflammatory disease, adenomyosis, uterine leiomyoma, menstruation, pregnancy, epithelial ovarian cancer, pancreatitis, and chronic liver disease.

Endometrioma—A solitary, nonneoplastic mass containing endometrial tissue and blood.

Endometriosis—The presence and growth of functioning endometrial tissue containing glandular and stromal elements in places other than the uterus that often results in severe pain and infertility.

Hydrodissection—Forceful injection of physiologic irrigant through a small defect created in the surfaces to be separated, such as the peritoneum from the retroperitoneal tissue. This may aid in establishment of the plane of dissection.

Presacral neurectomy—Division of the superior hypogastric plexus; useful as an adjunctive procedure to eliminate the uterine component of dysmenorrhea that results from endometriosis.

Reflux menstruation—Reflux of menses through fallopian tube to ectopic site, especially the peritoneal cavity. Proposed by John Sampson as a mechanism for the origin of endometriosis in many women.

Uterine suspension—Surgical technique of elevation of the adnexa to reduce adhesion formation at denuded peritoneal surfaces of the posterior cul-de-sac, uterine serosa, and broad ligament.

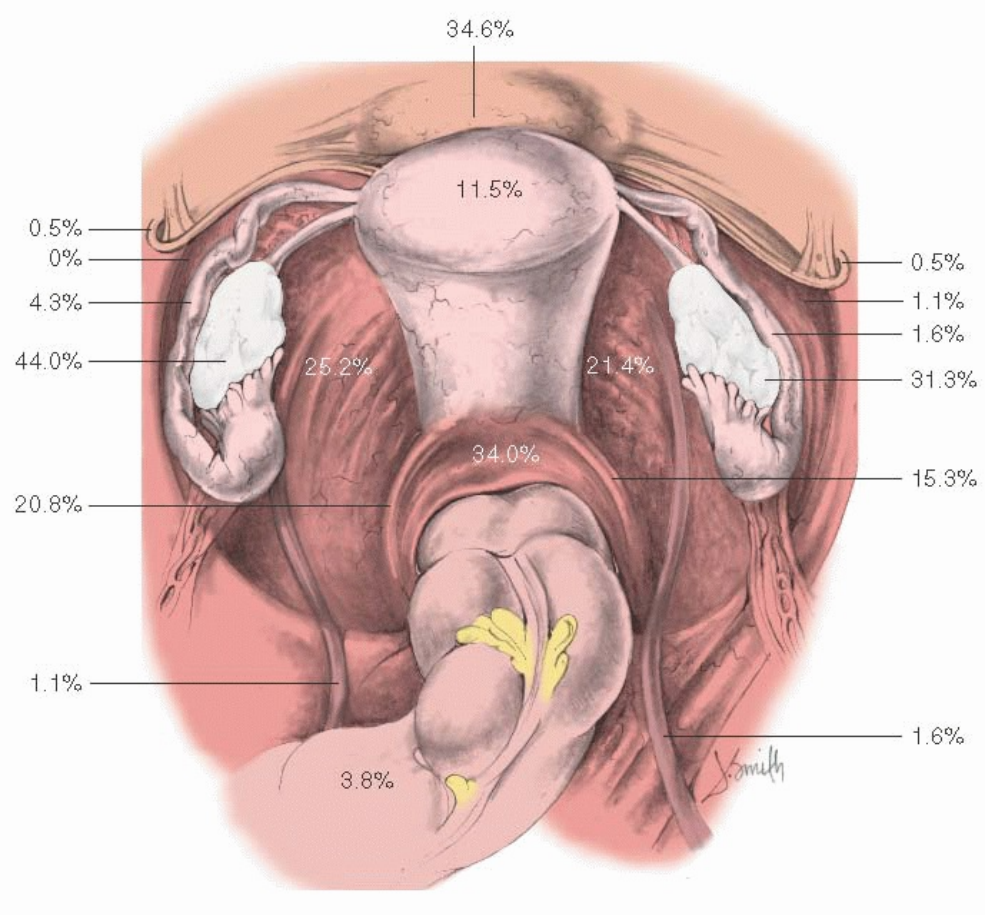

FIGURE 22.1 Anatomic locations of endometriosis implants in 182 consecutive infertility patients found to have endometriosis by laparoscopy. The rates shown indicate the percentage of all patients with implants in a given locale (Redrawn with permission from Jenkins S, Olive DL, Haney AF. Endometriosis: pathogenic implications of the anatomic distribution. *Obstet Gynecol* 1986;67:335. Copyright © 1986, The American College of Obstetricians and Gynecologists).

Endometriosis is a clinical and pathologic entity initially described by von Rokitansky in 1860 that is characterized by the presence of tissue resembling functioning endometrial glands and stroma outside the uterine cavity. These ectopic implants can be located throughout the pelvic cavity, including the ovaries, uterine ligaments, rectovaginal septum, parietal peritoneum, intestinal serosa, and appendix. Less common sites of involvement include the cervix, hernial sacs, the umbilicus, laparotomy and episiotomy scars, and the pleural and pericardial cavities (**Fig. 22.1**).

Although endometriosis has been extensively investigated over the past century, it remains an enigmatic disease process. The association between endometriosis and infertility is still undefined, and there are insufficient data to support many of the hormonal and surgical therapies that have been proposed. In addition, the often subtle and varied appearances of endometriosis can make recognition of lesions and surgical staging difficult, thereby casting doubt on the utility of the classification systems that have been developed. Nevertheless, the findings of well-designed clinical trials and recent studies that have elucidated the pathogenesis of endometriosis have enabled a more rational approach to the medical and surgical management of this disease.

PREVALENCE

The estimated prevalence of endometriosis among population groups varies depending on the presenting symptoms. Endometriosis affects 6% to 10% of reproductive-age women. Among women with pelvic pain, the prevalence of endometriosis ranges from approximately 30% to 80%. The disease has been diagnosed in 40% to 52% of women with severe dysmenorrhea and 70% of patients with chronic pelvic pain. Cramer and colleagues, in a multicenter study, diagnosed endometriosis in 17% of women with primary infertility, and in other series, the prevalence varied from approximately 9% to 50%. Verkauf prospectively identified endometriosis in 38.5% of infertile women and 5.2% of fertile women. Other studies have confirmed the odds that infertile women are seven to 10 times more likely to have endometriosis than are their fertile counterparts. However, any postmenarchal woman is at risk, because endometriotic implants have been identified in postmenopausal women, in women with primary amenorrhea secondary to müllerian anomalies, and in 69.6% of teenagers

who underwent diagnostic laparoscopy for chronic pelvic pain. Twin and family studies suggest a genetic component. Simpson and colleagues reported a 6.9% occurrence rate in first-degree female relatives, which compared with 1% for the non-blood-related control group. Genes involved in implantation of tissue, fibrinolysis, or ovarian steroidogenesis may be aberrantly expressed at a higher frequency in family members with endometriosis. Other risk factors include alcohol use, smoking, and low body mass index.

HISTOGENESIS

The mechanism by which endometriosis develops is unknown, although there has been much discussion as to its origin (**Table 22.1**). Variations in the location and presentation of implants have compromised a complete understanding of the histogenesis of the aberrant endometrial cells. Four major theories have been proposed:

1. The reflux and direct implantation theory suggests that viable endometrial cells reflux through the fallopian tubes during menstruation and implant on surrounding pelvic structures.
2. The coelomic metaplasia theory suggests that the multipotential cells of the coelomic epithelium may be stimulated to transform into endometrial-like cells.

3. The vascular dissemination theory suggests that endometrial cells enter the uterine vasculature or lymphatic system at menstruation and are transported to distant sites.
4. The autoimmune disease theory suggests that endometriosis is a disorder of immune surveillance that allows ectopic endometrial implants to grow.

TABLE 22.1 Theories for the Histogenesis of Endometriosis

Transtubal regurgitation or retrograde menstruation
Direct implantation of endometrial cells
Metaplasia of coelomic epithelium
Lymphatic dissemination
Hematogenous spread
Activation of embryonic cell rests
Activation of wolffian rests
Metaplasia of urothelium
Hereditary factor
Immunologic factor

Reflux and Direct Implantation Theory

John Sampson first postulated that endometriosis arose from retrograde flow of fragments of endometrial tissue through the oviducts and into the peritoneal cavity. Much evidence validates this theory. The anatomic distribution of endometriosis as noted at laparoscopy is consistent with a reflux pattern of development; the most common sites of disease in the infertile woman are the ovary and uterosacral ligament, followed by the posterior uterus, posterior cul-de-sac, and posterior broad ligament. Endometriosis developed in monkeys when the uterus was surgically inverted to cause menstruation to occur

intraperitoneally. Exposure of abraded peritoneum to endometrial cells has resulted in the growth of endometriotic implants in rabbits and rats. Endometriosis has developed in laparotomy, episiotomy, and cesarean section scars after surgical entrance into the endometrial cavity, and anomalies of the müllerian tract are associated with an increased occurrence of endometriosis. Endometriosis is a common finding in women with stenosis of the external cervical os. Epidemiologic data suggest that women who menstruate more frequently, more heavily, or for a longer duration have an increased likelihood of disease development. Prolonged lactation and multiparity are protective.

Peritoneal implants of endometriosis and the presence of endometriomas are more common on the left side of the pelvis than the right. The position of the sigmoid colon creates a sequestered microenvironment around the left adnexa, which facilitates implantation of endometrial cells regurgitated through the left tube. The large intestine does not provide the right hemipelvis with this anatomical shelter, because the cecum lies more cranial in position. In addition, the retrograde menstruation theory is supported by the finding of a higher prevalence of endometriosis in the subphrenic region, since the falciform ligament may trap refluxed endometrium in the right hypochondrium.

Focal endometriosis has been identified in 16% to 63% of proximal tubal segments after cautery or Pomeroy tubal sterilization, perhaps as a consequence of recurrent bathing of the healing terminal area with menstrual products. Nevertheless, bloody peritoneal fluid has been observed in 90% of women with patent fallopian tubes undergoing laparoscopy during the perimenstrual time period, a figure much greater than the estimated 2% to 5% prevalence of symptomatic endometriosis in women of reproductive age. Additionally, peritoneal implants have been identified in women who had a prior tubal ligation procedure and were undergoing laparoscopy for the evaluation of pelvic pain. Hence, other factors evidently are present to promote the ectopic implantation.

Coelomic Metaplasia Theory

The germinal epithelia of the ovary, endometrium, and peritoneum all originate from the same totipotential coelomic epithelium. The metaplasia theory postulates that these totipotential cells are transformed by repeated exposure to hormonal or infectious stimuli. This may explain the development of endometriotic lesions in unusual locations and in the odd cases of male patients in whom endometriosis develops after prostatectomy, orchiectomy, or prolonged treatment with estrogen. Reports of endometriosis in women with primary amenorrhea and an absence of functioning uterine endometrium and of endometriosis identified in mature teratomas also lend support to the metaplasia theory.

Vascular Dissemination Theory

Endometrial cells can be transported to extrauterine sites by blood vessels or the lymphatic system or by contamination of the pelvis or abdominal wall incision if the uterine cavity is surgically entered. Retroperitoneal endometriosis is hypothesized to arise from lymph vascular spread; 29% of patients with pelvic endometriosis documented on autopsy had pelvic lymph nodes that contained endometriosis. Theories of vascular dissemination help explain how endometriosis can develop in the lung or pericardium.

Autoimmune Disease Theory

Alterations in cellular immunity can facilitate the successful implantation of translocated endometrial cells. Compared with control subjects, monkeys with spontaneous endometriosis had both a lowered cell-mediated response to autologous endometrial tissue, as determined by skin testing, and a decreased in vitro blastogenesis response. Similar studies performed in women demonstrated that lymphocytes obtained from control patients were significantly more efficient in cytolysis of isolated endometrial stromal cells than were lymphocytes obtained from patients with endometriosis. This decreased cytotoxic response to endometrial cells may be due to a defect in natural killer cell activity, such as a decreased lytic effect toward stroma that allows ectopic development of endometrial fragments. In addition, there may be an increased resistance of endometrium in women with endometriosis to natural killer cytotoxicity.

Promoting Factors

Clinical and laboratory studies support the concept that endometriosis is an estrogen-dependent condition. Estradiol concentrations greater than approximately 60 pg/mL have been identified as necessary for proliferation of endometriotic lesions. Nevertheless, estrogen and progesterone receptors are found in much lower concentrations in endometriotic tissue than in normal endometrium tissue; such endometriotic tissue also frequently fails to show cyclic variations of development in response to hormonal changes. Early data from primate studies suggested that endometriosis required no steroidal supplementation to become initially established, but later studies demonstrated that chronic exposure to ovarian steroids is

necessary for the survival of these experimentally induced endometrial plaques.

Growth factors can originate from the peritoneal environment to stimulate endometrial development. Platelet-derived growth factor, a macrophage secretory product, enhance endometrial stromal cell proliferation in a dose-dependent manner. Similarly, macrophage-conditioned media promote mouse endometrial stromal cell proliferation in vitro, and this activation is enhanced with the addition of estrogen. Increased concentrations of macrophage-derived growth factors, including vascular endothelial growth factor, have been identified in the peritoneal fluid of women with endometriosis. This suggests that changes in the vascular permeability and angiogenesis play an important role in the pathophysiology of this disease.

Molecular alterations in steroidogenic enzyme function have been implicated in the pathogenesis of endometriosis. Endometrial tissue from patients with endometriosis expresses aromatase P-450, whereas endometrium from control women without identifiable endometriosis does not. The presence of aromatase within endometriosis results in higher local production of estrogen necessary to support the growth and metabolic activity of the lesion.

Menstrual effluent contains factors that induce alterations in the peritoneal mesothelium, facilitating adhesion of endometrial cells. Attachment of endometrial cells is enhanced by induction of adhesion molecules and their receptors and the overexpression of matrix metalloproteinases and plasminogen activators. These factors ensure local destruction of the extracellular matrix. Suppression of matrix metalloproteinase production by progesterone decreased ectopic implantation of endometrium in the nude mouse, implicating these proteinases in the pathogenesis of endometriosis.

In summary, no single theory explains all cases of endometriosis, although the direct implantation mechanism seems the likely cause for most disease locations. Immunologic factors, inducing substances, or other mediators may explain the development of endometriosis in more distant sites.

NATURAL HISTORY

The natural history of endometriosis is not clearly understood. The disease appears to progress in most untreated patients, although spontaneous regression can occur in as many as 58% of milder cases. Falcone and Lebovic analyzed the findings of follow-up laparoscopies performed 6 to 39 months following the initial diagnostic procedure among 162 patients in several previous endometriosis surgical trials that were randomized to the placebo control group rather than surgical excision/ablation. There was nearly equal distribution of those with progressive disease (31%), unchanged (31%), and improvement in extent of lesions (38%).

Surgical and medical therapies may promote a temporal regression but may not effectively eliminate microscopic, retroperitoneal, and hormonally resistant disease. Dmowski and Cohen described persistent disease in 15% of patients treated with danazol, and Henzl and associates noted a progression of disease during the course of treatment in 4% to 8% of patients receiving danazol or an analogue of gonadotropin-releasing hormone (GnRH). When conservative surgery was combined with danazol or GnRH agonist therapy, the overall recurrence rate at 36 months was between 13.5% and 33%.

The effect of pregnancy on the clinical course of endometriosis is uncertain. Although Sampson proposed that pregnancy induces involution of implants, other authors recently described a variable response of endometriosis to pregnancy. McArthur and Ulfelder analyzed the clinical effect of pregnancy on endometriosis in 24 patients. They found that the behavior of endometriosis during the gravid state was extremely variable and that the regression of disease appeared to be due to decreased tissue responsiveness to hormonal stimulation rather than to actual necrosis of the lesions. More patients in their series experienced disease persistence than permanent regression. Monkey studies have confirmed these findings; the response of endometrial implants to pregnancy varied from total regression to significant progression.

Approximately 2% to 4% of early postmenopausal women suffer from endometriosis. These cases are usually associated with exogenous intake of estrogens or tamoxifen. Nevertheless, there are reports of symptomatic endometriosis in women older than 60 years of age who have not received steroid replacement therapy. Such cases presumably are secondary to the responsiveness of the residual lesions to low levels of estrogens that arise from peripheral conversion of ovarian and adrenal androgens.

PATHOPHYSIOLOGY

Gross Appearance

Signs of endometriosis may be evident on physical examination. Endometriosis can form tender nodules on the

uterosacral ligaments that are readily palpable on rectovaginal examination. It may infiltrate the deepest portion of the rectouterine pouch and cause pain with defecation and, rarely, cyclic rectal bleeding. Lesions of endometriosis have been identified in the umbilicus, in the vulva, and in episiotomy scars. Complete ureteral obstruction has been reported. This can be temporarily reversed with the administration of GnRH agonists, progestogens, and danazol. Diaphragmatic involvement can lead to chronic, recurrent pneumothorax at the time of menstruation. Lesions have been identified in the upper and lower extremities, the pericardium, and the lung.

The gross appearance of endometriosis is extremely variable. On entering the abdomen, the surgeon may find a small, adherent nodule on one or both sides of the pelvis, usually attached to the posterior cul-de-sac and posterior surface of the uterus. Frequently, release of ovarian adhesions to mobilize the adnexa results in an egress of chocolate-colored or dark red fluid that is highly suggestive of endometriosis. Examination of the ovary may disclose a cyst that is rarely larger than 10 cm and has a dark, hemorrhagic lining. Endometriomas develop over a time span of a few months as a result of extensive intracystic hemorrhage. Reddish blue, fibrinous areas that represent small islands of endometriosis may be present on the ovarian cortex. Peritoneal implants vary in appearance from black, puckered lesions surrounded by a variable extent of fibrosis, to red polypoid material, to clear vesicles. Other appearances include yellow-brown peritoneal discoloration, white plaques, or scarring. The strong inflammatory stimulus of superficial lesions of endometriosis may promote fibrosis and invagination of adjacent peritoneal surfaces. Red lesions are the most metabolically active and are found mainly in younger patients.

The fallopian tube is usually nonobstructed and free of gross disease, although peritubal adhesions can extend to adjacent structures, particularly in patients with extensive disease. Deeply infiltrating endometriotic nodules extend more than 5 mm beneath the peritoneum and may involve the uterosacral ligaments, bladder, ureters, or vagina. The depth of invasion has been correlated with pain symptomatology. Endometrial invasion of the rectal or sigmoidal wall can simulate malignancy or produce complete obstruction.

Microscopic Appearance

The essential diagnostic criterion is the presence of endometrial tissue, both stroma and glandular elements. This aberrant tissue resembles the uterine mucosa both histologically and physiologically. Secretory change and decidualization are seen in response to hormone influences in the luteal phase, and estrogen stimulates proliferation of the ectopic implants. Nevertheless, these functional changes are less uniform for implants than for the uterine mucosa.

The ultrastructural features of endometriosis are consistent with an incomplete response to the hormonal milieu. Endometriotic implants contain lower concentrations of progesterone receptors than do corresponding normal endometrium, so the histologic response to progesterone is less profound. Gould and colleagues reported that the nucleus of endometriotic stromal cells had a marked degree of estrogen binding throughout the menstrual cycle, whereas stromal binding sites in the uterine endometrium were present only during the proliferative phase and not the secretory phase of the cycle. The differing responses of the two tissue types to steroid hormones were reflected by the modulation of estrogen binding and changes in glandular histology. Estrogen receptors did not undergo downregulation during the luteal phase of the cycle in endometriotic foci, despite an increase in endogenous progesterone concentration. Alterations in the quantity, activation, or function of the progesterone receptor may be responsible for this lack of change in estradiol receptors, the abnormal response of the ectopic endometrium to progesterone, and the failure of hormonal therapy in some patients.

Estrogens play a primary role in the establishment and maintenance of endometriotic tissue. There is evidence of local estrogen production within endometriotic cells. Pellegrini and colleagues observed an overexpression of estrogen receptors α and β, which belong to the nuclear receptor family and act as activated transcription factors. Cyclin D1 and c-myc are estrogen-related genes implicated in cell cycle control that are overexpressed in endometriotic cells.

Because of the pressure of retained blood in the cyst cavities of endometriomas, a large concentration of endothelial leukocytes heavily laden with hemosiderin (pseudoxanthoma cells) may be found, and the glandular lining may be nearly absent and replaced by reactive connective tissue elements. Biopsy may fail to yield histologic proof of the endometrial glands and stroma in approximately one third of all cases of typical clinical endometriosis, even if many tissue sections are analyzed.

The “chocolate cyst” description of the ovary is used synonymously with endometrial cyst or endometrioma. Nevertheless, other types of ovarian cysts may have a similar fluid content, including the hemorrhagic follicle, corpus luteum, or cystadenoma. Pathologic confirmation of the diagnosis is always advised.

Approximately 0.7% to 1.0% of patients with endometriosis have lesions that undergo malignant transformation. Atypical glandular changes have been found in 3% to 6% of cases of ovarian endometriosis. Several histologic tumor types have been described (**Table 22.2**). Endometrioid adenocarcinomas account for 69% of reported lesions, with the ovary being the primary site in most cases. Rapidly enlarging endometriomas or those measuring greater than 10 cm should be sectioned carefully to search for malignant foci. Tumors arising in endometriosis are predominantly of low grade and confined to the site of origin. Progestogen therapy is recommended after surgical resection of these lesions.

Clinical Characteristics

The clinical features of endometriosis are varied, and the presentation depends on the site of growth and the severity of disease. The classic triad of dysmenorrhea, dyspareunia, and infertility has been described as characteristic of the disease (**Table 22.3**). Nevertheless, patients with extensive endometriosis may be clinically symptom-free, and women with only minimal involvement may manifest disabling pelvic pain. Dysmenorrhea is a common symptom that most likely is associated with endometriosis if it develops after age 20 years, is

progressive, and is not well relieved by nonsteroidal antiinflammatory agents or oral contraceptives. Spasmodic pain beginning before the onset of menstrual bleeding is another common symptom of patients with endometriosis. When the rectovaginal septum or uterosacral region is involved, the pain is often referred to the rectum or lower sacral and coccygeal regions because of premenstrual and menstrual swelling of ectopic implants. Dyschezia and constipation may be present. Dyspareunia is common, especially in cases of uterosacral or vaginal infiltration, fixed retroversion of the uterus, or ovarian fixation by adhesions. Again, there is no absolute correlation between the amount of visible endometriosis as seen at surgery and the extent of symptoms; minor disease involvement may result in severe pain, whereas massive areas of superficial endometriosis may cause no discomfort.

TABLE 22.2 Histology of Tumors Arising in Endometriosis

HISTOLOGY	NUMBERS[a]	INCIDENCE (%)
Endometrioid carcinoma		
Adenocarcinoma	96	46.4
Adenoacanthoma	43	20.8
Adenosquamous carcinoma	4	1.9
Clear cell carcinoma	28	13.5
Sarcoma, including mixed mesodermal tumor	24	11.6
Serous cystadenocarcinoma	6	2.9
Squamous cell carcinoma	3	1.4
Mucinous cystadenocarcinoma	2	1.0
Mixed germ cell tumor and adenocarcinoma	1	0.5
Totals	207	100

[a]Two patients had two different histologic patterns.

From Heaps JM, Nieberg RK, Berek JS. Malignant neoplasms arising in endometriosis. *Obstet Gynecol* 1990;75:1023, with permission. Copyright © 1990, The American College of Obstetricians and Gynecologists and Lippincott Williams & Wilkins.

TABLE 22.3 Symptoms Associated with Endometriosis

Pelvic
Dysmenorrhea
Dyspareunia
Chronic pelvic pain
Sciatica
Premenstrual spotting
Gastrointestinal
Constipation
Diarrhea
Dyschezia
Tenesmus
Hematochezia
Urinary
Flank pain
Back pain
Abdominal pain
Urgency
Frequency
Hematuria
Pulmonary
Hemoptysis

Catamenial chest pain
Pneumothorax
Infertility

Other presenting symptoms can include signs of urinary tract involvement, such as hematuria or ureteral obstruction, unusual abdominal or adnexal masses, cyclic sciatica, catamenial pneumothorax or hemoptysis, and swollen and painful scars. Premenstrual spotting can occur for 3 to 7 days before the start of menses; this is a poorly recognized but relatively consistent sign of endometriosis. An endometrioma can leak, causing considerable pain, or it can rupture and produce a clinical picture much like that seen with a ruptured ectopic pregnancy or acute appendicitis. Nearly 10% of patients with endometriosis present with acute symptoms that require exploration for diagnosis and treatment.

Approximately 20% to 40% of women with endometriosis are infertile. Vercellini and colleagues report the monthly fecundity rate for those with endometriosis is 2% to 10%, as compared to 15% to 20% in fertile couples. When extensive pelvic scarring or large endometriomas are present in the patient with endometriosis, the associated infertility can be clearly attributed to anatomic distortion. Also, the oxidative stress associated with endometriomas may lead to follicular depletion and vascular compromise of the ovarian cortex. However, the pathophysiology of infertility in patients with less advanced disease is more controversial.

Endometriotic implants within the fallopian tube or ovary may promote a local inflammatory response that has a direct, deleterious effect on tubal function (**Table 22.4**). Oocyte capture by the fallopian tube may be prevented despite the normal process of oocyte maturation and ovulation. Endometriosis and especially adenomyosis are associated with impeded hyperperistaltic and dysperistaltic uterotubal transport capacity. Chronic salpingitis was detected in 29 of 87 (33%) fallopian tubes of patients undergoing laparotomy for ovarian endometriosis; tubal obstruction was demonstrated in only one of these cases, although adhesions were present in 24%. Endometriosis has been identified in the resected segments of fallopian tubes in women undergoing tubocornual anastomosis for proximal tubal obstruction when there was no evidence of implants elsewhere in the pelvis. Others have reported a correlation between tubal endometriosis and chronic salpingitis in similar cases, although this finding has not been uniform.

Altered folliculogenesis or ovulation has been described in endometriotic patients who have undergone serial sonogram studies. An abnormal follicular growth rate and total growth period may disturb the normal synchronization of oocyte maturation, uterine receptivity, and ovulation. Tummon and coworkers reported that women with minimal endometriosis had more, yet smaller, follicles and lower preovulatory estradiol levels at the time of midcycle luteinizing hormone (LH) surge.

TABLE 22.4 Possible Mechanisms by Which Endometriosis Causes Infertility

Mechanical interference
Pelvic adhesions
Chronic salpingitis
Altered tubal motility
Distortion of tuboovarian relations
Impaired oocyte pickup
Alterations in peritoneal fluid
Increased concentration of prostaglandins

	Increased number of activated macrophages
	Increased production of cytokines
	Enhanced phagocytosis of sperm
Abnormal systemic immune system response	
	Increased cell-mediated gamete injury
	Increased prevalence of autoantibodies
	Antiendometrial antibody production
Hormonal or ovulatory dysfunction	
	Defective folliculogenesis
	Luteinized unruptured follicle syndrome
	Hyperprolactinemia
	Luteal phase deficiency
Fertilization or implantation failure	
Early spontaneous abortion	

From Surrey ES, Halme J. Endometriosis as a cause of infertility. *Obstet Gynecol Clin North Am* 1989;16:79, with permission. Copyright © 1989, Elsevier.

Luteinized unruptured follicle (LUF) syndrome, a condition of normal ovulatory hormone secretion and luteinization of the follicle without the expected occurrence of ovulation, has been reported to be more common in patients with endometriosis. Mio and colleagues performed transvaginal ultrasound at least every other day from cycle day 8 through the third day after human chorionic gonadotropin (hCG) administration on 47 patients with endometriosis, predominantly minimal and mild, and 28 control patients with male factor infertility. Luteinized unruptured follicle syndrome was diagnosed in 20 of 81 (24.7%) monitored cycles in endometriosis patients and in only 3 of 44 (6.8%) monitored cycles in control patients, a difference that achieved statistical significance. Schenken and associates also noted an increased rate of LUF and associated luteal phase deficiency in monkeys with surgically induced moderate-to-severe endometriosis. An absence of sonographic evidence of midcycle follicular collapse in patients with mild endometriosis has ranged from 4% to 35% in the literature.

Luteal phase function has been evaluated by endometrial biopsy and peripheral progesterone concentrations. There is insufficient evidence to conclusively link endometriosis with a deficiency of corpus luteum activity, although some studies have suggested the existence of a shortened luteal phase, delayed increase in progesterone secretion after ovulation, decreased progesterone secretion in the late luteal phase, and lowered serum estradiol levels during the early follicular phase.

The effect of endometriosis on fertilization and preimplantation development is widely debated. Peritoneal fluid from patients with endometriosis had a deleterious effect on sperm-oocyte interaction in homologous mouse and hamster

fertilization assays. In vitro studies involving human zona pellucida confirmed an adverse effect of peritoneal fluid on sperm binding in this patient population, although others reported that peritoneal fluid from women with low-stage endometriosis had no detrimental effect on sperm motility characteristics. Peritoneal fluid from women with moderate and severe endometriosis caused declines in sperm motility and velocity. Exposure of two-cell mouse embryos to the peritoneal fluid or serum of patients with endometriosis has resulted in a decreased rate of cleavage and development to the blastocyst and hatching stages as compared with control nonendometriotic specimens. However, this association was not verified by similar studies of mouse embryo development and apoptosis.

Aberrant gene expression in eutopic and ectopic endometrium may be related to infertility or the establishment of the disease. Integrins are ubiquitous cell adhesion molecules that undergo dynamic alterations during the normal menstrual cycle in the human endometrium. The $\alpha v\beta 3$ vitronectin receptor integrin is normally expressed in endometrium during the periimplantation period; such expression may be lost in women with mild endometriosis, which may affect uterine receptivity. The endometrium of infertile women with endometriosis may synthesize low levels of L-selectin, a protein that coats the trophoblast on the surface of the blastocyst. This may be another mechanism for impaired implantation. Women with lower levels of expression of *HOXA*10 have lower implantation rates. This gene is involved in endometrial regeneration in each menstrual cycle.

A high frequency of spontaneous abortions in infertile women with endometriosis has been reported, although the relation was questioned because of potential control group bias. Naples and coworkers found that patients with endometriosis who refused treatment had the same abortion rate before and after diagnosis (26% and 25.5%). Studies of the last decade with appropriate control groups have demonstrated no substantial increase in the incidence of spontaneous abortion in women with endometriosis.

Mechanisms Influencing Symptoms

Because of the uncertain mechanisms causing infertility and pelvic pain in patients with minimal and mild endometriosis, many investigators have attempted to identify specific alterations in the peritoneal environment that would explain these symptoms. Significant increases or decreases in peritoneal fluid volume that are due to increased production by the ovaries, altered mesothelial permeability, or increases in the colloid osmotic pressure have been hypothesized to inhibit ovum capture by the fallopian tube or to adversely affect tubal transport. Koninckx and associates reported elevations in peritoneal fluid volume during cycle days 1 through 5 in patients with mild and moderate endometriosis. The quantity of fluid was comparable to that in control subjects during the remainder of the follicular phase. These authors described reduced volumes in the early luteal phase, which directly contrasts with findings reported by Oak and colleagues. Rock and associates evaluated patients during cycle days 8 through 12 and measured no difference in fluid vols in patients with endometriosis compared with that in control subjects. Similar findings were noted by Rezai and associates. Hence, it appears unlikely that fluid volume alone plays a role in the establishment of infertility.

Peritoneal fluid from patients with minimal and mild endometriosis has been shown to increase macrophage proliferation in vitro. In addition, several studies have described increases in total macrophage number in the peritoneal fluid of patients with endometriosis. Hill and coworkers measured significant elevations in total leukocytes, macrophages, helper T cells, lymphocytes, and natural killer cells in women with stages I and II endometriosis. Activated macrophages may affect the reproductive process by altering sperm motility, fimbrial ovum capture, sperm-oocyte interaction, and early embryonic growth. Increased sperm phagocytosis by macrophages has been demonstrated by in vivo animal and in vitro human studies. Suginami and Yano demonstrated the presence of an ovum capture inhibitor in peritoneal fluid from patients with endometriosis, which reduces fimbrial activity for ovum capture in vitro. This macromolecule may prevent contact between the fimbrial cells and cumulus oophorus.

Prostaglandins, interleukins, and other substances produced by macrophages may be harmful to reproduction. Fakih and colleagues demonstrated that interleukin-1 was present in the peritoneal fluid of almost all patients with endometriosis, but not in the fertile control group. Interleukins have been shown to adversely affect mouse embryo growth in vitro. In addition, interleukin-1 stimulated fibroblast proliferation, collagen deposition, and fibrinogen formation; hence, elevated concentrations of such lymphokines may account for the development of fibrosis and adhesions in advanced stages of endometriosis. Interleukin-6 secretion in vitro is up-regulated in ectopic and eutopic endometrial stromal cells from women with endometriosis. Nevertheless, not all studies have confirmed the existence of a difference in interleukin activity between endometriosis patients and control groups. Decreased plasminogen activator activity in endometriotic implants may also be a cause for increased adhesion formation.

Bleeding from ectopic endometrial implants may promote the formation of free oxygen radicals. The iron in hemoglobin

may be the catalyst of free radical reactions. Free radicals may damage proteins, carbohydrates, nucleotides, and lipids, resulting in tissue damage and de novo adhesions.

Chronic elevations in the level of peritoneal prostaglandins have been hypothesized to interfere with ovulation, to alter tubal mobility such that the embryo may arrive in the uterus at a suboptimal time for implantation, or to diminish corpus luteum function. Drake and associates measured the metabolites of prostacyclin and thromboxane A_2 in peritoneal fluid and noted a 10-fold increase in these levels in patients with endometriosis. Ylikorkla and colleagues confirmed these observations, although the increase in prostanoid metabolites in the patients with endometriosis was less than twice that of the controls. When cycle stage was experimentally controlled, Rock and coworkers, Rezai and associates, and others failed to demonstrate a significant change in prostaglandin levels in peritoneal fluid from patients with endometriosis as compared with control groups. In addition, prostaglandin concentrations did not vary between the follicular and luteal phase in either endometriosis patients or controls. Variations in collection of samples during the menstrual cycle, selection of control groups, and collection techniques have compromised the interpretation of data regarding the relative importance of prostanoid content in peritoneal fluid in the studies that have been published on this topic.

Alterations in the systemic immune response of endometriosis patients may influence fecundity. Cellular and humoral abnormalities have been reported in the peripheral blood and peritoneal fluid of women with endometriosis. Translocated endometrial cells may implant only in patients with an inherent defect in cell-mediated immunity. Functional changes in monocytes and macrophages, natural killer cells, cytotoxic T lymphocytes, and B cells suggest decreased surveillance, recognition, and destruction of misplaced endometrial cells and possible facilitation of their implantation. The endometrial proteins of menstrual fluid may be recognized as foreign by the host and trigger an autoimmune response. This host reaction can be variable, thus explaining why some women with a weak autoimmune response and varying extent of disease can conceive with no difficulty. Other investigators have confirmed a high prevalence of autoantibodies against endometrial and ovarian tissues in the sera and cervical and vaginal secretions of women with endometriosis. Nonspecific polyclonal B-cell activation has been postulated to exist in endometriosis, but there is a lack of substantive data to demonstrate that this association contributes significantly to endometriosisassociated subfertility.

Dioxin, a pollutant that is known to decrease cell-mediated cytotoxicity by reducing the number of helper T cells, has been suggested as a causative factor in the high incidence of endometriosis in developed countries. Heilier and associates documented an increase in dioxin-like compounds in the serum of women with peritoneal endometriosis and deep endometriotic (adenomyotic) nodules. Moreover, a dose-dependent relation existed between dioxin exposure and the subsequent development and severity of endometriosis in the rhesus monkey after a latent period of more than 5 years.

Nevertheless, other studies have suggested that endometriosis may not be associated with immunologic alterations in the pelvis. In a retrospective analysis of the cell count and volume of peritoneal fluid in 135 infertile women with endometriosis, Haney and colleagues found a negative correlation between total cell numbers and extent of disease and no significant correlation between fluid volume and extent of disease. Similarly, in the rabbit model of endometriosis, there was no difference in peritoneal fluid volume, macrophage numbers, or macrophage activation in treated versus control animals.

Hence, the exact cause-and-effect relation between endometriosis and infertility in the absence of a distortion in pelvic anatomy remains unknown. In a recent study using an adhesion-free rabbit model of endometriosis, peritoneal implants did not adversely affect the number of corpora lutea, the oocyte recovery or fertilization rates, tubal transport, embryonic development and cleavage, or nidation index. Similarly, Mahmood and Templeton were unable to detect differences in hormonal patterns of the menstrual cycle, follicular growth, preovulatory peritoneal fluid volume and sex steroid concentration, rate of LUF, oocyte maturity, fertilization rate, or cleavage rate between patients with minimal and mild endometriosis and control women.

Little is known about the mechanisms by which endometriosis induces pain symptoms. Dyspareunia may be related to stimulation of pain fibers by stretching of scarred, inelastic tissue or by direct pressure on nodules of endometriosis embedded in fibrotic tissue. Endometriosis implants may secrete inflammatory substances such as prostaglandins, cytokines, and growth factors that initiate the sequence of events that result in the development of pain. Moreover, the extravasated debris and blood from endometriotic implants may stimulate an inflammatory reaction within the peritoneal cavity with production of the aforementioned substances.

DIAGNOSIS

Symptoms

Dysmenorrhea, dyspareunia, and pelvic, back, and rectal pain—the more common symptoms of endometriosis—have been assumed to be caused by endometrial implants. However, the development of such symptoms is not diagnostic of the disease state. In one random survey of women in the general population, more than 60% reported dyspareunia at some point in their lives, and 33% had persistent discomfort. The prevalence of laparoscopically diagnosed endometriosis in patients with chronic pelvic pain has ranged from 4% to 52% in published series. Leibson et al. reported the age of peak diagnosis of endometriosis based on presenting symptom is pelvic pain, age 15 to 24 years; infertility, age 25 to 34 years; and dysfunctional uterine bleeding, age 35 to 44 years.

Some authorities have suggested that the symptoms may be dependent on the location of the implants, the presence of adhesions, distortion of ovarian anatomy by endometriosis, and involvement of other organs, such as the ureter or rectum. However, Fedele and colleagues found no significant association between the American Fertility Society (AFS; now known as the American Society for Reproductive Medicine) classification of stage and the presence and severity of dysmenorrhea, pelvic pain, and dyspareunia in a prospective study of 160 women. The pain profiles of the patients with ovarian lesions were similar to those of the patients with peritoneal or ovarian and peritoneal disease. Conversely, in a later study by the same group, ovarian endometriomas were the only lesions significantly associated with severe dysmenorrhea and pelvic pain in infertile women. In a more recent prospective study of symptoms experienced by women diagnosed with histologically proven endometriomas, Chapron et al. showed no correlation of the intensity of the pain with the size of the endometrioma. In this study, severe pelvic pain was significantly associated with the secondary finding of deeply infiltrating endometriotic lesions.

Koninckx and coworkers demonstrated that the presence of pelvic pain did not correlate with the total area of endometriosis, type of lesion, or volume of disease. The only significant discriminator proved to be the depth of infiltration; endometriotic lesions greater than 1 cm in depth were associated with

severe discomfort (**Fig. 22.2**). This supports earlier data that strongly linked pain with deep infiltration of the fibromuscular tissue of the pelvis. Hsu and colleagues found dysuria and midline anterior pain were the only symptoms associated with the location of superficial endometriosis lesions.

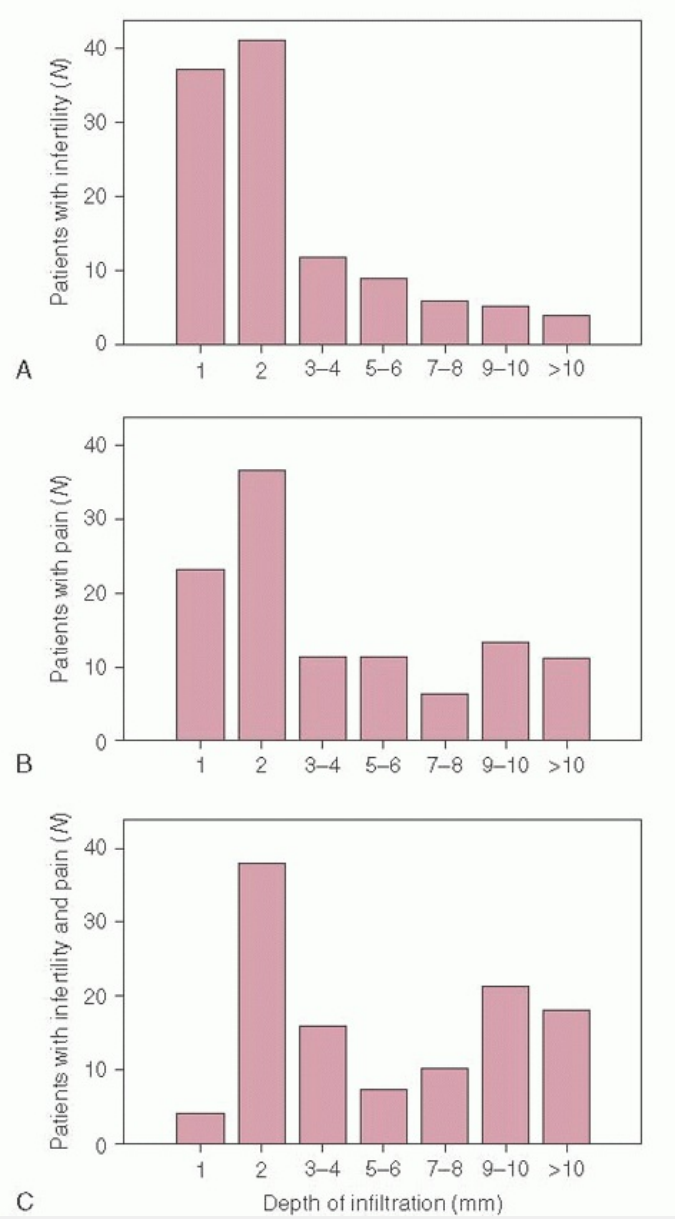

FIGURE 22.2 Frequency distributions of depth of infiltration of pelvic endometriosis in women with (**A**) infertility (*N* = 283), (**B**) pain (*N* = 119), or (**C**) infertility and pain (*N* = 48) (Redrawn with permission from Koninckx PR, Mueleman C, Demeyere S, et al. Suggestive evidence that pelvic endometriosis is a progressive disease, whereas deeply infiltrating endometriosis is associated with pelvic pain. *Fertil Steril* 1991;55:759. Copyright © 1991, Elsevier).

Pain symptoms generally correlate with fluctuations in steroid hormone concentrations. In response to cyclic stimulation by ovarian estradiol and progesterone, endometriotic lesions undergo epithelial and stromal proliferation, variable secretory changes, stromal pseudodecidual reaction, and periodic regression in a manner more disorganized than, yet similar to, that of normal endometrium. Surgical castration and ovarian hormonal suppressive therapy result in diminution of pain in most patients.

Physical Findings

Bimanual pelvic examination may reveal tender uterosacral ligaments, cul-de-sac nodularity, induration of the rectovaginal septum, fixed retroversion of the uterus, adnexal masses, and generalized or localized pelvic tenderness. The adherent tube and ovary may constitute a tender, irregular mass that is similar in characteristics to the mass palpated in cases of chronic salpingo-oophoritis. Uterosacral nodules occasionally reach 1 cm or more in size. Lesions implanted in the retrocervical area or rectovaginal wall are frequently more easily felt than seen and can be missed if the physical examination is omitted. A perceptible, painful swelling of the implant before and at menstruation remains a classic and reliable clinical sign of active rectovaginal or retrocervical endometriosis.

Cancer antigen 125 (CA-125), a high molecular weight glycoprotein expressed on the cell surface of some derivatives of embryonic coelomic epithelium, is often elevated toward the end of the luteal phase and during menstruation in patients with AFS stages II to IV endometriosis. Barbieri and colleagues reported that a value higher than 35 U/mL had a positive

predictive value of 0.58 and a negative predictive value of 0.96 in establishing the presence of endometriosis. Many other conditions have been associated with an elevated CA-125 concentration, including acute pelvic inflammatory disease, adenomyosis, uterine leiomyoma, menstruation, pregnancy, epithelial ovarian cancer, pancreatitis, and chronic liver disease. Pittaway and colleagues reported that 80% of women with pelvic pain and endometriosis had a CA-125 titer greater than 16 U/mL, whereas only 6% of patients with pelvic pain and without endometriosis had an increased serum concentration of this cell surface antigen.

Increased concentrations of CA-125 and placental protein 14 (PP14) have been related specifically to the presence of endometriotic cysts and deep endometriosis. The results of most studies, however, suggest that CA-125 is not sufficiently sensitive to identify lesser stages of endometriosis and is therefore not reliable as a screening test.

Somigliana and colleagues report transvaginal ultrasonography has high sensitivity (84% to 100%) and specificity (90% to 100%) in identifying ovarian endometriomas as based upon characteristics of low-level, homogeneous internal echoes. Doppler sonographic evaluation of resistance indices in the vessels of adnexal masses increases the sensitivity and negative predictive values of two-dimensional sonography and CA-125, but this yields many false-positive results because of the neovascularity of benign tumors. Magnetic resonance imaging (MRI) may be helpful in assessing deep pelvic and extrapelvic endometriosis, including lesions that involve the bladder, vagina, or sigmoid (**Table 22.5**). Small studies have indicated that transrectal sonography or rectal endoscopic sonography is useful for detecting rectal wall involvement if performed by a skilled radiologist or gastroenterologist.

Visual Findings

The patient with unexplained lower abdominal pain or a presentation suggesting endometriosis requires laparoscopy for definitive diagnosis. Ultrasonography and other noninvasive procedures cannot provide the specific information needed to diagnose or classify the extent or severity of disease. For proper laparoscopic evaluation, a double puncture technique is essential. The ancillary probe or forceps placed through the lower abdominal sheath permits mobilization of the tubes and ovaries. A methodical regimented approach should be used to thoroughly inspect the lateral sidewalls, all ovarian surfaces, both sides of the broad ligaments, the

bladder and bowel serosa, and the inferior aspects of the cul-de-sac. Uterine manipulation with a cannula fixed to the cervix facilitates evaluation of the uterosacral ligaments and rectal serosa. Photography and video recording are useful for documentation of findings.

TABLE 22.5 Accuracy of MRI for the Diagnosis of Adenomyotic Endometriosis According to Location

LOCATION	SENSITIVITY (%)	SPECIFICITY (%)	ACCURACY (%)
Uterosacral ligaments	76	83	80
Rectovaginal	80	98	97
Rectosigmoid	88	98	95
Bladder	88	99	98
Vagina	76	95	93

From Bazot M, Darai E, Hourani R, et al. Deep pelvic endometriosis: MR imaging for diagnosis and prediction of extension of disease. *Radiology* 2004;232:379, with permission. Copyright © 2004 RSNA.

Awareness of the wide range of visual appearances of endometriosis is necessary for accurate diagnosis and appropriate surgical therapy of the disease. Although darkly pigmented lesions are readily recognizable and are considered a classic presentation of endometriosis, less discernible yet common forms of implants were described as early as the 1920s,

when Sampson noted “red raspberries, purple raspberries, blueberries, blebs, and peritoneal pockets.” The black or blue puckered “powder-burn” implant is a late consequence of cyclic growth and regression of the lesion, to the point that bleeding and hemosiderin staining of the tissue have occurred. Biopsy of such areas reveals inactive endometrial glands and fibrous stroma.

Distinctive morphologic variations include vesicles, flat plaques, raised lesions, polypoid structures, areas of fibrosis and adhesion formation, and peritoneal defects (**Table 22.6**). Yellow, brown, blue, or black coloration is proportional to the amount of hemosiderin deposition. Red polypoid lesions share the closest histologic characteristics with native endometrium and are thought to have the greatest metabolic activity, as is suggested by their high concentrations of prostaglandin metabolites. Biopsy of nonpigmented implants (i.e., implants that are the same color as adjacent peritoneum) may reveal active endometriotic glands and stroma. White lesions are predominantly fibromuscular scarring with scattered glandular and stromal elements, and brown lesions are mainly hemosiderin deposits. Peritoneal defects and subovarian adhesions contain endometriosis in 40% to 70% of cases. Because other peritoneal lesions share morphologic features similar to those of endometriosis, the differential diagnosis is broad and includes old suture locations, epithelial malignancies, endosalpingiosis, hemangioma, inflammatory reaction to infection or oil-based hysterosalpingogram dye, and carbon deposition from laser surgery. Rectovaginal endometriotic lesions consist of smooth muscle with active glandular epithelium and scanty stroma. They share similar characteristics to adenomyomas.

Small endometriotic lesions become more visible during the premenstrual and menstrual phases of the cycle, because during this time, microfoci of peritoneal disease become congested with blood and debris. In addition, vascular dilatation, superficial hemorrhage, and ecchymosis formation cause accentuation of the more typical features of endometriosis. Performance of laparoscopy at a time when ovarian steroidogenesis is suppressed by medications such as GnRH analogues or progestogens can lead to inaccuracies in the assessment of extent of disease.

Jansen and Russell reported the presence of nonpigmented lesions in 38% of their 202 patients with biopsy-proven endometriosis; 15% had only nonpigmented implants. Most areas of pigmented endometriosis are surrounded by nonpigmented endometriosis. These subtle lesions may represent the first stage of development of peritoneal disease. Recognition of nonpigmented endometriosis may be enhanced by “painting” the peritoneum with the patient’s blood or by filling the pelvis with irrigation fluid and submerging the laparoscope to appreciate the three-dimensional configuration of clear lesions. Subtle lesions are likely to originate from microscopic glands; they appear and disappear like blebs on the peritoneal surface. With progressive fibrosis, these implants become the classic pigmented, scarred lesions, and finally, when fibrosis replaces the stroma, they appear as white, inactive disease.

The ability to detect subtle lesions of endometriosis increases with the experience of the surgeon and is reinforced by histologic confirmation. Although depth perception is impaired when the monocular lens of the laparoscope is used to view the pelvic cavity, the magnification ability of this lens when closely approximated to the peritoneum may allow identification of subtle surface irregularities present in occult disease. Magnification up to 10× power can be obtained with the laparoscope, depending on the working distance. Microscopic implants of endometriosis not visible even with 10× magnification have been documented by scanning electron microscopy in peritoneal biopsies of patients with unexplained infertility who had no evidence of disease at the time of laparoscopy. A scanning electron microscopy study of samples of supposedly normal tissue from endometriosis patients has documented the presence of endometriotic foci in 25% of cases. Lesions as

small as 200 μm have been identified through this technique. Hence, surgical treatment of all visible disease is more accurately described as cytoreductive rather than ablative.

TABLE 22.6 Histologic Confirmation of Lesions Categorized by Appearance

	CONFIRMATION BY APPEARANCE (%)						
INVESTIGATORS	BLACK	WHITE	RED	GLANDULAR	SUBOVARIAN ADHESIONS	YELLOW-BROWN PATCHES	POCKETS
Jansen and	—	81	81	67	50	47	47

Russell (1986)							
Stripling et al. (1988)	97	91	75	—	—	33	—
Martin et al. (1989)	94	80	75	66	39	22	39

An ovarian endometrial cyst is usually formed by an inversion of the ovarian cortex. The frontal surface of the ovary in proximity to the hilus is the most common site for the invagination process to occur. Repetitive bleeding from the endometrial implants on the surface of the ovary may promote the growth of such lesions. Alternatively, invaginated epithelial inclusions may form endometriomas through coelomic metaplasia. Adhesions are common from the ovary to the fossa ovarica or to the posterior leaf of the parametrium.

Preoperative sonographic evaluation is a useful screening test for the presence of small endometrial cysts; their identification may affect the disease categorization to which the patient is assigned. Sonographic patterns may indicate purely cystic features, cystic features with few septations or minimal debris, complex combinations of cystic and solid elements, and largely solid features. More recently, fat-saturated MRI has been shown to be an acceptable tool for detecting endometriomas larger than 4 mm in diameter.

An adnexal mass in a patient with known pelvic endometriosis cannot be assumed to be an endometrial cyst of the ovary. Ovarian malignancy must remain in the differential diagnosis; the size of the mass has been correlated with malignancy. In a study of 180 women, 1% of masses smaller than 5 cm, 11% of masses between 5 and 10 cm, and 72% of masses larger than 10 cm were malignant. Most of these malignant tumors were adenocarcinoma.

The rules that apply to the management of all women in whom an adnexal mass develops also apply to patients with endometriosis with an adnexal mass. Among women of reproductive age, unilateral adnexal masses that are cystic and unilocular with regular borders on ultrasound examination are likely to be benign, whereas masses with solid areas, septa, papillations, or irregular borders have a greater likelihood of being malignant. Endometriomas vary in their appearance but usually have regular borders and slightly thickened and diffuse internal echoes unless fresh hemorrhage is present. Sensitivity and specificity of transvaginal ultrasound have been reported by Eskenazi and colleagues to be 84% to 100% and 90% to 100%, respectively.

Recognition of deep ovarian endometriosis is necessary for correct surgical staging. Small endometriomas were diagnosed in 48% of infertile women with mildly enlarged ovaries (3.5 to 5 cm in diameter) when the ovaries were punctured with a 16-gauge needle. The ovarian surfaces were without gross disease in this series of patients. Deep ovarian endometriosis is frequently associated with the presence of intestinal or more extensive pelvic disease.

Vercellini and colleagues studied the visual diagnostic parameters of ovarian endometriomas at laparotomy in 245 women with ovarian cysts. The gross characteristics that established the diagnosis included a size smaller than 12 cm in diameter; adhesions to the pelvic sidewall, to the posterior broad ligament, or to both; the presence of powder-burn lesions; superficial endometriosis with adjacent puckering on the surface of the ovary; and tarry, thick, chocolate-colored fluid content. These criteria yielded a sensitivity of 97%, a specificity of 95%, and an accuracy of 96%.

The depth of peritoneal infiltration by endometriosis cannot be evaluated by inspection alone. Deep endometriosis, which is almost exclusively localized to the posterior cul-desac and the uterosacral ligaments, is better detected by palpation and becomes even more apparent during excision. Deep endometriosis has been recognized to become smaller with increasing depth, although in some women, the largest volume is hidden under an adhesion involving the bowel or is buried in the rectovaginal septum. Diagnosis is enhanced if clinical examinations are performed during menstruation in women with chronic pelvic pain, severe dysmenorrhea, or deep dyspareunia. In most cases, a nodule is more palpable at this time. Koninckx and Martin have described three types of infiltrating endometriosis. Type I is characterized by a large pelvic area of typical or subtle lesions surrounded by white sclerotic tissue. During excision, deep disease becomes obvious and grows progressively smaller with deeper sectioning of tissue (like a cone). Type II is formed by retraction of the bowel and is recognized clinically as a small classic lesion associated with retraction. In some women, no implant is visible, but induration is associated with the retraction. Excision usually reveals the presence of a nodule. Type III is nodular endometriosis of the rectovaginal septum. This category is clinically suspected at the time of rectovaginal

examination when painful nodularities are noted. Occasionally, nodular endometriosis presents as small, typical lesions at laparoscopy or as dark blue cysts at the vaginal fornix during speculum examination. Type III disease is the most severe and often spreads laterally to involve the ureter.

CLASSIFICATIONS

Many endometriosis classification systems have been introduced to allow direct comparison of patient responses to medical and surgical treatments and to identify factors predictive of disease outcome. No system has yet been devised that is entirely satisfactory. The AFS (renamed the American Society for Reproductive Medicine) organized a panel of experts in 1979 to develop a classification system that might serve as a basis for evaluating various therapies. The committee devised an innovative scheme based on the natural progression of the disease. Three anatomic areas—the peritoneum, ovary, and fallopian tube—were examined for the presence of endometriosis or adhesions, with allowances made for unilateral involvement. However, the system was not weighted for depth of infiltration of peritoneal implants. A point system instead assigned values to each area of disease involvement based on the presumption that implant area and adhesion characteristics were most often associated with disease prognosis. The stage of disease was determined by the cumulative score of the assigned points. This classification system was criticized for its arbitrary division of endometriosis into categories that did not necessarily reflect the true relative risk of disease sequelae, pain, and infertility.

The AFS classification was revised in 1985 to provide a more standard assessment of endometriosis for correlation of surgical treatment with distribution and severity of implants (**Table 22.7**). The point range of mild disease was expanded, and greater weight was given to deep endometriosis, dense adhesions, and cul-de-sac obliteration by adhesive disease. Although the revised staging system appropriately acknowledges the importance of adhesive disease and endometriomas, most women with extensive peritoneal disease in the absence of ovarian involvement, particularly deeply invasive implants, receive a very low score on laparoscopic inspection of the lesions.

This revised AFS classification has been widely used by investigators to categorize disease states. Nevertheless, direct comparison of treatment outcome is compromised by inconsistencies in the application of the staging criteria and by the great variations in medical and surgical therapeutic options being applied in the management of endometriosis. Evaluation of the extent of disease by laparoscopy may be limited by a lack of recognition of atypical implants, particularly if the patient is hypoestrogenic as a result of recent discontinuation of medical therapy for endometriosis. Furthermore, the divisions between stages of endometriosis remained arbitrary, the

point score for ovarian involvement was weighted too heavily, and the classification scheme did not address disease involving the fallopian tubes, intestines, or urinary tract. Also, there were no parameters to indicate the present activity and state of evolution of the disease.

TABLE 22.7 The American Society for Reproductive Medicine Revised Classification of Endometriosis[a]

ENDOMETRIOSIS	<1 CM	1-3 CM	> 3 CM
Peritoneum			
Superficial	1	2	4
Deep	2	4	6
Ovary			
Right superficial	1	2	4
Right deep	4	16	20

Left superficial	1	2	4
Left deep	4	16	20
Posterior			
Cul-de-sac	Partial	Complete	
Obliteration	4	40	
Adhesions	<1/3 enclosure	1/3-2/3 enclosure	>2/3 enclosure
Ovary			
Right filmy	1	2	4
Right dense	4	8	16
Left filmy	1	2	4
Left dense	4	8	16
Tube			
Right filmy	1	2	4
Right dense	4[b]	8[b]	16
Left filmy	1	2	4
Left dense	4[b]	8[b]	16

[a]Determination of the stage or degree of endometrial involvement is based on a weighted point system. The following categories have been established: stage I (minimal disease) 1-5 points, stage II (mild disease) 6-15 points, stage III (moderate disease) 16-40 points, and stage IV (severe disease) >40 points.

[b]If the fimbriated end of the fallopian tube is completely enclosed, change the point assignment to 16.

The Endometriosis Classification Subcommittee of the American Society for Reproductive Medicine (ASRM) released new recommendations in 1996 for the documentation of the extent and location of disease. One concern over the reproducibility of the scoring system was directed at the variability in assessing ovarian endometriosis and cul-de-sac obliteration. The subcommittee indicated that an endometriotic cyst should be confirmed by histology or by the presence of the following features: (a) cyst diameter less than 12 cm, (b) adhesion to pelvic sidewall and/or broad ligament, (c) endometriosis on the surface of the ovary, and (d) tarry, thick, chocolate-colored fluid content. Cul-de-sac obliteration should be considered partial if some normal peritoneum is visible below the uterosacral ligaments, but adhesions or endometriosis has obliterated part of the cul-de-sac. Complete obliteration exists when no peritoneum is visible below the uterosacral ligaments. Because information is accumulating to suggest that the morphologic appearance of the endometriotic implants may correlate with biologic activity and consequently fertility, the newly revised classification scheme requests the categorization of lesions as red, white, and black. The percentage of surface involvement of each implant type is to be documented.

This revised ASRM classification system is oriented toward the infertile population. Muzii and colleagues, using a pain questionnaire administered to women before surgery, found a significant correlation between the severity of dysmenorrhea and total revised ASRM score, partial score for deep disease, and partial score for adhesions. However, they found no correlation between the pain score for dysmenorrhea and the partial score for superficial disease, number of typical and atypical implants, or the total number of implants. Limited knowledge of the specific pathophysiologic alterations by which endometriosis can cause these symptoms has so far prevented any precise categorization of disease based on response to conventional therapies for these symptoms.

The Enzian classification was developed in 2005 and subsequently revised in 2010 and 2011 to provide a means to characterize deeply infiltrating endometriosis, retroperitoneal structures, and the involvement of other organs. In 2003, Haas et al. observed a correlation was observed between the rASRM severity grade and the location of lesions in the Enzian classification, and pain and dysmenorrhea correlated strongly with the Enzian staging system score. The Enzian classification has thus far not been widely accepted and applied in clinical settings outside of Europe.

THERAPIES

Although women with endometriosis can present with a range of symptoms, therapy is usually initiated for the correction of pain, infertility, or a persistent pelvic mass. Pain and infertility can coexist in a patient; nevertheless, many women with

endometriosis-associated infertility have relatively little or no discomfort. Treatment options vary depending on the clinical history and findings at the time of surgery.

Expectant Management

Treatment of mild and moderate endometriosis with hormonal preparations does not offer any advantage over expectant management in promoting conception in women with infertility. A Cochrane review of 13 randomized controlled trials that included almost 800 infertile women with endometriosis found no evidence that medications that suppressed ovulation were superior to placebo in women who wished to conceive. In studies by Seibel and colleagues, Hull and associates, and Telimaa, patients assigned to expectant management conceived earlier than the medically treated group, and the cumulative pregnancy rate was not higher for women receiving progestogens or danazol. This lack of enhancement of fecundity may be related to the lower number of estrogen, progesterone, and androgen receptors in endometriotic lesions as compared with normal endometrium. Nevertheless, patients who have pelvic pain or dysmenorrhea and minimal or mild disease do benefit from hormonal therapy.

The age of the patient and the duration of her infertility are important factors to consider in determining the appropriate therapy for the symptomatic individual. Laparoscopic laser ablation of milder stages of endometriosis appears to lessen the interval to conception, although the cumulative pregnancy rate may not be greater than that of women managed expectantly. Surgical therapy for more advanced disease results in a higher pregnancy rate than does expectant management or hormonal treatment, partly because of correction of mechanical factors that may be inhibiting ovulation or tubal function.

There is no direct evidence to support the contention that surgical treatment of minimal or mild endometriosis in the asymptomatic patient will hinder future disease progression and sequelae. The potential benefits of cytoreductive therapy must be weighed against the risk of adhesion formation through surgical devitalization of peritoneal surfaces.

Medical Treatment

Mild pain symptoms associated with endometriosis may be effectively treated with nonsteroidal anti-inflammatory agents and oral contraceptives (**Fig. 22.3**). Additional endocrinologic therapies include progestogens, GnRH agonists, and danazol.

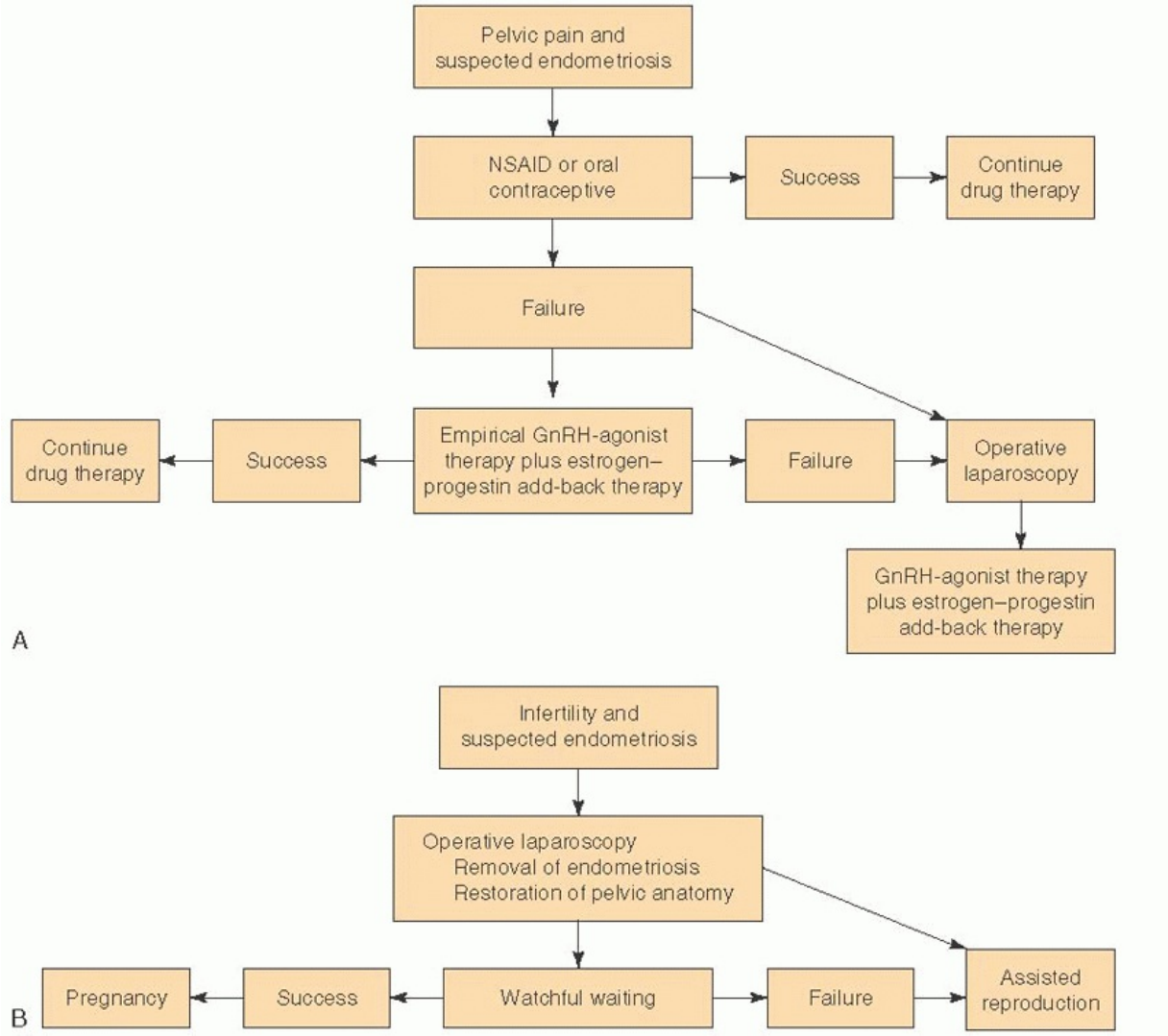

FIGURE 22.3 Algorithm for treatment of endometriosis-associated pain (**A**) and infertility (**B**). Where multiple pathways are shown, the path is guided by medical judgment and patient preference. In the infertility pathway, some practitioners dispense with the operative laparoscopy and recommend assisted reproductive technologies directly (From Olive DL, Pritts EA. Drug therapy: treatment of endometriosis. *N Engl J Med* 2001;345:267, with permission. Copyright © 2001, Massachusetts Medical Society).

These agents have similar degrees of efficacy in the relief of pain symptoms; side effects vary depending on their mechanism of action. At restoration of ovulation and of physiologic levels of estrogen, both eutopic and ectopic endometria resume metabolic activity. Therefore, medical therapy is symptomatic rather than curative, and most patients experience pain relapse at suspension of treatment.

Progestogens

By inhibiting the pituitary release of LH, progestogens suppress ovarian steroidogenesis and promote endometrial glandular atrophy, apoptosis, and extensive decidual transformation of the stroma. Progestogens oppose the growth-promoting effects of estrogens on the endometrial tissue by altering the clearance of the nuclear estrogen receptor and inducing 17β-hydroxysteroid dehydrogenase, which converts estradiol to the weaker estrone. Moreover, by eliminating cyclic bleeding and suppressing uterine contractility, progestogens prevent reflux menstruation, a potential stimulus for continued endometriosis development. Progestogens may prevent implantation and growth of regurgitated endometrium by inhibiting the expression of matrix metalloproteinase and plasminogen activators. Moreover, progestogens have anti-inflammatory properties.

Luciano and colleagues administered medroxyprogesterone acetate, 50 mg daily for 4 months, to symptomatic women with moderate-to-severe endometriosis. Improvement of pain, pelvic nodularity, and tenderness on examination occurred in 80% of patients. Twenty percent of women experienced breakthrough bleeding, and an additional 10% reported persistent cyclic bleeding. Minor weight gain, edema, and increased irritability were other described side effects, which were generally well

tolerated. A lower daily dose of 30 mg may provide equivalent relief of symptoms. Bergqvist and Theorell administered this dose to patients for 6 months and found a similar improvement in quality-of-life scores as that achieved with the GnRH agonist nafarelin. Compared with the cost of GnRH agonists and danazol, which are the other commonly prescribed agents, the low cost of the medroxyprogesterone acetate is a notable advantage.

Norethindrone acetate, a 19-nortestosterone progestin, has been shown to be effective in achieving amenorrhea and controlling disease symptoms, even with rectovaginal endometriosis. When used to treat moderate or severe pelvic pain after unsuccessful conservative surgery for symptomatic rectovaginal endometriosis, a dose of 3.5 mg per day for 12 months resulted in a 73% satisfaction rate (33/45). In 2005, Vercellini and colleagues reported a substantial reduction in dysmenorrhea, deep dyspareunia, nonmenstrual pelvic pain, and dyschezia scores. Low-dose norethindrone acetate could be considered an effective, tolerable, and inexpensive first-choice medical alternative to repeat surgery in those with recurrent pain. More recently, Vercellini et al. compared the effect of conservative surgery at laparoscopy with daily oral norethindrone acetate 2.5 mg per day. The progestin group took longer to respond to therapy, but the laparoscopy group started to experience a return of symptoms before the end of the study. At 12 months, surgery and progestin therapy were equally effective in the treatment of deep dyspareunia in women with rectovaginal endometriosis, whereas medical therapy performed significantly better than excisional treatment in those without deeply infiltrating lesions (33% vs. 63%; adjusted odds ratio [OR], 0.23; 95% confidence interval [CI], 0.07 to 0.76; $P = 0.02$).

A similar response rate can be obtained with megestrol acetate. Doses of 40 mg per day for up to 24 months resulted in significant relief of dysmenorrhea, noncyclic pelvic pain, and dyspareunia in 86% of subjects.

Parenteral depot medroxyprogesterone acetate has also been used to produce long periods of amenorrhea and elicit direct progestational changes of the endometrial tissue. A regimen of 150 mg intramuscularly every 3 months for 1 year has been used to manage endometriosis patients with moderate-tosevere pelvic pain. Twenty-nine of 40 subjects (72.5%) were satisfied with their pain relief after 1 year of therapy. An alternative regimen is 104 mg subcutaneously every 3 months. Frequent breakthrough bleeding can be troublesome to correct.

The rate of recurrence of symptomatic endometriosis after progestogen therapy appears to be related to the length of follow-up. Riva and colleagues reported an 18% rate after an average of 11 months, whereas Moghissi and Boyce described a 42% recurrence rate during a 2-year interval after discontinuation of medication.

Cyclic administration of low-dose oral contraceptive pills may result in relief of pelvic pain, particularly cramping associated with menstruation. This line of therapy should be considered for the woman with mild symptoms who is not attempting to conceive. A randomized, controlled trial by Harada and colleagues showed the superiority of combined oral contraceptives over placebo in decreasing baseline pain scores for dysmenorrhea (by 45% to 52% vs. 14% to 17%) and the volume of ovarian endometriomas (by 48% vs. 32%). Long-term continuous oral contraceptive use has been proposed for women with symptomatic endometriosis and menstruation-related pain who have failed a cyclic pill regimen. With such a regimen, the endometrium remains thin on sonogram studies, and endometriotic plaques subjected to a progestin-dominant pill are less active and usually less painful and will undergo apoptosis.

Low-dose (20 to 35 mg ethinyl estradiol) combination oral contraceptives may be given daily for 6 to 9 months without break to relieve pain or more severe dysmenorrhea. The dose may be increased to two or more tablets per day for several days to alleviate episodes of breakthrough bleeding. In a study by Vercellini and colleagues in 2003, 80% (40/50) of patients were satisfied or very satisfied with continuous use of an oral contraceptive containing ethinyl estradiol (0.02 mg) and desogestrel (0.15 mg) for 2 years, and 96% experienced pain relief, although spotting and breakthrough bleeding were frequent side effects.

The levonorgestrel intrauterine device (IUD) has proven effective in relieving pelvic pain symptoms caused by peritoneal and rectovaginal endometriosis and in reducing the risk of recurrence of dysmenorrhea after conservative surgery. In a study by Lockhat and colleagues, an improvement in symptoms was observed in 96% throughout the 36 months of use, with only 11% experiencing pain symptoms at 18 months. A recent randomized study by Tanmahasamut showed that the immediate postoperative placement of a levonorgestrel-releasing IUD after conservative surgery significantly prevented recurrence of moderate-to-severe dysmenorrhea, pelvic pain, and dyspareunia and improved the quality-of-life scores of the patients in the treatment group at 1 year postlaparoscopy. The progestogen released by the IUD is rapidly absorbed by the subendometrial vascular network, which reduces menstrual flow by 70% to 90%.

Danazol

Danazol is a synthetic (2,3-isoxazole) derivative of 17α-ethinyl testosterone that was introduced into clinical practice by Greenblatt and colleagues in 1971 after good performance in uncontrolled trials. The drug gained rapid acceptance because of its effectiveness in relieving pain associated with endometriosis and in enhancing fertility. All of the progestational and

the weak androgenic effects of the drug result from retention of the methyl group in the 19 position of the steroid nucleus, whereas the oral activity of danazol is ascribed to the ethinyl group at position 17.

The pharmacologic action of danazol is complex. By directly inhibiting GnRH secretion, the midcycle LH surge is ablated, although basal gonadotropin concentrations are maintained. The drug interacts with endometrial androgen and progesterone receptors, suppresses the activity of multiple enzymes necessary for ovarian and adrenal steroidogenesis, and displaces androgens from sex hormone-binding globulin, thereby augmenting androgen action on endometrial receptors. The decline in sex hormone-binding globulin induced by danazol lowers estradiol binding, increases estradiol clearance, and promotes a decline in the circulating level of this hormone. Hence, the derivative has direct androgenic and antiprogestational action on endometrial implants and creates a hypoestrogenic, hypoprogestational environment antagonistic to endometriosis. Moreover, by producing amenorrhea, danazol prevents peritoneal seeding of refluxed endometrial tissue. In addition, danazol is capable of suppressing elevated autoantibodies in several autoimmune diseases and has been shown to decrease immunoglobulin and autoantibody levels in women with endometriosis. In contrast to GnRH agonists, danazol use maintains a normal estrogenic state and increases bone mineral density over baseline.

The adverse effects of danazol reflect its anabolic, androgenic, and antiestrogenic properties and may be dose related. Weight gain, muscle cramps, decreased breast size, and vasomotor symptoms are noted in 50% or more of patients maintained on doses of 400 to 800 mg per day. In Buttram's 1985 series, 41% of patients treated with the standard dose of 800 mg per day gained more than 10 pounds during the course of therapy. The threefold increase in free testosterone can cause acne, oily skin, and deepening of the voice in a small percentage of recipients. High-density lipoprotein (HDL) cholesterol declines by 50% or more in response to the altered steroid concentrations; an 80% decrease in the HDL_2 subfraction has been reported.

Most series have described a concomitant increase in low-density lipoprotein (LDL) cholesterol; the alteration in the ratio of HDL to LDL cholesterol may be an unacceptable risk to some patients. Because danazol is metabolized by the liver, modest elevations in serum glutamic oxaloacetic transaminase and serum glutamate pyruvate transaminase may arise. Reported idiopathic drug reactions include gastrointestinal disturbances, weakness, dizziness, skin rashes, headaches, and muscle cramps. Bothersome side effects occur in as many as 85% of patients, and at least 10% of women receiving danazol discontinue pharmacologic treatment because the adverse effects are intolerable. Combining danazol therapy with aerobic exercise appears to reduce the incidence of many of these androgenic side effects. Preliminary data from trials using danazol vaginal rings and insertion of daily 200 mg vaginal tablets suggest that this route of administration may result in symptomatic improvement of pain while avoiding the androgenic side effects noted with oral administration.

Because of the potential androgenic action of this hormone on the developing fetus, the patient must not be pregnant when initiating therapy. Barrier contraception has been recommended for the entire course of treatment to eliminate the possibility of conception, although high doses of danazol usually cause anovulation.

The amenorrhea induced by danazol has been found to benefit patients with dysmenorrhea, dyspareunia, and cyclic pelvic pain associated with endometriosis. Young and Blackmore reviewed the effects of different dosages of oral danazol with respect to relief of symptoms in 452 patients. At a dose of 800 mg, 95% of patients noted relief of dysmenorrhea, and 89% reported relief of pelvic pain. At a dose of 400 mg, posttherapeutic relief was reduced by 10%. Moore and associates reported that pain associated with minimal and moderate pelvic endometriosis appeared to respond well to doses of danazol of 400 mg or less per day, whereas severe endometriosis was best treated with doses greater than 400 mg per day. A 6-year prospective study that evaluated the effectiveness of danazol at two doses (400 and 800 mg) in carefully classified patients concluded that there was no difference in side effects between the two doses and that gross resolutions of disease at second-look laparoscopy were similar. However, ovarian endometriosis greater than 1 cm did not respond as well to either dose of danazol as did peritoneal or ovarian disease less than 1 cm.

Recurrence of pain symptoms within 4 to 12 months of discontinuation of danazol therapy approached 50% in most studies. Lower daily doses of medication or courses of treatment less than 4 months in duration may result in a shorter symptom-free interval.

Clinical trials designed to assess the efficacy of medical therapy of minimal, mild, and moderate stages of disease refute the notion that danazol may enhance conception. Furthermore, conception is delayed while the patient is receiving danazol.

Gonadotropin-Releasing Hormone Agonists

Gonadotropin-releasing hormone (GnRH) agonists are available for use in the treatment of estrogen-dependent diseases such as endometriosis. Some of the more frequently studied analogues include leuprolide, nafarelin, buserelin, and goserelin. Alteration of the amino acid at position 6 and ethylamide replacement of the C-terminal amino acid of the native decapeptide hormone results in a GnRH agonist with increased resistance to lysosomal degradation. Pituitary receptor binding is enhanced, resulting in a decline in the number of receptors available for further occupancy. Continued administration of the GnRH agonist leads to a desensitization of the pituitary gonadotrope receptor and a reversible down-regulation of the pituitary-ovarian axis. Ovarian estrogen secretion may reach castrate levels.

The initial response to GnRH agonist administration is a markedly increased secretion of pituitary stores of folliclestimulating hormone (FSH) and LH. If therapy is begun in the follicular phase of the menstrual cycle, the developing follicle may respond to the flare in circulating gonadotropin levels with a rapid increase in estradiol production. Estradiol levels may remain elevated for 3 weeks before declining. GnRH agonist administration in the luteal phase leads to a more rapid decline in estrogen secretion, although FSH and LH levels remain elevated for 1 and 4 weeks, respectively.

Gonadotropin-releasing hormone agonist treatment results in improvement or resolution of pain symptoms in all stages of disease. Lemay and colleagues reported resolution of pain in 70% and improvement in discomfort in 15% of 24 subjects after 2 to 4 months of treatment with the agonist buserelin. Dyspareunia improved in 9% and disappeared in 91% of patients studied. The depot formulation of leuprolide acetate has also been shown to significantly reduce dysmenorrhea, pelvic pain, and pelvic tenderness in patients with endometriosis.

Henzl and associates, in a double-blind, multicenter study, treated 213 patients with either danazol or nafarelin. After 6 months of treatment, more than 80% of patients in all groups experienced a significant reduction in visible implants. A 43% reduction in AFS score was noted for each treatment

group; there was no difference in response among patients receiving the 0.4- and 0.8-mg daily dose of nafarelin. Most patients continued to demonstrate some visible implants at the time of follow-up laparoscopy, and, as with danazol, there was some diminution in size of endometriomas but no effect on preexisting adhesions.

The optimal interval of GnRH analogue administration has been widely debated. Six months of medication has been traditionally prescribed, although a significant reduction in implant volume occurs as early as 2 weeks after initiation of treatment in the rat model. A maximal effect was measured after 4 weeks of therapy in this animal study, suggesting that short courses of drug may be as efficacious as 6 months of continuous therapy. The regrowth of lesions after estrogen therapy has been reported years after the menopause; hence, hypoestrogenism results in inactivation rather than resolution of the disease.

Response to therapy may be dependent on route of administration. Donnez and colleagues reported that buserelin administration by a long-acting subcutaneous implant led to a greater reduction in endometriosis score, mitotic index, and endometrial cyst diameter than when given in an intranasal form. This may have been due to a greater consistency in hormonal release by the injected preparation.

As occurs with danazol and progestogen regimens, symptoms recur at variable periods after discontinuation of GnRH analogue therapy. Subjective return of pain occurred in 57% of patients within 6 months of discontinuing leuprolide, although 37% with moderate or severe pelvic pain at baseline were still improved at 1 year. Franssen and colleagues noted a lasting and significant amelioration of dysmenorrhea and dyspareunia 6 months after completion of treatment; however, scores for chronic pelvic pain had nearly reached their pretreatment level once this time had elapsed. Patients with a higher disease stage at the onset are more likely to experience recurrence and to experience it earlier than patients with minimal disease. One treatment option for such patients may be a second 3-month course of GnRH analogue. Henzl reported a significant decrease in mean pain scores and essentially no change in compact bone density in most patients when nafarelin was readministered for 3 months after a treatment-free interval of 6 months or more.

Most of the side effects associated with GnRH analogue therapy are related to hypoestrogenism. Hot flashes are common and can lead to sleep disturbances and chronic fatigue in extreme cases. Vaginal dryness, superficial dyspareunia, headaches, and depression have been reported. In general, these adverse effects are better tolerated than those experienced with danazol use. In addition, there are no undesirable changes in HDL, LDL, or total cholesterol throughout the prolonged period of hypoestrogenism induced by GnRH analogue, unlike the changes accompanying danazol intake.

A decline in trabecular bone mineral content and an increase in urinary calcium excretion to menopausal levels occur during the course of GnRH analogue therapy in approximately two thirds of patients. Quantitated computed tomographic (CT) studies consistently show significant loss of trabecular bone of the vertebrae and hip with GnRH analogue exposure. Restoration of normal estrogen production after cessation of therapy appears to at least partially reverse these bone changes. In a study of the GnRH agonist goserelin, an 8.2% decline in density of the lumbar spine was measured after completion of 6 months of treatment; this improved to a mean loss of 5.4% at 6 month after cessation. Others found no significant change from baseline after a 6-month course of GnRH analogue when bone density was assessed 6 months after treatment.

Concomitant administration of a progestogen during the course of GnRH analogue therapy has been examined to ameliorate vasomotor symptoms and retard both urinary calcium excretion and radiologic evidence of loss of bone mineral density. Cedars and coworkers reported a diminution in the side effects mentioned earlier when medroxyprogesterone acetate was administered at a dose of 20 to 30 mg per day during the 6-month course of agonist therapy; however, laparoscopic evaluation after completion of therapy failed to reveal any improvement or suppression of active endometriosis with the combination regimen, and the regimen failed to significantly reduce symptoms of pelvic pain. Conversely, Makarainen and colleagues reported that medroxyprogesterone acetate, 100 mg per day, diminished hot flashes and the urinary excretion of calcium in women treated with goserelin acetate, 3.6 mg monthly, for 6 months. Second-look laparoscopy revealed equivalent diminution in extent of endometriosis when compared with the goserelin-progestin placebo group.

Norethindrone, the 19-nortestosterone progestin, has been shown to suppress both the painful symptoms of endometriosis and the extent of disease at laparoscopy when used in daily doses of 1.4 to 10 mg during GnRH agonist therapy. A randomized, double-blind study has demonstrated that GnRH agonist therapy may be safely and effectively extended for up to 1 year in the management of endometriosis-associated pelvic pain when prescribed in conjunction with low-dose sex steroid hormones. Hornstein et al. reported that norethindrone acetate, 5 mg, alone or in combination with conjugated equine estrogens, 0.625 mg daily, from the onset of depot leuprolide acetate therapy alleviated hypoestrogenic symptoms and preserved bone density while resulting in equivalent pain relief to that achieved by the placebo estrogen-progestin patient group. Others have treated a limited number of patients with a similar regimen for up to 10 years without detecting an adverse effect on bone mineral density. For women with relapse of endometriosis-associated pain, GnRH agonist with “add-back” progestin or progestin/estrogen therapy provides patients with a better quality of life than GnRH analogue alone or oral contraceptive regimens.

The addition of calcium carbonate and alendronate or etidronate sodium, which are organic bisphosphonates, to the low-dose norethindrone acetate add-back therapy in patients with symptomatic endometriosis receiving prolonged GnRH agonist treatment may further minimize the adverse side effects of hypoestrogenism.

In a review of randomized clinical trials of the Cochrane Menstrual Disorders and Subfertility Group register, there was no difference in pain relief between GnRHas, levonorgestrel, and danazol. Additional controlled studies will better establish the optimal medical management of this condition.

Conservative Surgery

Surgery is indicated for correction of pain, infertility, or other symptoms in patients with extensive pelvic endometriosis or when hormonal manipulation fails to adequately diminish pain symptoms in women with lesser stages of disease. Surgery is successful in relieving pain in a very high percentage of cases and offers a better prognosis for pregnancy than does endocrine therapy in many cases of advanced disease.

The surgeon who has mastered the specialized techniques of operative laparoscopy can treat a wide range of pathologic findings at the time of diagnosis. Therapeutic planning depends on many factors, including the age of the patient, her desire for fertility or pain relief, the duration and intensity of her symptoms, the extent of disease, and previous treatments that have been undertaken. Preoperative rectoscopy-sigmoidoscopy and intravenous pyelography are recommended in patients with

symptoms suggestive of deeply invasive endometriosis of the posterior cul-de-sac and rectovaginal septum. Magnetic resonance imaging or sonography may also be helpful in predicting the extension of disease (**Table 22.5**).

The decision of whether to perform surgical resection of endometriosis through the laparoscope or open abdomen is not entirely dependent on the stage of disease that is encountered. Laparoscopy can be considered for all cases unless there is difficulty in establishing the appropriate tissue planes of dissection or unless improved access is necessary for atraumatic manipulation of the involved organs. Specific endoscopic procedures include ablation of endometriotic implants, adhesiolysis,

ovarian cystectomy, oophorectomy, and salpingectomy. Although the results and complications are similar, the cost savings with respect to decreased hospital expenses and loss of work time favor laparoscopy over laparotomy when other factors regarding risks and outcome are equal. Laparoscopy provides superior visualization of the posterior cul-de-sac and allows a high degree of magnification of peritoneal surfaces, which aids in the identification of subtle disease.

Conservative resection of disease by laparotomy is most valuable in cases of extensive, dense pelvic adhesions, or endometriomas greater than 5 cm in diameter. In addition, deep involvement of the rectovaginal septum with fibrotic extension into the perirectal fossa, invasion of the bowel muscularis, and endometriotic infiltration in the region of the uterine vessels and ureter is generally best approached through the open abdomen for all but advanced endoscopic surgeons. The objective of the laparotomy procedure is complete excision of all endometriosis and associated adhesive disease to restore normal functional anatomy of the reproductive tract. The usual surgical approach is through a transverse suprapubic incision. A Maylard incision provides adequate exposure for presacral neurectomy and reconstructive surgery of ovarian endometriomas of almost any size.

Principles of Microsurgery

Microsurgical technique, or the philosophy of gentle manipulation of tissue in an attempt to avoid trauma, is the major tenet of pelvic reconstruction. The inflammation, trauma, coagulation, and foreign materials associated with conventional macrosurgical technique lead to tissue ischemia and adhesion formation because of local failure of the intrinsic peritoneal fibrinolytic system. Adhesion formation can be reduced by the application of loupe magnification or use of the operating microscope; reconstruction with fine, nonreactive sutures; precise hemostasis; and frequent irrigation of tissues with warmed lactated Ringer solution. Nevertheless, there are no definitive data to suggest that use of the particularly costly ancillary laser and the operating microscope has appreciably improved the reproductive prognosis in the surgical management of endometriosis through laparotomy. The magnification provided by laparoscopy in a closed surgical field matches these microsurgical principles.

Several basic techniques are available for the endoscopic ablation of endometriosis, including excision, coagulation, and vaporization. Coagulation can be achieved by monopolar or bipolar cautery, thermocoagulation, or, in some circumstances, laser, depending on the wavelength of energy applied. The extent of tissue penetration in electrocautery is related to the power and type of current, the duration of application, and the size of the electrode. Less tissue damage is achieved with bipolar than with monopolar cautery. The carbon dioxide (CO_2) laser is more precise than the fiber lasers, although CO_2 laser energy is strongly absorbed by water molecules and is rendered ineffective in the presence of blood. Meticulous technique that maintains serosal integrity may reduce the incidence of de novo adhesion formation.

Sites of Conservative Surgery

Peritoneum

Small lesions of superficial peritoneal endometriosis less than 5 mm in diameter are easily treated with laser or bipolar coagulation while under a constant stream of irrigation. Deep lesions or more extensive peritoneal disease must be excised with a tissue margin of at least 2 to 4 mm, because, as noted previously, microscopic lesions are commonly present in tissue adjacent to visible implants (**Fig. 22.4**). Ablation of deep disease by monopolar microdiathermy or CO_2 laser vaporization rather than excision of the disease may result in inadequate resection and a greater amount of ischemic damage to the tissue, heightening the propensity toward adhesion formation. Immobilizing adhesions can be merely divided during the preparatory phase of the procedure; precise excision is more easily accomplished after the involved organs are freed. Before dissection of the pelvic sidewall, the ureter must be identified and isolated; it frequently is displaced from its normal location by endometriotic adhesive disease. A Lucite, Teflon, or laparoscopic titanium probe can be used to isolate adhesions and protect adjacent structures during separation of the tissue planes. Suture placement can lead to foreign body reaction, tissue anoxia, and fibrosis and should therefore be avoided. Covering hemostatic, deperitonealized surfaces with an absorbable, oxidized, regenerated cellulose barrier (Interceed) significantly reduces the incidence, extent, and severity of postsurgical pelvic adhesions, even in patients with severe endometriosis. Alternatively, application of the Gore-Tex surgical membrane has been shown to result in a statistical reduction in adhesion score; this barrier can be removed at the time of a second-look laparoscopic procedure if its presence would impair tuboovarian function.

Estimations of the depth of endometrial implants at the time of laparoscopic resection relate well with histologic measurements. Superficial implants can be destroyed by bipolar cauterization; however, 25% of patients have lesions greater than 5 mm in

depth. Deep (<5 mm) and very deep (< 10 mm) lesions represent an active form of the disease and occur almost exclusively in patients who report pain. The superficial action of nonvaporizing modalities such as bipolar or thermal coagulation is not sufficient for deep disease. The diagnosis of retroperitoneal endometriosis is suggested by preoperative digital rectovaginal palpation and laparoscopic blunt probe palpation. The depth of infiltration of deep lesions appears to correlate poorly with the visible surface area of involvement. The laparoscopic treatment of deep disease is often complicated by the proximity of implants to vital structures such as the ureter, bladder, and vessels (**Table 22.8**).

Laparoscopic forceps are used to elevate and isolate the tissue to be excised. Instruments should be placed with care, because surgical manipulation of tissue that will not be resected may result in de novo adhesion formation. The diseased peritoneum may also be separated from underlying tissue by the technique of hydrodissection, which forcefully injects physiologic irrigant retroperitoneally through a small defect created in the peritoneum (**Fig. 22.5**). This retroperitoneal placement of fluid acts to dissipate CO_2 laser energy and, in so doing, promotes safer dissection or vaporization of the peritoneal surface. Coagulation or vaporization of disease in the ovarian fossa or near the uterosacral ligament should be undertaken only after clear identification of the ureter. Uterine manipulation with a Valtchev retractor or other uterine manipulator may be used while treating lesions of the posterior cul-de-sac.

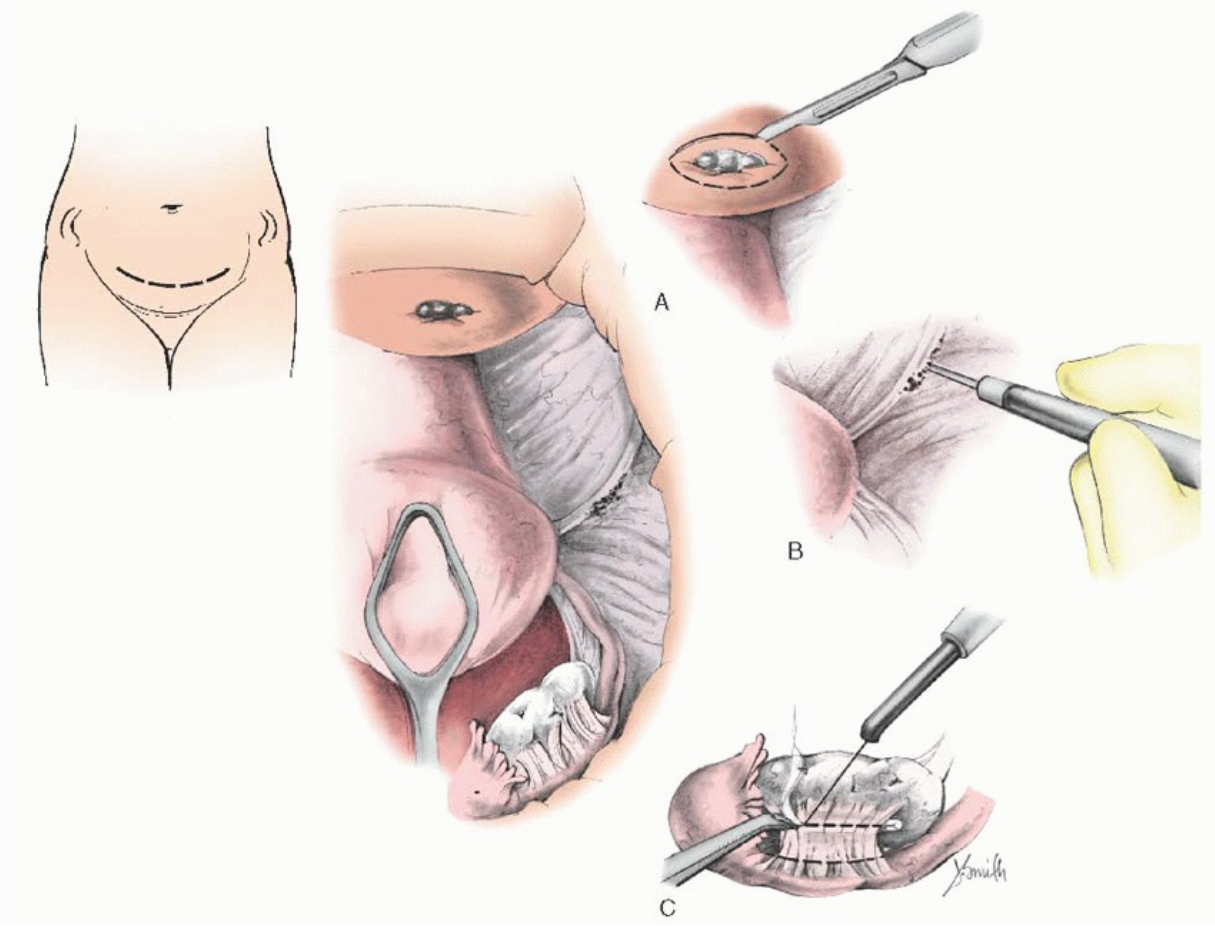

FIGURE 22.4 Excision or CO_2 laser vaporization of peritoneal implants. **A:** Superficial implants are vaporized by use of power densities between 1,000 and 3,000 W/cm^2, with a spot size of 0.8 to 1 mm, or they are cauterized with microbipolar forceps. More extensive peritoneal disease is excised. Very large defects can be closed with 5-0 or 6-0 polyglactin or polydioxanone sutures. Adhesion barriers can be placed. **B:** Endometriosis can be associated with extensive adnexal adhesions. **C:** Wide adhesion bands can be retracted with a glass rod or similar nonconductive probe and completely excised with a monopolar microelectrode.

TABLE 22.8 Suggested Surgical Procedure According to Classification of Deeply Infiltrating Endometriosis (DIE)

DIE CLASSIFICATION	OPERATIVE PROCEDURE

A: Anterior DIE	
AI: Bladder	Laparoscopic partial cystectomy
P: Posterior DIE	
P1: Uterosacral ligament	Laparoscopic resection of USL
P2: Vagina	Laparoscopically assisted vaginal resection of DIE infiltrating the posterior fornix
P3: Intestine	
Solely intestinal location	
Without vaginal infiltration (V-)	Intestinal resection by laparoscopy or by laparotomy
With vaginal infiltration (V+)	Laparoscopically assisted vaginal intestinal resection or exeresis by laparotomy
Multiple intestinal location	Intestinal resection by laparotomy

USL, uterosacral ligament.

From Chapron C, Fauconnier A, Vieira M, et al. Anatomical distribution of deeply infiltrating endometriosis: surgical implications and proposition for a classification. *Hum Reprod* 2003;18:157, with permission. Copyright © 2003, Oxford University Press.

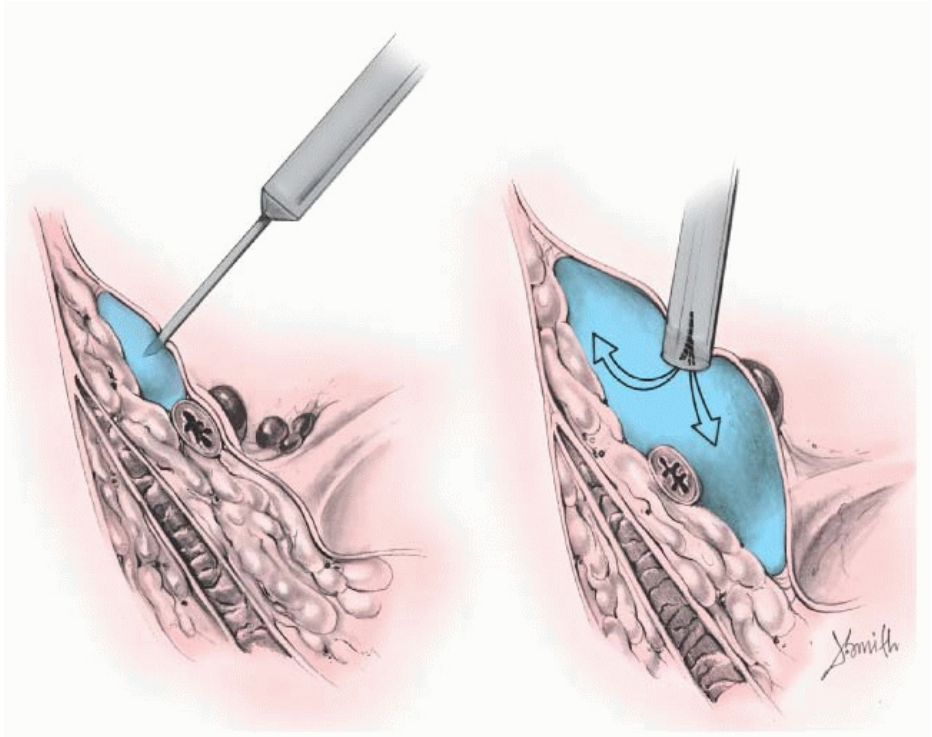

FIGURE 22.5 Hydrodissection.

It is difficult to evaluate the depth of tissue damage with electrocauterization; however, laser vaporization allows visualization of the three-dimensional boundaries of every lesion. The laser beam should be applied until the bubbling of retroperitoneal areolar tissue is noted. The zone of thermal necrosis is minimal with the CO_2 laser, particularly when applied in the superpulse mode. In the region of the ureter, urinary bladder, colon, or large blood vessels, a single or repeat pulse mode of 0.05 to 0.1 second allows a depth of penetration of 100 to 200 μm. Irrigation of the pelvis washes off debris and carbon deposition and better exposes the base of the site of laser impact. A 2- to 4-mm clear margin is desired around each lesion treated. Excision of the involved peritoneum is superior to vaporization of implants when the extent of tissue penetration cannot be recognized.

Dissection of retroperitoneal disease can be facilitated by placing a bougie probe in the rectum and a sponge forceps in the vagina (**Fig. 22.6**). Traction in either direction opens the rectovaginal and perirectal spaces. Initial dissection of the anterior rectum provides a landmark of the rectovaginal space and permits posterior mobilization of the nodule. Subsequent lateral dissection is performed, followed by anterior dissection, which permits retrieval of the involved tissue.

Resection of deep posterior cul-de-sac nodules requires great endoscopic expertise. A combined laparoscopic-vaginal approach may be necessary to effectively remove these implants (**Fig. 22.7**). It is often helpful to have an assistant place his or her fingers deep in the vaginal fornices or a bougie probe in the rectum to indicate the sites of the nodules to ensure their complete removal. The direct palpation made possible through laparotomy may be required to recognize all indurated, deep lesions. A complete bowel preparation is mandatory in all cases of suspected deep endometriosis.

Electrosurgery should be avoided when extensive dissection is performed because it may be associated with widespread thermal damage and difficulty in recognizing tissue planes. Superficial invasion of the muscularis of bowel or bladder can be treated with laser vaporization or endocoagulation because of the precision and lack of penetration of these energy sources. Anterior cul-de-sac treatment should be accompanied by continuous bladder drainage.

Tubal endometriosis may distort the normal anatomic relationship of the distal tube to the ovary and in severe cases may cause complete fimbrial obstruction. Short pulses of CO_2 laser may be used to vaporize lesions while minimizing thermal damage. Endoscopic adhesiolysis of the distal tube may be accomplished with fine scissors or careful application of laser. Unipolar electrocautery should not be used on this tissue.

Defects in the parietal peritoneal surface are frequently associated with endometriosis and are most commonly found in the posterior cul-de-sac region. These defects should be explored and ablated even if they appear grossly normal because of the frequency of microscopic disease.

Ovary

Superficial endometriosis of the ovary usually presents as small, dark, punctate lesions located on and immediately beneath the cortical surface. This disease can be readily treated with laser or bipolar forceps under constant irrigation. Occasionally, however, the small, visible lesion may be merely the tip of a large endometrial cyst. If there is any doubt, the implant should be excised and the ovary explored to determine the extent of disease. Care should be taken to minimize thermal injury to surrounding ovarian tissue. This is particularly important near the fimbria ovarica, because postoperative adhesion formation could compromise distal tubal function. Inability to elevate the ovary is usually a sign of adhesions and endometriotic implants of the inferolateral surface of the ovary and the peritoneum of the ovarian fossa. Excising the fibrotic pelvic sidewall and/or uterosacral ligament lesions to which the ovary was attached will reduce disease recurrence.

RECONSTRUCTION BY LAPAROTOMY

Extensive ovarian endometriosis is often associated with periovarian and peritubal adhesions. These adhesions may become apparent while manipulating the ovary to visualize the lateral surface adjacent to the broad ligament. Filmy adhesions are elevated with delicate tissue forceps and can be resected with fine-needle cautery, a scalpel, or the laser. Care must be taken to maintain the integrity of the ovarian capsule. After the appropriate adhesiolysis is accomplished, the posterior cul-de-sac is packed with moist, lint-free packs, and a silicone surgical platform can be placed to stabilize the adnexa. The ovary should be carefully

examined for extent of disease involvement before creation of the initial incision. Peritoneal spillage of the contents of the endometrioma can be avoided by placement of a lint-free pack around the platform.

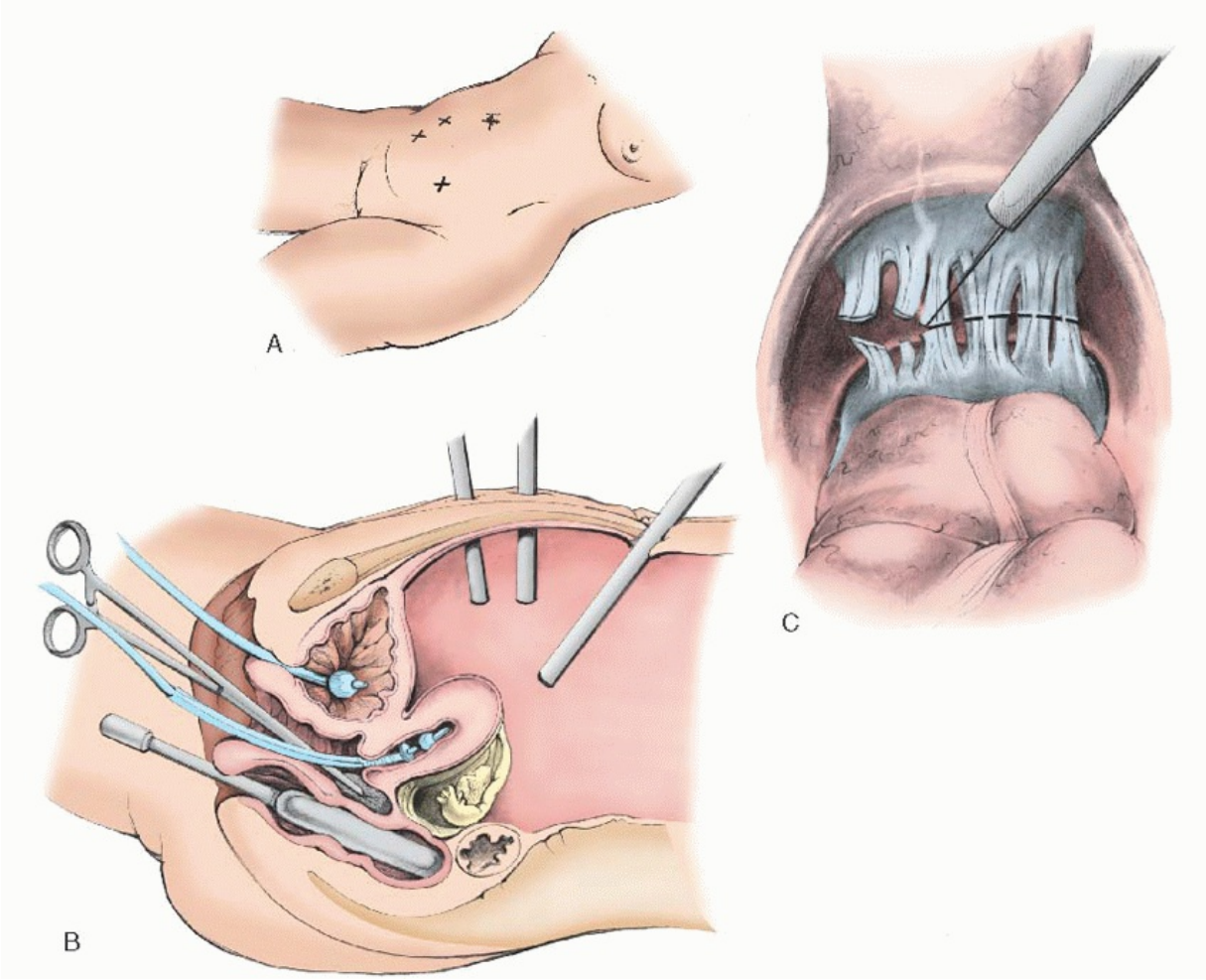

FIGURE 22.6 Laparoscopic therapy for endometriosis. **A:** Dorsal lithotomy positioning for surgery, with multiple puncture sites marked for placement of ancillary instruments. **B:** Traction on bougie in rectum and sponge forceps in vagina mobilize rectovaginal and perirectal spaces. Uterine manipulation cannula, bladder drainage, and multiple transabdominal instruments facilitate safe dissection. **C:** CO_2 laser division of endometriosisassociated adhesions extending from lower uterus to rectal serosa.

The cortical incision should be made in a way that will preserve the normal anatomic relations of the ovary with the uteroovarian ligament and fimbria ovarica (Fig. 22.8). This is best accomplished by making a shallow longitudinal incision over the endometrioma with the monopolar microneedle, scalpel, or laser. The surgeon should attempt to remove the endometrioma in an intact state; however, if the cyst cavity is inadvertently entered, an elliptical incision around the site of rupture is useful for exposure. The intact endometrioma can be transfixed with a traction suture of 2-0 nylon to facilitate creation of a cleavage plane between the cyst and normal ovarian tissue. Blunt, curved scissors or a flat probe or knife handle is used for dissection. Particular care must be taken when dissecting the hilar region to maintain hemostasis and preserve primordial follicles. An attempt should be made to preserve as much of the normal ovarian cortex as possible; pregnancies have been achieved with only a small fraction of remaining ovary.

The ovary is reconstructed by placing one or two purse-string sutures of 4-0 or 5-0 polyglactin, polyglycolic acid, or polydioxanone to eliminate the dead space and maximize hemostasis. This may be followed by placement of a running subcortical 5-0 suture of the same delayed absorbable material (Fig. 22.8), if necessary. In some circumstances, less tissue distortion can be achieved by placing a deep layer of interrupted mattress sutures followed by additional layers of running sutures (Fig. 22.8). Suture on or extruding through the surface should be strictly avoided because of its adhesiogenic properties.

After the ovary has been carefully approximated, the posterior surfaces of the uterus and broad ligament are inspected for hemostasis wherever the ovary was previously adhered. Microbipolar cauterization may be necessary. Placement of an adhesion barrier is useful in separating raw peritoneal surfaces during the healing process.

ENDOSCOPIC THERAPY OF OVARIAN ENDOMETRIOSIS

Surgical treatment of endometriosis less than 4 to 5 cm in diameter can be accomplished with relative ease. However, endoscopic resection of larger lesions may be compromised by the presence of dense, cohesive adhesions and by difficulties removing the entire cyst wall because of the inability to find the plane of attachment of the fibrotic endometrioma to the ovarian cortex. When performing a cystectomy, the experience and skill of the surgeon influence the extent to which healthy ovarian tissue is removed and the ovary is devascularized. A recent histologic study of endometriomas by Romualdi et al. indicated that more follicles are involuntarily removed when smaller cysts are excised, particularly when the capsule is less defined due to fibrosis.

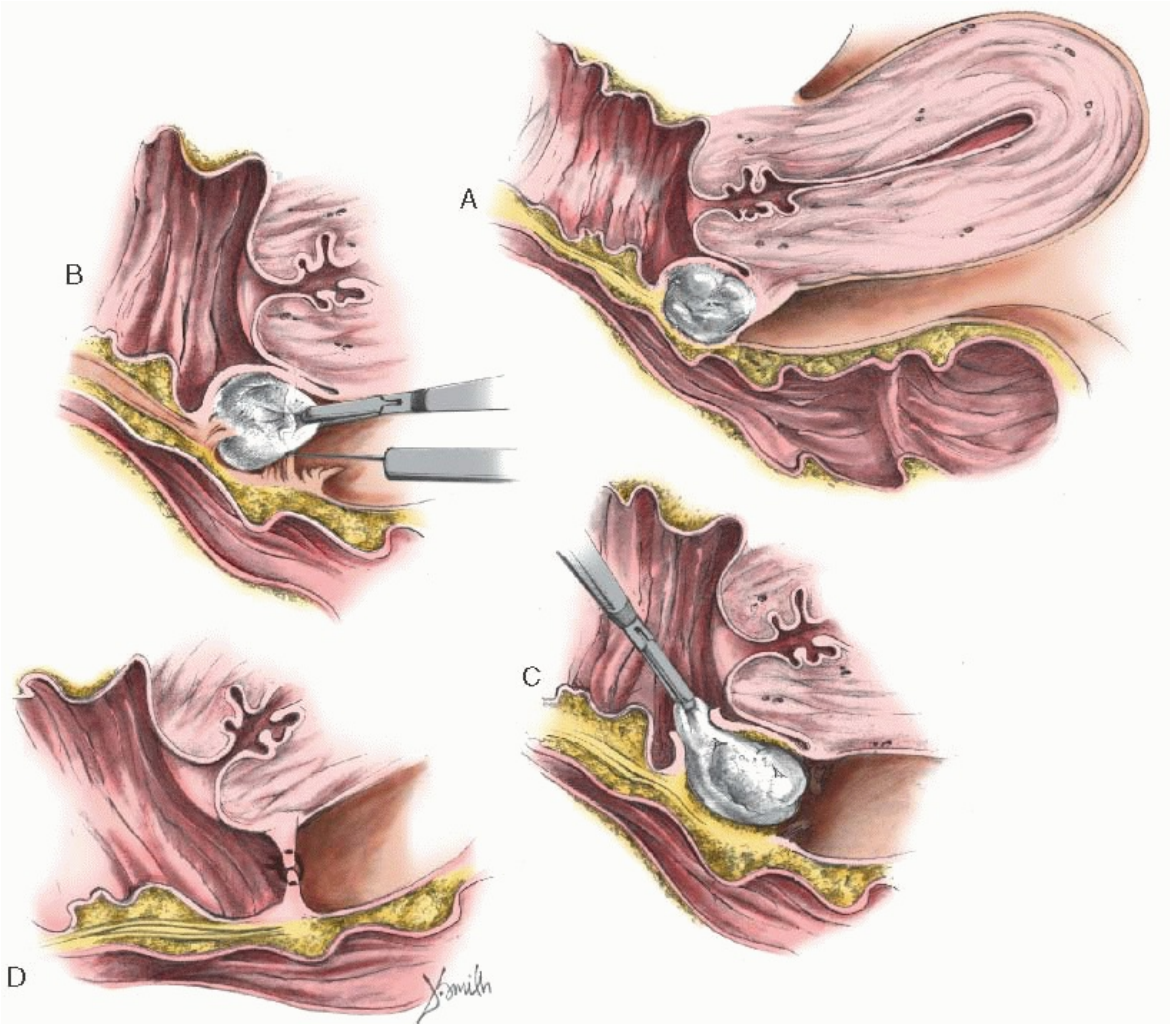

FIGURE 22.7 A: Deep laparoscopic dissection of the rectovaginal space, in combination with colpotomy, for the excision of a large endometriotic nodule of the rectovaginal septum. **B:** Initial laparoscopic dissection of nodule. **C:** Completion of dissection by way of colpotomy incision. **D:** Vaginal suture placement to reapproximate the rectovaginal septal defect.

The endometrioma can be excised in an intact or ruptured state during the laparoscopic procedure. In either case, the technique is initiated by longitudinally incising the cortex overlying the cyst after achieving full mobilization of the ovary by adhesiolysis. The incision is generally made along the inferior pole on the opposite side to the hilus in such a manner as to preserve the apposition of healthy ovarian tissue to the fimbria. Laser, scissors, or a unipolar needle electrode may be used for this purpose. Hydrodissection may be used to separate the cyst wall from the ovarian stroma. If the cyst is entered, its contents are immediately drained with the suction cannula, and the cavity is irrigated and inspected for papillary structures or other suspicious features. Often, the cyst ruptures during dissection of adhesions that bind the ovary to the pelvic sidewall. Under this circumstance, the plane of dissection between the cyst wall and the ovarian cortex can be established after identifying the site of rupture. The endometriosis tissue typically penetrates the cyst wall less than 2 mm. The opening can be extended with the use of the needle electrode or laser.

With larger endometriomas, the normal ovarian cortex is stabilized with atraumatic forceps, and the cyst wall is grasped with a second pair of 5-mm forceps and stripped from the bed of normal ovarian tissue (**Fig. 22.9**). As demonstrated by Muzii et al., dissection may be facilitated by removing a small circular rim of tissue around the adhesion site to begin the stripping

procedure in a clearer field, where the endometrioma wall is less adhered to healthy ovarian tissue. Judicious use of the needle electrode or hydrodissection may facilitate separation of the tissue planes. Remaining fragments of the cyst wall near the hilum should be vaporized with CO_2 laser, if possible, rather than electrocautery to destroy the mucosal lining and reduce the extent of thermal damage to the vasculature. If necessary, hemostasis may be achieved with minimized application of bipolar cautery. The key to successful surgery is to avoid bleeding, since the application of energy to control bleeding results in loss of functional ovarian tissue.

An alternative technique involves sharp and blunt dissection to remove the cyst in an intact state. Hydrodissection is particularly useful with this approach. The cyst contents are carefully drained in a plastic laparoscopy pouch to facilitate clean removal from the peritoneal cavity.

Very small endometriomas less than 1 to 2 cm in size may be effectively treated by electrocoagulation of the mucosal lining. Because CO_2 laser is absorbed by fluid, complete ablation of the cyst wall with this energy source may be compromised in an environment rich in blood and hemosiderin, although laser ablation may be less harmful to healthy ovarian tissue than electrocoagulation.

The ovarian defect is usually left to heal spontaneously. Ischemia associated with suture placement can provoke adhesion formation after laparoscopic ovarian reconstruction. Low-power continuous CO_2 laser or bipolar coagulation can be applied to the inside wall of the redundant ovarian capsule

to cause an inversion of the incised cortex. Most authors have reported excellent results with this no-suture technique.

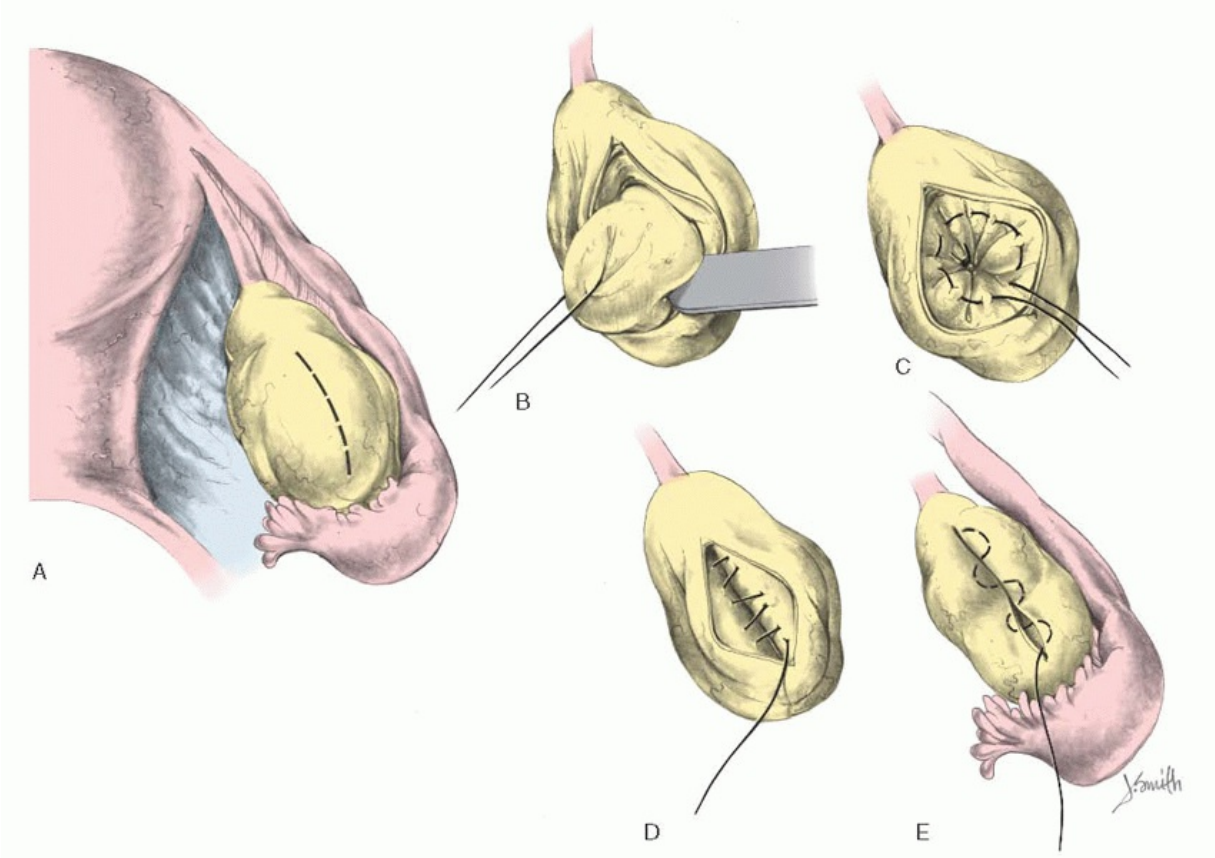

FIGURE 22.8 Excision of ovarian endometrioma through laparotomy. **A:** The ovarian cortex is gently incised so that the endometrial cyst is not entered. The incision is made along the longitudinal axis of the ovary. **B:** The endometrioma is then peeled out with the blunt knife handle. **C and D:** The ovarian defect is closed with two layers of purse-string sutures of 4-0 or 5-0 absorbable, nonreactive material. **E:** In the case of a deep defect, a more superficial running suture may be necessary before the cortical edges are approximated with 5-0 nonreactive, delayed absorbable sutures.

Under the rare circumstances of persistent bleeding or poor apposition of ovarian tissue, the cortex may be reapproximated with sutures. If fine absorbable suture is used, the knot should be placed internally to minimize the possibility of it becoming a nidus for adhesion formation. The high incidence of adhesion formation after surgery for endometriosis, particularly at the site of the ovary or where dense adhesions were divided, underscores the importance of optimizing surgical techniques to

potentially reduce adhesion formation.

Extensive cauterization of ovarian tissue can lead to a rise in FSH levels postoperatively and should be avoided. Goksever Celik et al. demonstrated that laparoscopic removal of endometriomas by the stripping technique causes a decrease in ovarian follicular reserve at 6 months after surgery as measured by serum antimüllerian hormone levels. This change in serum markers of ovarian reserve was not different whether laparoscopic suturing or bipolar coagulation was used to achieve hemostasis in a recent randomized trial by Ferrero et al. Postsurgical ovarian failure after laparoscopic excision of bilateral endometriomas is a rare but possible complication. There were three cases of premature ovarian failure among 126 patients who underwent laparoscopic excision of bilateral endometriomas in a recent series by Busaccca and colleagues, corresponding to a rate of 2.4%. This may be caused by irreversible trauma to ovarian vasculature by electrocoagulation, excessive removal of ovarian tissue, and an autoimmune reaction caused by a severe, local inflammatory process. Coccia et al. found the mean age of menopause is lower in patients who have undergone surgery for bilateral endometriomas.

Fayez and Vogel prospectively evaluated four laparoscopic methods for the treatment of endometriomas. Patients were treated postoperatively with danazol and underwent a secondlook laparoscopy 8 weeks after their initial surgery. Complete excision with scissors successfully eliminated recurrence of the cysts, but adnexal adhesions had developed postoperatively in all cases. Mere incision and drainage of the cyst contents, followed by stripping or CO_2 laser vaporization of the lining, resulted in adhesion formation in only 25% to 37% of cases, but endometrioma cysts recurred in 21% to 22%. Other authors have used the potassium titanyl phosphate laser to photocoagulate or remove the cyst lining of large endometriomas and have reported a very low rate of recurrence at 6 months after the procedure.

In a prospective study by Beretta and colleagues, patients were randomly allocated at the time of laparoscopy to undergo either cystectomy or drainage of the endometrioma and bipolar coagulation of the inner lining. No preoperative or postoperative adjunctive medical therapies were administered. The excision technique resulted in a lower 24-month cumulative recurrence rate of dysmenorrhea, deep dyspareunia, and

nonmenstrual pelvic pain. The median interval between the operation and the recurrence of moderate-to-severe pelvic pain was longer in the cystectomy group (19 months) versus the drainage and coagulation group (9.5 months). In addition, the 24-month cumulative pregnancy rate was statistically significantly higher in the former group than in the latter group (66.7% vs. 23.5%, respectively).

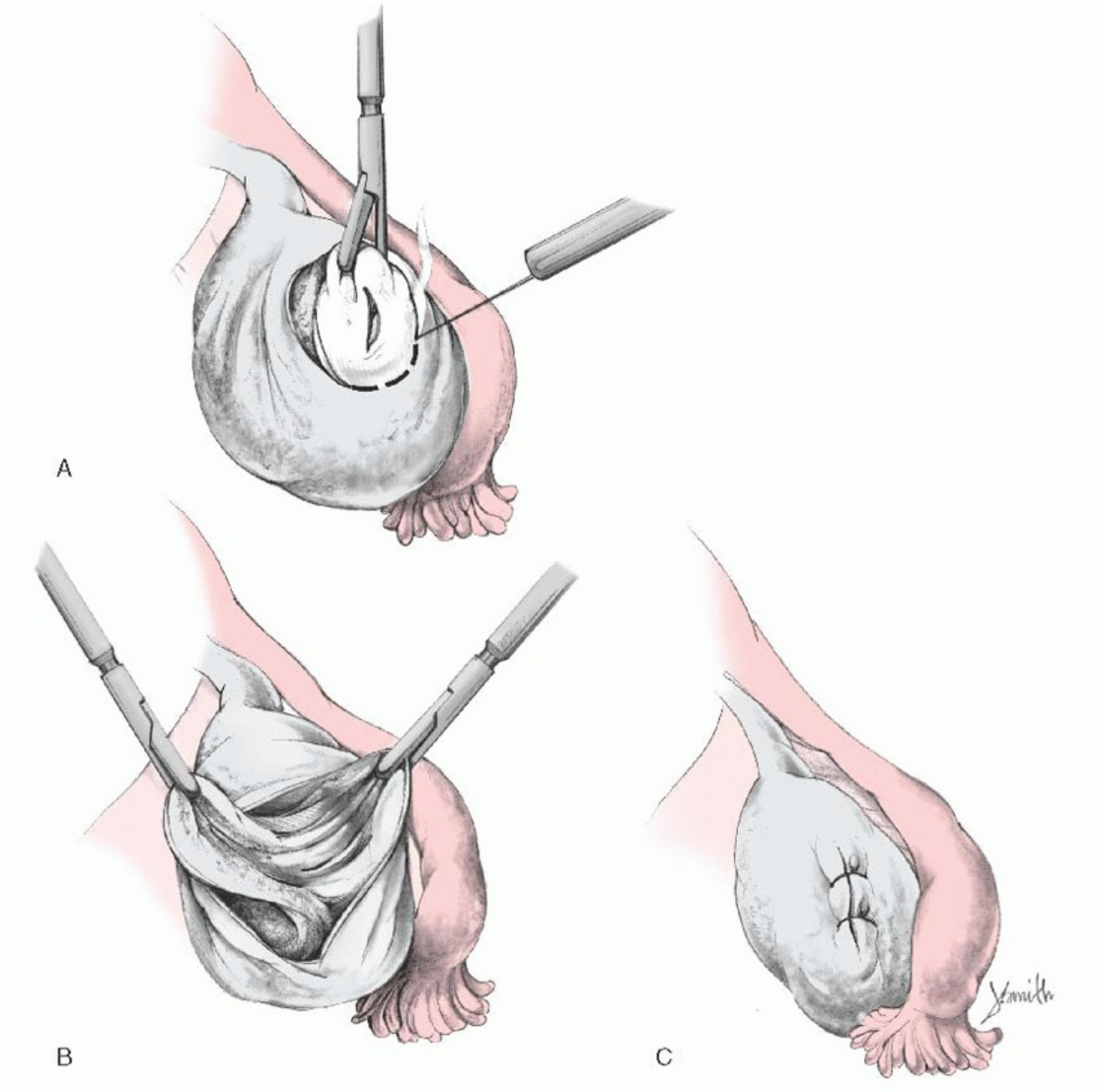

FIGURE 22.9 Laparoscopic ovarian cystectomy after fenestration of the cyst. **A:** The cut edges of the ovarian cortex and cyst wall are held and teased apart. **B:** The cyst wall can be stripped off by twisting it around the grasping forceps. Hydrodissection may be helpful. **C:** Large defects can be closed with laparoscopic suturing. Most incisions are left to heal by second intention.

In a 2004 prospective, randomized clinical trial by Alborzi and associates, the rate of recurrence of pelvic pain and dysmenorrhea over a 2-year postoperative period was significantly less for those who underwent cystectomy (15.8%) as compared with those undergoing fenestration and coagulation (56.7%). Moreover, the rate of reoperation was 5.8% in the former group and 22.9% in the latter group. The cumulative pregnancy rate was significantly higher in the cystectomy group (59.4%) than in fenestration/coagulation group (23.3%) at 1-year follow-up.

If there is evidence of functional destruction of the ovary or if the patient has chronic, incapacitating pelvic pain secondary to ovarian endometriosis and does not plan to become pregnant in the future, appropriate therapy may consist of oophorectomy. The infundibulopelvic and utero-ovarian ligaments can be ligated with an Endoloop ligature, bipolar coagulation, the harmonic scalpel, or surgical staples before excision of the structure. The ovary is retrieved by morcellation, minilaparotomy, or posterior colpotomy. This type of surgery must be performed carefully when adnexal adhesions are present to avoid ovarian remnant syndrome.

Intestines

Intestinal involvement has been estimated to occur in 3% to 15% of women with endometriosis and in up to 50% of patients with severe disease. The most common areas of intestinal involvement are the rectum and rectosigmoid colon, followed by the sigmoid colon, cecum, terminal ileum, proximal colon, and appendix. The incidence of appendiceal endometriosis has been estimated at approximately 0.8% of all appendectomies; 3% to 5% of patients with endometriosis have appendiceal

involvement.

Symptoms that should arouse suspicion of colorectal involvement include constipation alternating with diarrhea,

rectal pain, tenesmus, dyspareunia, and dysmenorrhea. Cyclic rectal bleeding is seen in as many as one third of women with rectosigmoid involvement, but the mucosa is rarely invaded. Small intestine disease accounts for up to 16% of gastrointestinal endometriosis and most often involves the terminal ileum. The most common symptom associated with disease in this location is midabdominal cramping pain. Ten percent of small bowel involvement presents with obstruction requiring surgery. The more common large bowel disease results in clinical obstruction in only 1% of cases.

The differential diagnosis of intestinal endometriosis includes primary carcinoma, metastatic carcinoma, diverticulitis, inflammatory bowel disease, irritable bowel syndrome, pelvic inflammatory disease, radiation colitis, and ischemic stricture. Endometrial adenocarcinomas have been reported in the colon and rectum but are exceedingly rare in comparison with the relatively large numbers of patients with colorectal endometriosis.

Preoperative or intraoperative rigid sigmoidoscopy may be helpful in ruling out primary colorectal malignancy. An intact mucosa effectively rules out primary colorectal malignancy. The greatest chance of diagnosing colorectal endometriosis occurs when the examination is performed at the time of menstruation. Although endometriosis rarely invades the intestinal mucosa, mucosal distortion is possible secondary to infiltration of the submucosa.

Pelvic and rectal pain is the major symptom that leads to colorectal resection in patients with advanced endometriosis. Bowel resection should be undertaken in the symptomatic patient or when there is a suspicion of malignancy; however, the frequency of such indications is small. In a series authored by Prystowsky and colleagues of 1,573 consecutive patients with endometriosis, only 11 women (0.7%) required bowel resection. Bowel resection is usually undertaken for lesions producing partial obstruction because most of these lesions are fibrotic and unresponsive to hormonal manipulation. This would include those with bowel occlusion of greater than 50% of the circumference, lesions of greater than 2 to 3 cm in size, or when muscularis involvement of disease is greater than 7 to 8 cm. Recommended approaches for less extensive lesions include CO_2 laser vaporization of superficial serosal disease of the rectum or large intestine, excision without entering the mucosa, and oophorectomy or hormonal suppression. A harmonic scalpel may be used laparoscopically to shave an endometriotic nodule in the prerectal fascia. As demonstrated by Koninckx et al., most recurrences occur at the posterior fornix of the vagina, and complete excision is important in this area, particularly since the vaginal cuff heals well following resection of deep endometriosis in this area. The use of electrocautery or fiber lasers should be avoided because of their greater risk of causing transmural thermal damage.

A full mechanical and antibiotic bowel preparation is carried out preoperatively. A technically difficult and prolonged surgery is expected when the nodule is greater than 3 cm in diameter, firmly attached to the ischial spine, and localized in the sigmoid or when adhesions are present because of previous incomplete surgery or past in vitro fertilization (IVF) procedures that resulted in perforation of the nodule with the aspiration needle. When the nodule of deep endometriosis is attached to the ischial spine or ischiosacral ligament, dissection should be performed carefully because of the risk of extensive bleeding that may be difficult to control.

Lesions less than 2 cm in size or less than one third of the rectal circumference can be excised in a full-thickness manner either transabdominally or laparoscopically. In cases of large lesions that encroach on the mucosa, full-thickness excision of involved bowel can be undertaken either by disk excision of small, isolated lesions or by segmental resection for larger lesions, particularly those invading the bowel lumen. During the dissection of the nodule from the bowel, a layer of fibrosis may be left in situ to avoid entering the mucosa. The anastomosis can be hand sewn with a continuous single layer of absorbable monofilament suture or created with surgical staples; however, patients with cul-de-sac disease must be in the lithotomy position to allow transanal placement of the stapler. A circular end-to-end stapler has limitations to the amount of rectal wall that can be resected. The risks of rectovaginal fistula may be reduced by the interposition of a pedicled omentoplasty between the two suture lines and performance of a defunctioning stoma and pelvic drainage.

Excision of a sigmoid nodule is difficult without sigmoid resection, since the nodule is often localized mesenterically, thus impairing blood flow after excision, and the mobility of the sigmoid makes discoid resection and suture repair technically challenging. These procedures have been performed by or with the assistance of general surgeons.

A one-time dose of antibiotic is administered intraoperatively if the vagina is entered; a course of 4 to 7 days is recommended for muscularis defect with single-layer suturing or full-thickness resection and double-layer suture repair, respectively.

The short-term complications associated with bowel resection for endometriosis include leak at the anastomosis site, pelvic abscess and fistula, and bowel and bladder dysfunction. The lower the anastomosis, the higher the probability of postoperative leakage and rectovaginal fistula formation. Bowel perforation is usually identified within the week after surgery and may be treated with suturing and lavage if laparoscopy is performed within 24 hours after perforation. Later diagnoses associated with peritonitis necessitate colostomy. For those who have undergone low rectal resections, 15% or more experience leaks. Urinary retention usually resolves within a few weeks. Local excision with transmural discoid excision is associated with a lower risk of short- and long-term complications than rectal resection and has acceptable clinical outcomes for most patients.

Appendectomy should be considered when there is physical evidence of peritonitis, when implants are large and active, when associated adhesive disease to adjacent bowel may result in partial or complete angulation and obstruction, or when the benign nature of the lesion is in doubt. Spontaneous perforation of the appendix that is due to endometriotic involvement is very rare. The technique of incidental endoscopic appendectomy is similar to that performed through laparotomy, although the stump need not be buried in the cecum. The tip of the appendix is grasped and elevated. The appendiceal vessels are bipolar cauterized or occluded with surgical clips near the base of the appendix before being excised. Two loop ligatures are placed immediately next to each other at the base, and a third Endoloop is then secured approximately 5 mm distal to the first two. The appendix may then be transected between the second and third ligature and placed in a surgical pouch for safe retrieval from the abdominal cavity. Judicious application of bipolar cautery at the stump sterilizes the raw surface of the pedicle without causing damage to the adjacent cecum.

Coronado and colleagues reported a complete relief of pelvic symptoms in 49% and an improvement in 39% of patients who underwent full-thickness resection of the colon; 39% of patients in the series achieved a term pregnancy. In a later series by the same colorectal surgeons of 130 patients who underwent aggressive, conservative surgical management for advanced disease, the operative procedures performed included low anterior resection with anastomosis to the extraperitoneal

rectum (*n* = 109), sigmoid resection (*n* = 10), disk excision of the rectum (*n* = 7), ileocecal resection (*n* = 2), and small bowel resection (*n* = 2). Twenty-four of forty nine patients (49%) who attempted to conceive delivered a viable child.

Ferrero and colleagues compared open-bowel resection to laparoscopic resection in women with rectosigmoid endometriosis. They showed improved pregnancy rates when the procedure was performed laparoscopically. However, Vercellini et al., in a nonrandomized study in 2006, showed no higher rate of conception following resection of deeply infiltrating rectovaginal endometriosis via laparotomy over that achieved with expectant management among 105 women who were followed over a 2-year period. The cumulative 24-month probability of becoming pregnant was 44.9% in the surgery arm and 46.9% in the expectant management arm.

The sequelae of intestinal endometriosis may not appear until the patient is postmenopausal. Although the endometriosis can become inactive, the resulting cicatrization can lead to a decrease in the bowel lumen and to symptoms of obstruction.

Urinary Tract

Endometriosis involving the urinary tract is relatively rare. The spectrum of disease severity varies from incidental findings at laparoscopy, laparotomy, or cystoscopy to more significantly associated hematuria, flank pain, hypertension, and ureteral obstruction. Bladder and ureteral involvement represent 85% and 15% of cases, respectively. Cystoscopy and intravenous pyelography are helpful studies in documenting the extent of disease. Magnetic resonance imaging may further delineate the extent of involvement. Vesical endometriosis can be treated by hormonal suppressive therapy or partial cystectomy. These nodular lesions develop within the muscularis and are typically seen with partial or complete obliteration of the anterior cul-de-sac. Fedele et al. deomonstated conservative surgical treatment of bladder endometriosis is effective in ensuring long-term relief in most cases of endometriosis affecting the vesical dome, whereas success rates for deeper lesions involving the vesical base and the vesicouterine septum are lower, depending on the degree of surgical radicalness. The bladder wall is sutured in two layers, and a bladder catheter is left in place for 7 to 10 days postoperatively.

Extrinsic ureteral compression by endometriosis presents four times more frequently than intrinsic involvement and is most likely to occur in the distal third near the region of the ovarian fossa. The left ureter is more commonly affected. Patients with paracervical and extensive uterosacral ligament disease are also at risk. In patients with deep endometriosis, hydronephrosis should be excluded before surgery because it requires preoperative placement of a ureteral stent. The preferred treatment for ureteral obstruction is ureterolysis or resection of the involved segment followed by ureteroneocystostomy or

ureteroureterostomy. When hydronephrosis is present, the stricture can be removed over the stent with resection of a defined lesion in greater than 80% of patients.

Involvement of peritoneum overlying the ureter is amenable to resection by laparotomy or laparoscopy. An incision is made in normal peritoneum adjacent to the involved area. The inferior margin of the incision is grasped and deviated medially, and the ureter is separated from the peritoneum bluntly or by hydrodissection. The peritoneal lesion can be excised or vaporized. Periureteral vessels must remain intact to prevent ischemia and resultant fistula formation. If the peritoneum is adhered and the lesion cannot be dissected, the ureter is likely involved in the disease process. Ureteroneocystostomy should be considered.

Incisional Scars

Surgical scars are occasionally the sites of endometriotic implantation. Perineal, vaginal, and vulvar scars, particularly episiotomies, colporrhaphies, and Bartholin gland excisions, are likely areas for involvement by endometriosis. There is often a history of delayed wound healing of the incisional scar infiltrated with endometriosis. These implants typically appear as either deep-lying or subcutaneous nodules infiltrating the fascia and muscle. Bleeding into the tissues at the time of menstruation can cause cyclic local pain, tenderness, and discoloration; however, the nodule may lie too deep for detection of any color change through the skin. If the nodule is superficial, cyclic bleeding or ulceration may be apparent.

In most instances, incisional endometriomas have followed surgical procedures that violated the uterine cavity and allowed the endometrium to be transplanted. Wespi and Kletzhändler suggested that the frequency might approach 5% among patients having cesarean section or hysterectomy. Metroplasty and myomectomy also increase the risk of incisional endometriosis. Indeed, endometriosis has been reported along the needle tracts after amniocentesis or saline injection for abortion. Careful flushing and irrigation of the abdomen and of the incision during closure should minimize the chance of contamination when incision into the uterine cavity is required.

Episiotomy scars and cervical and vaginal lacerations also serve as implantation sites after delivery. The chance is significantly increased when postpartum curettage is performed. Paull and Tedeschi reported 15 instances in 2,208 deliveries when curettage was carried out and no instances in 13,800 deliveries without curettage.

Management, usually best accomplished by local excision, is both diagnostic and curative. Various hormonal regimens may be appropriate if it is imperative to avoid surgery. However, malignancy can occur in each area of ectopic endometriosis, and histologic confirmation of the tentative diagnosis is recommended.

Thorax

Thoracic endometriosis is an uncommon disease with varying clinical presentations. The diagnosis is almost always established on clinical grounds. In a report of 65 cases of thoracic endometriosis by Foster et al., pleural and lung parenchymal disease presented with different clinical features. Ninety-three percent of women with pleural disease developed pain with right-sided pneumothorax or pleural effusion. Because numerous right diaphragmatic defects were noted in patients with pleural involvement, pleural implants are believed to be secondary to tubal regurgitation and transport of endometrial tissue through the diaphragmatic defects. Other symptoms may include upper quadrant abdominal pain or referred pain to the shoulder. Disease involving the lung parenchyma produced hemoptysis rather than the pleuritic symptoms. Previous pelvic surgery was more common among women who had parenchymal endometriosis; however, pelvic endometriosis was found more often in those with pleural disease.

Catamenial pneumothorax or hemoptysis should alert the physician to the possibility of thoracic endometriosis. The chest roentgenogram is usually of little value in diagnosing this disease; however, cytology, aspiration biopsy, and pleuroscopy may be useful. Chest CT scan may reveal pulmonary or pleural nodules, particularly if performed during menses. Massive effusion and bleeding can occur, but this presentation is more commonly associated with a malignancy. GnRH agonist or surgical treatment may be effective in the symptomatic patient. Chemical pleurodesis or surgical pleural abrasion may be superior to hormonal treatment in the long-term management of pneumothorax.

Sciatic Nerve

Endometriosis may compress the sciatic nerve within the pelvis, at the sciatic notch, in the gluteal region distal to the notch, or within the sheath of the sciatic nerve. The

lesion may be identified with magnetic resonance neurography. Patients present with pain in the hip and the buttock radiating

down the back of the leg to the foot. The discomfort begins a few days before menstruation and becomes progressively more severe before subsiding 2 or 3 days to 2 weeks after cessation of menstruation. Over time, the sciatica may be constantly present, with excruciating exacerbation during menses. Neuropathic injury and muscle denervation may lead to progressive weakness of the leg. Two thirds of patients with sciatic nerve endometriosis have right-sided lesions. CT-guided biopsy is possible to confirm the diagnosis. Surgical exploration of the sciatic nerve is not necessary in most cases. Patients may experience remission of symptoms with GnRH agonist administration or during pregnancy.

Adjunctive Procedures of Conservative Surgery

Uterine Suspension

Uterine suspension techniques have been devised to reduce adhesion formation at denuded peritoneal surfaces of the posterior cul-de-sac, uterine serosa, and broad ligament. Elevation of the adnexa may prevent adhesion reformation of the ovary or fallopian tube at a site where existing adhesions have been excised. This procedure may be particularly useful in the case of a posterior or retroflexed uterus. It is indicated in selected cases of dyspareunia after resection of posterior cul-de-sac endometriosis. There is no evidence to suggest that uterine suspension is detrimental to subsequent pregnancies, although it is of unproven efficacy in enhancing fertility or as an adjunct in the treatment of endometriosis-associated pelvic pain. The modified Gilliam procedure offers certain advantages over other uterine suspensions because of its maintenance of normal anatomic relations. Shortening the round ligament through the internal inguinal ring eliminates the opening that is made lateral to the point of the ligament's attachment to the abdominal wall in the Olshausen suspension procedure.

When a modified Gilliam suspension is performed via laparotomy, the uterus is elevated, and a 2-0 absorbable suture is placed around each round ligament approximately 3 to 4 cm from its insertion into the uterus (**Fig. 22.10**). The edge of the rectus fascia is grasped by a Kocher clamp at the level of the anterosuperior spine of the ileum. The adjacent peritoneal edge is grasped with a Kelly clamp. The rectus fascia is separated from the underlying musculature with blunt dissection. A long Kelly clamp is inserted between the fascia and muscle to the level of the inguinal ring while displacing the peritoneum superiorly. This clamp is inserted through the ring and along the round ligament by gently opening and closing the instrument. The insertion is facilitated by placing traction on the suture to stabilize the round ligament. The peritoneum overlying the ligament is then incised at a point adjacent to the suture, and the suture is grasped by the Kelly clamp. By withdrawing the clamp, the round ligament is brought through the internal ring and outside of the peritoneal cavity; it can then be sutured to the rectus sheath with 2-0 interrupted delayed absorbable sutures. These sutures must be placed through the round ligament without encircling the ligament and thus occluding its blood supply. This procedure is repeated on the opposite side.

At the end of the suspension, the surgeon's hands should be introduced into the abdomen to ascertain whether there is a loop of round ligament lateral to the point where the ligament has been withdrawn from the peritoneal cavity. If so, this should be corrected to prevent strangulation of the involved segment lying between the ligament and abdominal wall. In addition, the fallopian tube should be inspected to ensure that its course has not been disturbed. This can occur if the traction suture has been placed through a segment of round ligament too close to the uterus.

Laparoscopic suspension is possible after placement of a trocar and sheath approximately 5 cm lateral to the midline and 3 cm above the inguinal ligament. The anterior rectus fascia in this site is tagged with suture. The round ligament is grasped at the usual site with laparoscopic forceps to elevate the ligament to the tagged anterior fascia, where it is sutured in place with nonabsorbable suture. The desired positioning of the uterus is confirmed laparoscopically.

Presacral Neurectomy

Presacral neurectomy, or division of the superior hypogastric plexus, is useful as an adjunctive procedure to eliminate the uterine component of dysmenorrhea that results from endometriosis. Sixty to eighty-five percent of patients with secondary dysmenorrhea experience complete relief of symptoms. There is no evidence that presacral neurectomy enhances fertility.

A significantly greater relief of midline pelvic pain is achieved when endometriosis resection is combined with presacral neurectomy as compared with conservative resection alone. In a series by Tjaden and colleagues, all 17 patients undergoing presacral neurectomy noted a complete resolution of midline pelvic pain, and only two of these had a recurrence of pain within the 42-month follow-up period. Endometriosis rarely provokes exclusively midline pelvic pain, however, and lateralizing adnexal pain and deep dyspareunia are not affected by this procedure. Careful patient selection is necessary if the desired outcome is to be achieved.

The hypogastric plexus consists of fine strands of nerves embedded in a delicate areolar tissue. The plexus is formed as a

continuation of the aortic and inferior mesenteric plexuses and passes over the bifurcation of the aorta. It then continues below the promontory of the sacrum before dividing into the right and left inferior hypogastric nerves. The presacral neurectomy procedure can be performed through a transverse Maylard incision or longitudinal incision that adequately exposes the region of the bifurcation of the aorta (**Fig. 22.11**). At the time of laparotomy, the descending colon is packed superiorly and to the left to expose the left margin of the hypogastric plexus. The posterior peritoneum overlying the sacrum is elevated and incised with the scalpel. The incision is extended caudally with scissors for approximately 5 cm to the third or fourth sacral vertebra and cranially to just below the bifurcation of the aorta. The margin of the posterior peritoneum can be drawn upward and outward by a stay suture or an Allis clamp. A Kittner sponge is then used to dissect the areolar tissue and associated nerve fibers off the posterior aspect of the peritoneal flap. The right ureter is readily visible and can be retracted laterally, and the areolar tissue is dissected from it without disturbing its blood supply. The common iliac artery, which lies just below the ureter, is freed superiorly from the adjacent tissue. A right angle clamp or probe can be introduced medially next to the promontory to elevate the sheath and allow blunt dissection underneath it. Care must be taken to avoid the middle sacral vessels that may be left intact on the surface of the promontory. Injury to the middle sacral vein can result in significant blood loss. Hemorrhage is controlled with cautery, suture ligation, hot packs, hypogastric vessel ligation, use of an absorbable gelatin sponge (Gelfoam) or microfibrillar collagen (Avitene), or packing with bone wax.

The areolar tissue is taken off the left flap of peritoneum until the superior hemorrhoidal vessels are exposed. These vessels should remain on the peritoneum but are bluntly freed from the overlying tissue. By elevating the sheath, several vessels that feed into the left common iliac vein can be identified. These branches are isolated, clamped, and tied as they are visualized. When the plexus has been isolated, a Babcock clamp

can be used to elevate the sheath. Two 2-0 absorbable or silk sutures are placed around the proximal and distal aspects of a 5-cm segment of the plexus and are loosely tied. The tonsil clamp is applied to each end of the nerve bundle. As the clamps are removed, the sutures are slipped down over the crushed areas and tied securely. The intervening portion of the plexus is then excised. The peritoneum may then be approximated with absorbable suture.

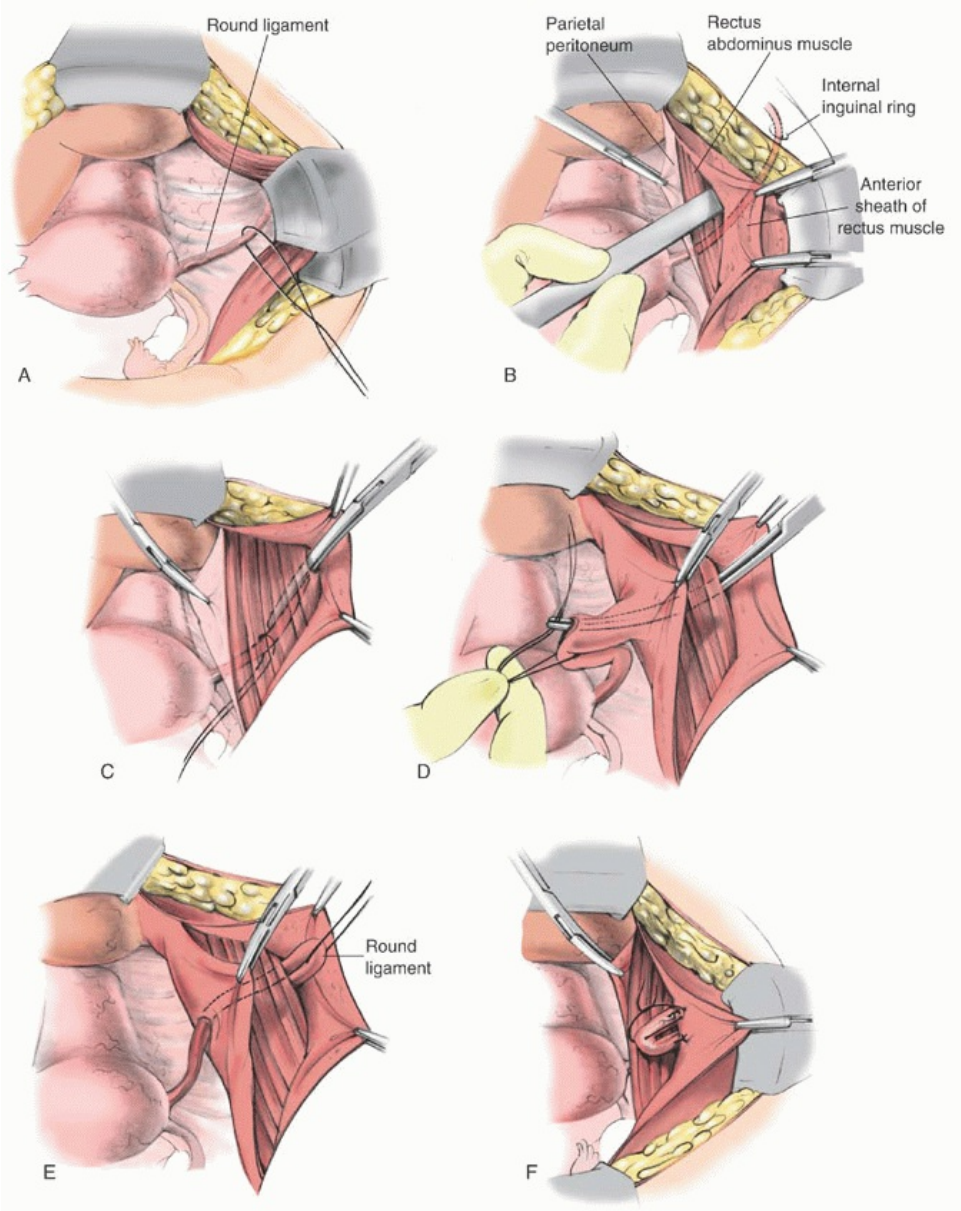

FIGURE 22.10 Modified Gilliam suspension. **A:** A chromic suture is placed around the round ligament approximately 3 to 4 cm from the uterine cornu. **B:** The rectus fascia is grasped with Kocher clamps and separated from the belly of the rectus muscle bluntly with the index finger or knife handle. **C:** The parietal peritoneum is grasped with Kelly forceps. A long Kelly forceps is introduced through the internal inguinal ring as it passes over the belly of the rectus. **D:** The Kelly clamp is brought through the internal inguinal ring and along the round ligament to a point adjacent to the chromic stay suture. A knife is used to open the peritoneum. The ends of the chromic suture are grasped by the Kelly clamp. **E:** As traction is applied to the suture, a knuckle of the round ligament passes through the internal ring. **F:** Three sutures of 2-0 delayed absorbable or silk suture are placed, fixing the ligament to the rectus fascia in a manner that will not interrupt the blood supply.

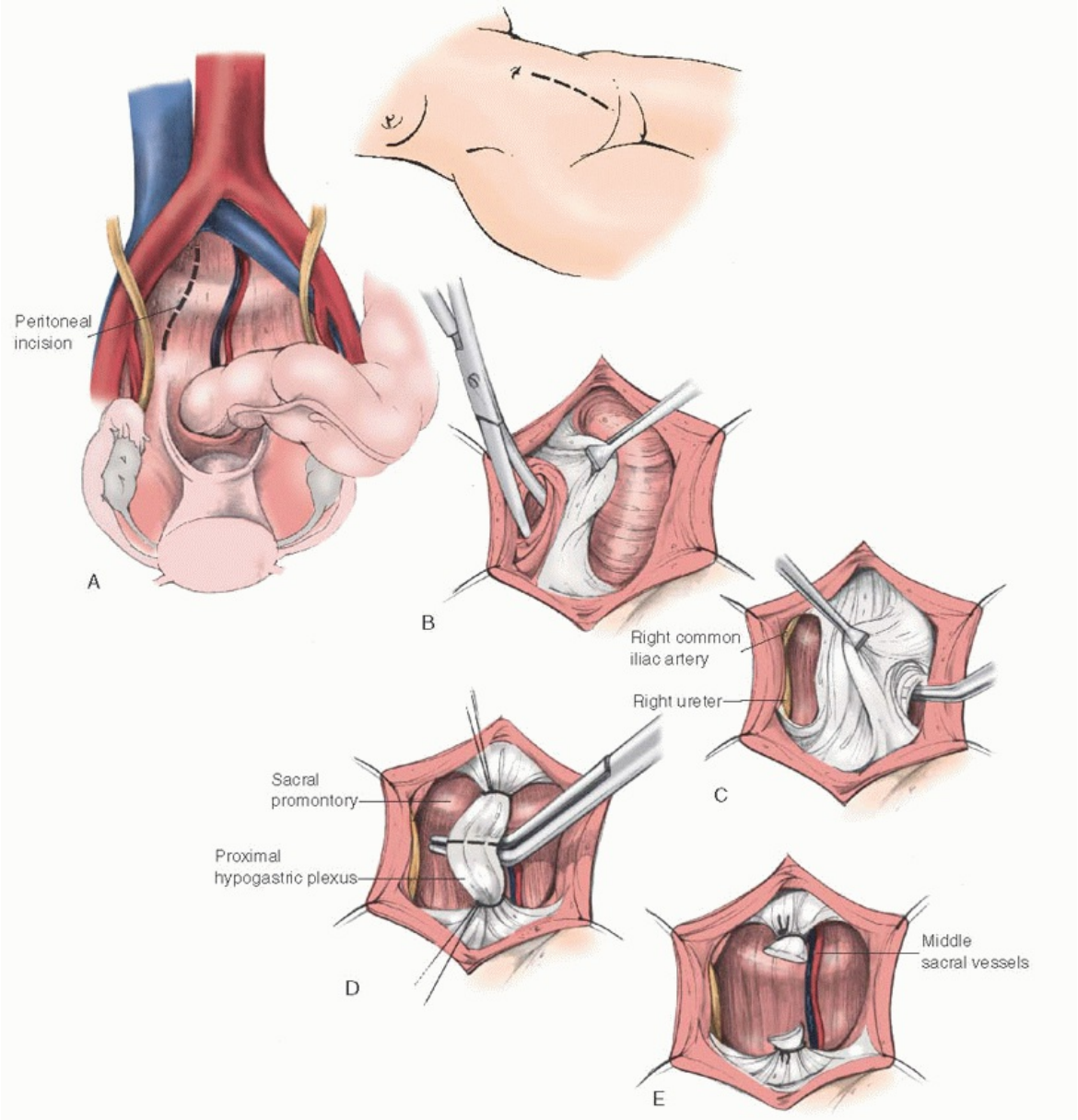

FIGURE 22.11 Presacral neurectomy. **A:** Location of incision in relation to anatomic landmarks. A Maylard incision can also be used in some cases. The descending colon is displaced superiorly and to the left for good exposure of the left margin of the hypogastric plexus. **B:** A Kittner sponge is used to dissect the areolar tissue medially and off the posterior aspect of the peritoneal flap. The right ureter can be identified easily. **C:** The areolar nerve-bearing tissue is dissected from the peritoneum on the left side, exposing the left internal iliac vessels and superior hemorrhoidal vessels. **D:** The plexus is isolated and elevated off the sacral promontory. A segment of plexus approximately 5 cm in length is isolated with 2-0 silk sutures. **E:** The plexus is excised. Note the relation between pedicles of the nerve bundle and adjacent structures.

In less than 10% of cases, the pelvic mesocolon is inserted in front of the interiliac trigone and the nerve bundle cannot be reached by simple incision of the peritoneum. In these cases, the chief branches of the inferior mesenteric artery must be moved

to the left to expose the triangular space between the two common iliac arteries. Unless there is adequate exposure and meticulous dissection, incomplete resection of the superior hypogastric plexus can occur, resulting in suboptimal denervation.

A laparoscopic approach to presacral neurectomy has also been described. This technique involves insertion of a 10-mm trocar sheath 3 cm above the symphysis pubis and placement of two accessory ports in each iliac fossa. Steep Trendelenburg position with a left lateral tilt is required to allow displacement of the intestines cephalad to expose the bifurcation of the aorta and sacral promontory. After retraction of the sigmoid colon and vasopressin infiltration of the sacral promontory area, the parietal peritoneum is grasped and elevated, and a transverse incision is performed from the major vessels or ureter on the right to the mesentery of the sigmoid on the left. The presacral nerve is isolated by developing the avascular space between the nerve and right internal iliac artery down to the periosteum via blunt dissection. Segments of the superior hypogastric

plexus are removed by sharp dissection after thorough diathermy. The entire length of removed nerve plexus should not exceed 3 to 4 cm. Venous bleeding is controlled with bipolar cautery. Meticulous hemostasis must be ensured at the completion of the operation. This technique should only be performed by experienced laparoscopic surgeons because the vascular complications can be serious. In a review of 655 laparoscopic presacral neurectomy procedures, Chen and Soong reported a 0.6% rate of major complications, including one case of injury of the right internal iliac artery and three cases of chylous ascites.

Polan and DeCherney reported that the combination of presacral neurectomy and conservative surgery in women with chronic pelvic pain, endometriosis, and pelvic inflammatory disease increased total postoperative pain relief from 26% to 75%, although only a small number of patients were included in this laparotomy series. Lee and coworkers performed presacral neurectomy via laparotomy in 50 women with chronic pelvic pain. Dysmenorrhea resolved in 73% of the cases, dyspareunia lessened in 77%, and acyclic pain improved in 63%. The uterosacral ligaments were resected in half of the subjects in this study, but this did not seem to affect the overall rate of pain relief. In a randomized clinical trial of women with moderate-to-severe endometriosis and pelvic pain undergoing conservative surgical therapy, Candiani and colleagues reported a recurrence of midline menstrual pain in 23% of women who underwent presacral neurectomy versus a 42% recurrence in those who did not. This difference reached the limit of statistical significance ($P = 0.06$).

In an uncontrolled laparoscopic study by Nezhat and associates of 100 women subjected to vaporization of endometriosis and presacral neurectomy, the symptoms of pelvic pain, dysmenorrhea, and dyspareunia were reduced by more than 50% in 74, 61, and 55 patients, respectively, over the 1-year follow-up period. The stage of endometriosis did not correlate with the degree of pain improvement achieved. More recently, in a prospective, randomized, double-blind, controlled trial, Zullo and colleagues reported that the performance of laparoscopic presacral neurectomy improved the cure rate in women treated with conservative laparoscopic surgery for severe dysmenorrhea caused by endometriosis as compared with those who underwent mere ablation of endometriosis (85.7% vs. 57.1% at 12 months, $P < 0.05$). A significant improvement in the quality of life was observed after surgery in both groups.

Two common side effects of the presacral neurectomy procedure have been observed. Constipation may require laxatives or stool softeners for a period of 3 to 4 months. The vaginal dryness that develops in as many as 10% to 15% of patients is transient and usually resolves within 6 months. Difficulty with micturition is an infrequent complication that rarely lasts for more than 1 or 2 months. A painless first stage of labor has been reported in women who have undergone presacral neurectomy.

Uterine Nerve Ablation

The technique of uterosacral neurectomy was initially described by Ruggi in 1899. Later popularized by Doyle, it has since been adapted for performance during laparoscopic procedures for the alleviation of dysmenorrhea. Sympathetic fibers T10 to L1 are contained within the inferior hypogastric plexus and course along the inferior vena cava and sacrum to enter the uterus through the nerves of the uterosacral ligaments and accompanying uterine arteries. The parasympathetic components of the paracervical nerves originate from S1 through S3 or S4, travel within the nervi erigentes, and emerge in the lateral pelvis to form the Frankenhäuser ganglia lateral to the cervix. Division of the uterosacral ligaments at a point approximately 1.5 cm distal to the cervix should interrupt many sensory nerve fibers of the cervix and uterine corpus.

Lichten and Bombard published a small randomized, prospective, double-blind study of laparoscopic uterosacral nerve ablation for the treatment of severe or incapacitating dysmenorrhea unresponsive to oral contraceptives and nonsteroidal anti-inflammatory agents. None of the control patients noted improvement, whereas 9 of 11 in the treated group had almost complete relief at 3 months, and 5 of 11 described complete relief from dysmenorrhea 1 year after surgery. Patients with endometriosis were not included in this small series.

Surgical resection of pelvic endometrial implants may be all that is necessary to alleviate discomfort in most endometriosis patients. In a double-blind, randomized controlled laparoscopic trial, Johnson and colleagues found that uterine nerve ablation was effective in reducing dysmenorrhea in the absence of endometriosis, but the addition of this procedure to the surgical treatment of endometriosis was not associated with a significant difference in any pain outcomes. Similarly, Vercellini and colleagues could not demonstrate the efficacy of this procedure.

Uterine nerve ablation by laparotomy fell from favor before it was revived as an endoscopic technique. The potential neurologic, intestinal, orthopedic, and psychological components of pain should be considered before subjecting the patient to a procedure that, although now performed endoscopically, carries some surgical risk and whose effectiveness has been questioned because of the small number of cases evaluated. Complications associated with transection of the uterosacral

ligaments include ureteral damage, bowel damage, and postoperative hemorrhage, which, if undetected, may result in death. Uterine prolapse has been described as a potential longterm side effect of the procedure.

Second-Look Laparoscopy

Second-look laparoscopy has been suggested as an appropriate procedure for additional lysis of pelvic adhesions in patients who have undergone a laparotomy or a laparoscopy for the resection of endometriosis. If scheduled 8 days to 6 weeks after the initial dissection, second-look laparoscopy allows separation of de novo adhesions that are still relatively filmy in consistency. In addition, laparoscopy after pelvic reconstructive surgery provides an opportunity to assess future prognosis for fertility.

Early second-look laparoscopy after endoscopic treatment of endometriomas has revealed a recurrence rate of endometriomas of 15% to 20%. Equally significant are the nearly 20% incidence of de novo adhesion formation and the 40% to

82% recurrence rate of dense adhesions. Second-look laparoscopy allows treatment of these findings; however, there is little direct evidence that this secondary surgical procedure will increase the cumulative pregnancy rate.

Some surgeons have proposed a three-step protocol to both surgically and medically treat large endometriomas more than 5 to 6 cm in size. During the initial diagnostic laparoscopy, the endometrioma is opened, drained, and biopsied. The patient is then treated with GnRH agonists for 12 weeks, and the second-look laparoscopy is performed. The endometrioma is opened, and the interior wall of the cyst is laser vaporized. The epithelial lining of the cyst is atrophic and thinned, and the use of the CO_2 laser results in minimal thermal damage to the normal ovarian tissue. This three-step approach may result in less compromise to ovarian follicular reserve than stripping of the cyst wall.

Surgical Outcomes

No classification schedule for endometriosis provides an accurate correlation between extent of disease and pregnancy rate. Nevertheless, point categorization through the revised ASRM classification does provide a framework in which to report outcomes of therapy.

Fertility

In a review of the surgical outcome expected through laparoscopic therapy for minimal and mild endometriosis, Cook and Rock found the crude pregnancy rate following cautery or laser ablation of implants was 54% to 58%. Life table analysis showed similar conception rates following laparoscopy and laparotomy to excise minimal or mild stages of endometriosis. Hence, the performance of a laparotomy is not warranted for lesser stages of disease.

Treatment of mild endometriosis via laparoscopic excision or electrocoagulation resulted in similar reproductive outcomes in a retrospective study by Tulandi and Al-Took. The total pregnancy rate was 53.5% in the excision group and 57.1% in the electrosurgery group. The mean interval between surgery and conception was 10.7 months in the electrosurgery group and 13.3 months in the excision group. Excision of tissue may result in more complete removal of infiltrating endometriosis, which should be of particular benefit to patients with deep nodules.

The stage of disease as categorized by the modified ASRM classification of endometriosis did not predict subsequent reproductive performance in a 2006 study by Vercellini and colleagues. Five hundred and thirty-seven infertile women with endometriosis undergoing first-line conservative laparoscopic surgery were followed for a mean of 32 months postoperatively. The cumulative probability of pregnancy at 3 years following laparoscopy was 47% (51% at stage I, 45% at stage II, 46% at stage III, and 44% at stage IV; log-rank test, $[chi]^2 = 1.50$, $P = 0.68$).

Expectant management of mild-to-moderate endometriosis after diagnosis by laparoscopy yields a crude pregnancy rate of approximately 50%, which has brought into question whether surgical therapy of lesser stages of disease actually enhances fertility. In a retrospective study comparing the efficacy of electrosurgical treatment of endometriosis with the efficacy of expectant management in minimal and mild endometriosis-associated infertility, Tulandi and Mouchawar reported that the cumulative probability of conception was significantly higher among patients treated surgically. Moreover, meta-analysis of the two randomized prospective trials showed that laparoscopic electrosurgery or laser to resect or ablate stages I-II endometriosis implants and adhesions resulted in a significantly higher fecundity rate as compared with the control group undergoing diagnostic laparoscopy only. The largest trial, conducted by Marcoux et al. in 1997, clearly supported this outcome, with an

increased chance of pregnancy (OR 2.03, 95% CI 1.28 to 3.24) and ongoing pregnancy rate after 20 weeks (OR 1.95, 95% CI 1.18 to 3.22) (Fig. 22.12), but the smaller trial, by Parazzini in 1999, did not show benefit (pregnancy OR 0.76, 95% CI 0.31 to 1.88; live birth OR 0.85, 95% CI 0.32 to 2.28). When the ongoing pregnancy and live birth rates from these two studies were combined, Jacobson et al. found a statistically significant increase with surgery (OR 1.64, 95% CI 1.05 to 2.57). The findings suggest that for every 12 patients having stage I or II endometriosis diagnosed at laparoscopy, there will be one additional successful pregnancy if ablation or resection of visible endometriosis is performed, compared with no treatment. This number needed to treat applies only to those patients who are found to have endometriosis. Approximately 70% of patients with otherwise unexplained infertility and no signs or symptoms to suggest endometriosis would be found to not have endometriosis during diagnostic laparoscopy.

Operative treatment of moderate or severe disease does offer a greater likelihood of conception than expectant management, in part because of correction of mechanical factors such as adhesions. The overall crude pregnancy rate reported by various studies of conservative laparotomy for endometriosis that stratified reproductive results by disease severity was 38%, with a monthly fecundity rate averaging 1.4% to 1.5%. Laparoscopic treatment of severe endometriosis offered a mean crude pregnancy rate of 47.6% in a small compilation of series. Hence, expert laparoscopists have reported results that appear to be as good as those obtained through the open abdomen, although there are inadequate data for direct comparison of outcomes of the two surgical modalities, and the correct identification and classification of disease may vary between laparotomy and laparoscopy groups. A 2012 Cochrane review of two randomized control trials concluded that excision of ovarian endometriomas was superior to ablative therapy of endometriomas in improving the chance of spontaneous pregnancy, with an odds ratio of 5.21. Life table analysis demonstrated that pregnancy is most likely to occur during the first 36 months after surgery. Furthermore, the duration of

infertility and, perhaps, patient age may have a greater impact on cumulative pregnancy rates than the actual stage (revised ASRM stages I through IV) of the disease.

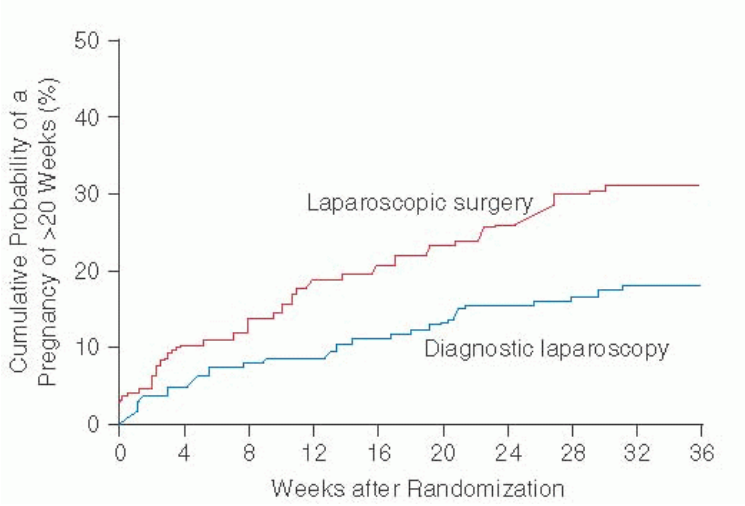

FIGURE 22.12 Cumulative probability of a pregnancy carried beyond 20 weeks in the 36 weeks after laparoscopy in women with endometriosis, according to study group (From Marcoux S, Maheux R, Béribé S. Laparoscopic surgery in infertile women with minimal or mild endometriosis. *N Engl J Med* 1997;337:217. Copyright © 1997, Massachusetts Medical Society).

Rectovaginal endometriosis is usually associated with pain symptoms, but the effect of disease in this location on fertility is uncertain. According to the results of 11 selected studies reviewed by Vercellini et al. in 2012, the mean postoperative conception rate in all women desiring pregnancy was 39% (223/571), irrespective of the preoperative fertility status and whether the patient pursued IVF after surgery. This rate dropped to 24% (123/510) in infertile patients who attempted to conceive spontaneously after surgery.

Pain

In a prospective, randomized, double-blind, controlled trial of laser laparoscopy in the treatment of pelvic pain associated with minimal-to-moderate endometriosis, Sutton and associates found that 62.5% of the laser-treated women reported symptom improvement at 6 months as compared with 22.6% of those treated expectantly. Symptom relief continued at 1 year in 90% of those who initially responded. Moreover, in a more recent randomized, blinded, crossover study by Abbott et al., 80% percent

of patients who underwent excisional surgery had symptomatic improvement as compared with 30% of the placebo group. A 2010 Cochrane analysis concluded that laparoscopic surgery for pelvic pain associated with endometriosis was superior to diagnostic laparoscopy alone, with an odds ratio of 7.72.

The technique of surgically treating lesser stages of endometriosis may not significantly influence pain relief, as long as the surgeon is aware of the depth of extension of the lesions. In a recent randomized study by Wright and colleagues, both excision and ablation of mild endometriosis produced good symptomatic relief and reduction of pelvic tenderness (67%).

Long-term improvement in quality of life can be achieved with laparoscopic excision of endometriosis. In a prospective, observational cohort study of 176 women with chronic pelvic pain with surgically diagnosed endometriosis, pain scores were highly significantly reduced at 2 to 5 years following resection in the categories of dysmenorrhea, dyspareunia, nonmenstrual pain, and dyschezia. The chance of requiring further surgery was 36%. Of note, almost one third who had further surgery had no evidence of endometriosis, either macroscopically or histologically, at the time of reoperation.

Aggressive and complete or near-complete excision of deep endometriosis is justified. Resection of deep endometriosis relieved dyspareunia in 40% and dysmenorrhea in 60% of cases. Nezhat and associates noted moderate-to-complete relief of pain in 162 of 175 women; however, some patients in this series had several surgical interventions. Preliminary analysis of the surgical results in 250 women in whom deep endometriosis had been excised with CO_2 laser showed a cure rate of pelvic pain in 70% and a recurrence rate of less than 5% over a 5-year follow-up period. Vercellini and colleagues reported that conservative surgery for rectovaginal endometriosis in infertile women did increase the pain-free survival time, although it did not modify the reproductive prognosis over expectant management. Recurrence of symptoms after surgery requiring reoperation may be dependent on surgeon experience and the use of postoperative suppressive therapy. It is progressive with time and is reported to by Falcone and Lebovic be approximately 15% at 1 year, 36% at 5 years, and 50% at 7 years. After bowel resection in patients with extensive endometriosis, pain symptoms have been improved by at least 70%, with recurrence in 0% to 34% in published trials. Women under 30 years of age at the time of initial operation are more likely to undergo a second surgical procedure to treat recurrent pain.

Endometriosis is often not identified in patients with chronic pelvic pain who undergo reoperation following their initial surgery for endometriosis. Persistence of dysmenorrhea and nonmenstrual pain after optimal endometriosis surgery may indicate adenomyosis. In a recent study by Parker and colleagues, chronic pelvic pain was significantly more likely to persist with uterine junctional zone thickness greater than 11 mm on preoperative MRI.

Recurrent Surgery

Rock and colleagues have shown that 13.5% of patients initially treated with conservative surgery required subsequent operative procedures. Wheeler and Malinak noted a cumulative recurrence rate at 3 and 5 years after conservative surgery of 13.5% and 40.3%, respectively. Neither the initial staging nor the ability to conceive after the initial surgery greatly affected the recurrence rates. Repeat conservative surgery for pelvic pain associated with recurrent endometriosis has similar efficacy and limitations as primary surgery, with long-term cumulative recurrence rates ranging from 20% to 40% as reported by Belanda et al.

Laparoscopic excision of ovarian endometriomas by the stripping technique is associated with a lower reoperation rate than that of fenestration. In a study of patients who underwent laparoscopic cystectomy of ovarian endometriomas of greater than 3 cm in diameter, Busacca and colleagues reported a cumulative rate of ultrasonographic recurrence of 11.7% over 48 months. Two studies that evaluated patients up to 49 and 60 months following surgery for endometriomas noted recurrent rates of up to 57%.

A second cytoreductive procedure may benefit some infertile women who have undergone surgery in the past if they do not pursue assisted reproductive technologies. A cumulative pregnancy rate of 32.4% at 35.4 months was achieved by Fedele and colleagues in 2006 after a second conservative laparoscopic stripping procedure for recurrent endometriomas. The recurrence of pain (17.4%) was similar to that experienced after the primary laparoscopic stripping procedure. However, if the initial surgery fails to restore fertility in patients with stage III or stage IV endometriosis, IVF may be more beneficial than reoperation for those who are otherwise asymptomatic. Pagidas and colleagues compared the outcome of a second operation for stage III or IV endometriosis-related infertility versus proceeding directly to IVF. The cumulative pregnancy rate 9 months after surgery was 24.4%, compared with a pregnancy rate of 33.4% after one trial of IVF and a cumulative pregnancy rate of 69.6% after two trials of IVF.

Combination Medical and Surgical Treatment

Preoperative and postoperative medical therapies have been proposed as treatment adjuncts to conservative resection of endometriosis to enhance fertility. Preoperative suppression of disease with hormonal agents may facilitate the surgical procedure by reducing tissue vascularity, and the greater ease in tissue dissection may decrease adhesion formation during the postoperative period. The preoperative hormonal agents also eliminate the corpus luteum that might otherwise be mistaken for an endometrioma. However, they may also reduce the size of endometriosis implants, making them less recognizable after short-term drug therapy. In a controlled clinical trial by Muzii et al., a 3-month course of GnRH agonist treatment before laparoscopy for endometrioma excision failed to result in a reduction in operative time or recurrence rate of disease during a 1-year follow-up period. There are no substantive data to justify hormonal treatments before surgery to improve the success of surgery.

Initiation of postoperative medical therapy may inhibit the activity of any residual disease, suppress ovulation, and decrease the possibility of adverse effects of peritoneal spillage of disease at the time of resection. However, postoperative medical therapy has a serious drawback; the patient is unable to attempt conception for several months. Andrews and Larsen have noted that the best chance for postsurgical conception occurs during the first 6 months after conservative surgery by laparotomy. Thus, suppressing ovulation during that critical period may be counterproductive. Treatment with a GnRH agonist after surgery does not improve fertility as compared with expectant management.

Contemporary management of women with endometriosisassociated pelvic pain involves both surgical and long-term medical therapy. When cytoreductive laparoscopy is followed by a 6-month course of GnRH analogue, there is a significant delay in the return of endometriosis symptoms requiring further treatment. In a randomized, prospective study, Hornstein and colleagues found that this interval was more than 24 months in those receiving nafarelin versus 11.7 months in the placebo group. A shorter duration of hormonal therapy during the postoperative period may be inadequate in reducing recurrence risk. A 3-month course of nafarelin following surgical therapy of stages III and IV endometriosis was ineffective in reducing pain scores as compared with placebo. Postoperative administration of low-dose, cyclic oral contraceptives for 6 months delayed the recurrence of pain symptoms and endometriomas at 12 months, but no significant differences were detected at 24 months or 36 months following laparoscopic excision. A 2012 systematic review and meta-analysis by Vercellini et al in 2012 indicated that a more prolonged course of postoperative oral contraceptive use (≥12 months) dramatically decreased the risk of endometrial cyst recurrence and pain symptoms. Because of these data, patients should be advised of the potential benefit of regular contraceptive use following surgery until such time as pregnancy is desired.

Hysterectomy

The number and rate of hysterectomies performed for endometriosis increased steadily from the 1960s to the 1980s, more so than for other diagnoses. The reported rate for 1982 to 1984 was more than double the rate for 1965 to 1967, although the exact reasons for the increase remain uncertain. Although statistically significant increases for hysterectomy rates were observed from 1994 through 1998, the increase was limited, and the curve remained nearly flat. Endometriosis was the primary indication for 20.8% of white women and 9.7% of black women undergoing hysterectomy in the United States from 1994 to 1999. Because of concern over the risk of recurrence even after definitive surgical therapy, bilateral oophorectomy was performed at the time of hysterectomy in 52% of women 44 years of age or younger and in 81% of women 45 years of age or older.

Definitive surgery offers prompt, complete, and long-term relief of pain from endometriosis more often than do the various available medical regimens. Most hysterectomies for endometriosis are performed by the abdominal route; in selected cases, laparoscopy may allow lysis of complicating adhesions or large implants, thus allowing safe vaginal hysterectomy. When the posterior cul-de-sac is obliterated and extensive fibrosis is present deep in the pelvis, subtotal hysterectomy may be indicated.

The recurrence of cyclic pain associated with endometriosis after hysterectomy with preservation of normal ovaries has been estimated at 3% to 7%. Nevertheless, in a study of 138 women who underwent hysterectomy with the diagnosis of endometriosis at the Johns Hopkins Hospital, ovarian conservation was associated with a 6.1 times greater risk of development of recurrent pain and an 8.1 times greater risk of reoperation as compared with oophorectomy at the time of hysterectomy. Recent data from a 7-year follow-up study by Shabika et al. showed that in women undergoing hysterectomy, the reoperation-free rates at 2, 5, and 7 years for those with ovarian preservation were 95%, 86%, and 77%, respectively, as compared with 96%, 91%, and 91% for those patients without ovarian preservation. Hysterectomy does not improve symptoms

in 25% of cases of chronic pelvic pain when the uterus is believed to be the source of the pain.

Minute, hormonally active ovarian fragments may be detected in women with symptomatic endometriosis, even after total abdominal hysterectomy and bilateral salpingooophorectomy. Laparoscopic resection of invasive peritoneal and intestinal disease that persists after castration may result in an improvement in pain symptoms. Ovarian remnant syndrome is the result of incomplete excision of cortical tissue at the time of extirpative surgery for endometriosis or pelvic inflammatory disease. Most ovarian remnants are retroperitoneal in location, and they are often densely adhered to pelvic sidewall structures, including the ureter, hypogastric vessels, and bladder base. Complete surgical removal may be difficult.

Estrogen replacement therapy after total hysterectomy and bilateral oophorectomy is associated with less than a 10% rate of recurrence of endometriosis. A cause-and-effect relation between estrogen replacement and malignancy in endometriosis has not been established, suggesting that progestational agents need not be prescribed together with estrogens after hysterectomy for a diagnosis of endometriosis. However, administering both progestin and estrogen may be theoretically beneficial if the disease was incompletely resected or deeply invasive, contained atypical epithelial changes, or is recurrent. A study by Matorras et al. showed an endometriosis recurrence rate of 3.5% in women treated with cyclic estrogen and progestogen replacement during a mean 46 months of follow-up as compared to 0% recurrence rate in untreated controls. Women who begin estrogen replacement therapy immediately after total abdominal hysterectomy and bilateral salpingo-oophorectomy are at no greater risk of recurrent pain than those who delay estrogen therapy for more than 6 weeks postoperatively.

Women with endometriosis were shown by Modugno and colleagues to be at increased risk of developing ovarian cancer (OR 1.32; 95% CI 1.06 to 1.65). An analysis by Melin et al. of data from the National Swedish Cancer Register showed that complete surgical removal of endometriosis lesions, even when the ovaries are unaffected, as well as removing the affected ovary in case of ovarian endometriosis, may significantly decrease the risk of ovarian cancer. In addition, hysterectomy and the use of oral contraceptives for greater than 10 years substantially reduce this risk.

ENDOMETRIOSIS AND ASSISTED REPRODUCTIVE TECHNOLOGIES

If spontaneous conception is not achieved within 3 years of surgical resection of endometriosis or within 1 year of repair of tubal obstruction associated with endometriosis, the odds are poor that it ever will occur. Techniques in assisted reproduction have been widely used during the past three decades. IVF removes gametes and zygotes from a potentially harmful environment and may bypass pelvic adhesions associated with endometriosis. Endometriosis is the sole identifiable cause of infertility in 25% to 35% of women undergoing IVF/embryo transfer.

The impact of endometriosis on the outcome of IVF has been controversial. Several studies have noted that the responses to gonadotropic stimulation, the numbers of preovulatory oocytes, the fertilization and cleavage rates, and the clinical pregnancy rates associated with stage I and stage II endometriosis have been equivalent to rates associated with tubal disease and unexplained infertility. Kuivasaari et al. reported that there was a significantly lower pregnancy rate and embryo implantation rate per fresh embryo transfer after pooled cycles (1 to 4) among women with stage III/IV endometriosis (22.6%) compared with stage I/II (40%) or tubal infertility (36.6%). However, when adjusted for confounding variables, Barnhart and colleagues in 2002 found that there was a significantly negative association between endometriosis of all stages and IVF outcome. This meta-analysis pooled data from 22 nonrandomized studies regarding IVF success rates in patients with endometriosis versus control patients without endometriosis and with tubal infertility. Most of these series included small numbers of subjects. The authors concluded that there was a 54% reduction in pregnancy rate after IVF in patients with endometriosis and that the success rate was even lower when the staging of endometriosis was higher. Subsequent studies have disputed these findings.

Poor IVF outcome in severe endometriosis may be related to oocyte or embryo factors rather than decreased uterine receptivity. Diaz and colleagues found that a history of severe endometriosis in recipients of donor oocytes had no effect on embryo implantation rates or clinical pregnancy rates as compared with recipients who did not have a history of endometriosis. Oocytes originating from women with endometriotic ovaries and donated to disease-free women led to reduced implantation rates.

In general, women with endometriosis have a lower ovarian response to gonadotropin stimulation. One reason for this response may be previous ovarian resection. Studies recruiting women with a history of surgical excision of a unilateral endometrioma and comparing subsequent ovarian responsiveness to gonadotropin stimulation in the affected and

contralateral intact gonad indicate that excision of endometriomas is associated with quantitative damage to ovarian follicular reserve. However, this lower oocyte yield following surgery has not necessarily led to decreased pregnancy rates.

Recent retrospective studies have suggested that routine laparoscopic cystectomy for endometriomas before commencing an IVF cycle does not improve IVF outcomes. Aside from a lower peak estradiol level on the day of hCG administration and a higher total gonadotropin dose administered to women previously operated on for an endometrioma, no significant differences were found between the resected endometrioma group and the intact endometrioma group among the different variables analyzed by Garcia-Velasco et al. Pre-IVF excision of ovarian endometriomas in symptomatic women did not impair nor enhance IVF or intracytoplasmic sperm injection success rates.

A 2005 retrospective study by Suzuki et al. indicated that women with a history of past or current endometriomas had fewer oocytes retrieved during IVF than tubal factor controls, but the fertilization rate, embryo quality, or pregnancy outcome was not affected. Conversely, Almog and colleagues found that the presence of an intact, unilateral ovarian endometrioma was not associated with a reduced number of oocytes retrieved from the affected ovary as compared to the opposite ovary or women without endometriomas.

Tinkanen and Kujansuu studied the effects of operative treatment of recurrent ovarian endometriosis on the pregnancy rate with IVF. They compared 45 patients with ultrasound-diagnosed ovarian endometriosis during IVF treatment, 36 of the cases being recurrences after previous operation, with 55 patients who had undergone past endometrioma resection and had no evidence of recurrence before IVF. Patients with endometriomas had significantly more embryos for transfer compared with women without endometriomas. The clinical pregnancy rate was 38% in the endometrioma group compared with 22% in the no-endometrioma group. The women who had surgery with no recurrent endometriosis may have had a more extensive resection as compared with those with recurrent endometriomas following initial surgery.

Hence, the hypothesis that surgical therapy of endometriosis increases IVF pregnancy rates is not clearly validated by the available evidence. Endometrioma resection may compromise or destroy adjacent normal ovarian tissue by removing part of the ovarian cortex and thus reducing ovarian reserve. On the other hand, larger endometriomas may interfere with follicular recruitment, may impose difficulties during oocyte retrieval, and may theoretically produce substances that are toxic to maturing oocytes and affect cell cleavage after fertilization. However, a systematic review by Benschop et al. concluded that surgical intervention for women with endometriomas 3 cm or larger has no benefit over expectant management on the outcome of assisted reproductive technology. The European Society of Human Reproduction and Embryology recommends laparoscopic ovarian cystectomy before IVF if the patient has an endometrioma ≥ 4 cm in diameter in order to confirm the diagnosis histologically and to reduce the potential risks of transvaginal aspiration of follicles in women with large cysts.

In vitro fertilization offers a high cumulative pregnancy rate in patients with colorectal endometriosis who have not undergone prior surgery for deep infiltrating endometriosis. However, the subgroup of patients with concomitant uterine adenomyosis has a low pregnancy rate. Several studies have found that adenomyosis had no adverse effects on IVF outcome in infertile women with proven endometriosis when they were pretreated with long-term GnRH agonist.

The presence of significant pelvic pain symptoms, number of previous surgical interventions for endometriosis, the size of the cyst, accessibility of ovaries for transvaginal aspiration of follicles, and the patient's age and ovarian reserve must be taken into consideration in establishing an individualized treatment plan (**Fig. 22.3**). Resection of large cysts before IVF may reduce the risk of inadvertent needle puncture or drainage of endometriomas at the time of oocyte retrieval for IVF, which is associated with an increased risk of infection, even if prophylactic antibiotics are administered. Further randomized clinical trials are needed to elucidate the relative effects of mild peritoneal endometriosis and advanced stages of disease associated with endometriomas and pelvic adhesions on the outcome of IVF.

The relative value of initial medical therapy before use of assisted reproductive technologies remains controversial. Dicker and associates noted that 35 women with severe endometriosis who underwent 6 months of ovarian suppression with a GnRH analogue had a higher clinical pregnancy rate per cycle and per transfer than did 32 women who received ovarian stimulation for IVF without prior GnRH treatment (per cycle, 25% vs. 3.9%; per transfer, 33% vs. 5.3%). Sallam et al., in a Cochrane review of three randomized, controlled trials involving 165 participants, ovarian steroid suppression with GnRH agonist for 3 to 6 months before IVF in women with stages II to IV endometriosis led to a fourfold increase in clinical pregnancy rates. However, the very high reported clinical pregnancy rates in the treatment arms of two of these studies suggest that more data are necessary to better understand the relative value of this suppressive therapy.

TABLE 22.9 Cycle Fecundity in Women with Stage I or II Endometriosis, According to Treatment

UNEXPLAINED INFERTILITY	ENDOMETRIOSIS-ASSOCIATED INFERTILITY				
GROUP TREATMENT	**GUZICK ET AL.**	**DEATON ET AL.**	**CHAFFKIN ET AL.**	**FEDELE ET AL.**	**KEMMANN ET AL.**
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]
Gonadotropins/IUI	0.09[a]	—	0.129[a]	0.15[a]	—
IVF	—	—	—	—	0.222[a]

[a] $P < 0.05$ for treatment versus no treatments.

IUI, intrauterine insemination; IVF, in vitro fertilization.

From the Practice Committee of the American Society for Reproductive Medicine. Endometiosis and infertility. *Fertil Steril* 2004;82 (suppl 1):S40, with permission. Copyright © 2004, Elsevier.

Controlled ovarian hyperstimulation (COH) with clomiphene citrate, letrozole, human menopausal gonadotropins, or FSH together with intrauterine insemination (IUI) has been proposed as a method to increase cycle fecundity of patients with endometriosis, although few series have been published to date (**Table 22.9**). By increasing the number of oocytes released at the time of ovulation and introducing a high concentration of spermatozoa into the female reproductive tract, the chance for conception is improved, merely because of the larger number of gametes available for fertilization. In addition, subtle abnormalities of folliculogenesis, corpus luteum function, tubal motility, or sperm function may be corrected with this therapy. Cycle fecundity rates associated with COH/IUI therapy in patients with endometriosis-associated infertility have ranged from 9% to 13%, although these series did not include a nontreatment control group. One recent prospective randomized study found a higher pregnancy rate with COH/IUI following at least 6 weeks of GnRH agonist suppression in patients with advanced stages of endometriosis.

Fedele and associates reported that superovulation with timed intercourse was not associated with a better cumulative, crude pregnancy rate than expectant management in infertile women with endometriosis stages I and II, although the cycle fecundity rate was improved. However, a more recent randomized, controlled trial of COH and IUI for infertility associated with stages I and II endometriosis demonstrated a live birth rate of 11% per cycle in the treatment group and 2% in the control group. Nuoja-Huttunen and colleagues reported that ovarian stimulation or induction using gonadotropins results in higher fecundity rates than no treatment, but the clinical pregnancy rate after treatment was still significantly lower in the endometriosis group (6.5%) than in women with unexplained infertility (15%). There was no surgical treatment of endometriosis before therapy with COH and IUI in these latter studies.

In a 2006 retrospective study by Webrouck and colleagues, the clinical pregnancy rate per cycle of COH and IUI in women with minimal or mild endometriosis who underwent laparoscopic excision of lesions within 7 months of onset of treatment was 21% or 18.9%, respectively, which was comparable to that achieved in patients with unexplained infertility, 20.5%. The mean age of the patients with endometriosis in this study was 31 years. The cumulative live birth rate of nearly 70% within four cycles suggests that COH and IUI may be appropriate first-line therapy in patients younger than 35 who have not become pregnant within 6 to 12 months after surgical treatment of minimal-to-mild endometriosis and who have no other infertility risk factors. In a 2012 study by Abu Hashim et al. of women with a mean age of 31 years who had undergone laparoscopic treatment of minimal-to-mild endometriosis 6 to 12 months earlier, the clinical pregnancy rates were 15.9% and 14.5%, respectively, with letrozole-IUI and clomiphene-IUI therapy.

Temporary exposure to very high estradiol levels in women during COH for IVF or IUI is not a major risk factor for endometriosis recurrence in women treated with assisted reproductive technology.

Women with endometriosis have been shown to have adverse obstetrical outcomes as compared to those without endometriosis. Preterm birth, preeclampsia, antepartum bleeding or placental complications, and cesarean sections were more common in women diagnosed with endometriosis in a Swedish cohort study by Stephansson et al. of data from the national medical birth registry. It is uncertain whether these associations were related to endometriosis, being infertile, or the antiretroviral therapy treatment that may have been undertaken to achieve the pregnancy.

ADENOMYOSIS

Adenomyosis is defined as heterotopic endometrial glands and stroma located deep within the myometrium associated by hyperplasia of the adjacent smooth muscle. This disease can be categorized as diffuse or local in its distribution. Diffuse adenomyosis can be relatively localized but is never encapsulated (**Fig. 22.13**). The uterus itself is usually mildly enlarged, rarely to more than twice-normal size, and is generally symmetric. Cut sections of the myometrium reveal a coarse trabecular pattern of interlacing musculature and fibrous tissue with small islands of endometrium that are often dark and hemorrhagic. Localized, encapsulated disease of the uterine wall is termed *adenomyoma,* to distinguish this manifestation of adenomyosis from the more usual diffuse pattern. An adenomyoma is always located mainly within the wall of the uterus but may project into the uterine cavity to become further known as a *submucous adenomyoma.* This encapsulated, submucous form of adenomyosis disease resembles the leiomyoma.

The most widely accepted theory of the origin of adenomyosis is that endometrial tissue within the myometrium is of müllerian origin. Its presence in this location is the result of a direct, downward extension of the endometrium of the uterine cavity.

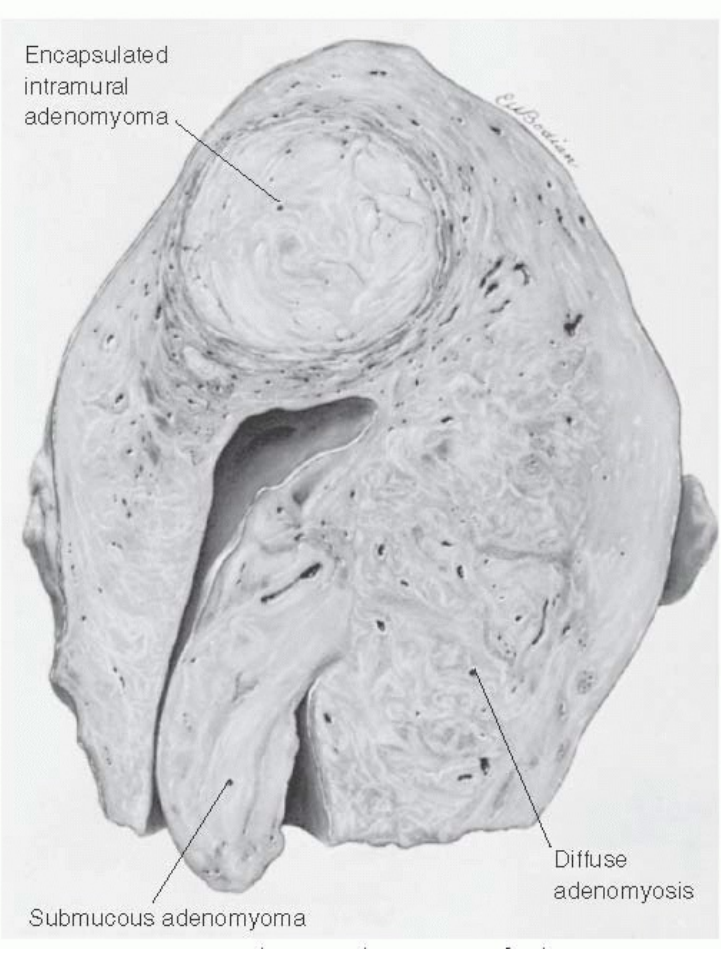

FIGURE 22.13 Uterus showing three types of adenomyomatous growth: encapsulated intramural adenomyoma, submucous adenomyoma, and diffuse adenomyosis of walls.

Serial sectioning of tissue has revealed a direct continuity between the basalis portion of the endometrium and the endometrial islands within the areas of adenomyosis. Endometrial extensions sometimes are present through the full thickness of the myometrium to the serosal surface of the uterus. Occasionally, only subserosal adenomyosis is seen. Subserosal adenomyosis is often associated with pelvic endometriosis and may cause the lymphatic spread of endometrial fragments.

The intramural islands generally have the same histologic appearance as the basalis of the endometrium (**Fig. 22.14**) and often respond to estrogen stimulation by demonstrating a proliferative or, occasionally, cystic hyperplastic pattern. Cellular atypia is rare. The effect of progestational agents on the ectopic endometrium is less predictable. Secretory changes in the glands are uncommon except in pregnancy, when a decidual reaction of the stroma is anticipated. Unlike endometriosis, adenomyotic lesions are not characterized by a pronounced hemorrhagic tendency or inflammatory response. In the absence of hormonal stimulation, adenomyosis becomes atrophic. Adenocarcinomas involving adenomyosis are characterized by a history of prior exogenous estrogen use, by low histologic grades, and by an excellent prognosis.

Adenomyosis can be definitively diagnosed only through histologic sections of myometrium. The reported incidence of the disease varies widely among from 8% to 62%, depending on the criteria used for diagnosis and on the thoroughness with which the excised uterine tissue is studied. The usual criterion for diagnosis is glandular extension below the endometrial-myometrial interface of greater than 2.5 mm, whereas adenomyosis subbasalis can be defined as minimally invasive adenomyosis extending less than 2 mm beneath the basal endometrium. The incidence of adenomyosis begins to rise in the mid-30s and peaks in the fifth decade. Infertility is not common, although most patients are multiparous. Approximately 12% have coexisting external endometriosis. Adenomyosis is often discovered incidentally in patients undergoing surgery for uterine leiomyomata.

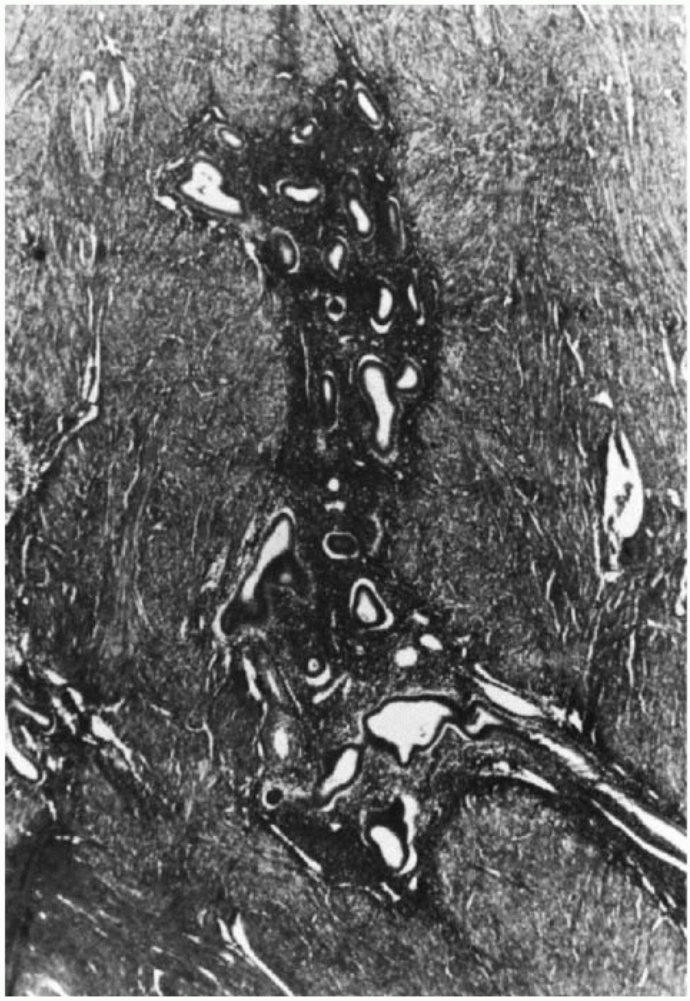

FIGURE 22.14 Area of adenomyosis. Compact stroma and proliferative, slightly hyperplastic glands surrounded by hypertrophied myometrium.

Symptoms

Adenomyosis is often an incidental pathologic finding, and approximately 35% of cases are asymptomatic. Dysmenorrhea is more likely to be reported when glandular invasion exceeds 80% or more of the myometrium. Pain can be severe, cramping, or knifelike and may occur up to 1 week before the onset of menstrual flow. The pattern of dysmenorrhea is likely associated with bleeding episodes within the deep-lying islands of endometrium. Menorrhagia can be a consequence of the increased surface area of the enlarged uterine cavity. In addition, extensive involvement of the myometrium can interfere with the normal contractility of the uterine musculature and can lead to excessive bleeding. Nevertheless, data collected from 1,851 hysterectomies for the prospective, multicenter Collaborative Review of Sterilization study indicate that adenomyosis occurs as often in asymptomatic uteri removed for prolapse (19%) as in uteri removed for excessive bleeding (22%) or pain symptoms (15%). Uterine adenomyosis is significantly associated with pelvic endometriosis, with a prevalence of up to 90%. By impairing uterine sperm transport, adenomyosis may be a leading factor of infertility in women with endometriosis.

Pelvic Findings

The uterus may be very firm to palpation and is usually enlarged to not more than twice its normal size. As it is classically described, the adenomyotic enlargement occurs in the anteroposterior dimension, a reflection of the more prominent involvement of the posterior uterine wall. In the more common diffuse type of adenomyosis, the uterus is a symmetrically enlarged, globular structure. Encapsulated adenomyomas may cause the uterus to be irregular or asymmetric, much as it is when leiomyomata are present. At times, particularly during menstruation, the enlarged uterus is tender on examination.

Diagnosis

Adenomyosis should always be suspected in a woman with dysmenorrhea and menorrhagia of increasing severity her fourth or fifth decade, particularly if the uterus is symmetrically enlarged, firm, and tender. An exact preoperative diagnosis is often difficult to establish because dysfunctional uterine bleeding and multiple small leiomyomata can present in a similar fashion. Gambone and colleagues reported that a presumptive diagnosis of adenomyosis was verified in only 38% of hysterectomy specimens. The diagnosis can be histologically established before hysterectomy only in the rare case in which excessive myometrium is removed during curettage or a polypoid submucous adenomyoma is excised. However, hysteroscopic myometrial biopsy of the posterior uterine wall with use of a 5-mm loop electrode has been shown to effectively establish the diagnosis in women with menorrhagia.

Hysterosalpingography of the adenomyomatous uterus with water-based media can occasionally demonstrate multiple spiculations or tuft defects leading from the uterine cavity to the myometrial wall; however, similar findings can occur in cases of vascular or lymphatic extravasation. MRI has proved to be highly accurate for distinguishing adenomyosis from leiomyomata; on T2-weighted images, adenomyosis appears as an ill-defined, relatively homogeneous, low-signal-intensity area embedded with sparse, high-intensity spots. The optimal junctional zone thickness value for establishing the diagnosis of adenomyosis is 12 mm or more. Several studies have shown that the sensitivity and specificity of MRI to diagnose adenomyosis range from 86% to 100% in a symptomatic patient population.

Recent studies have also suggested an important role for transvaginal ultrasound in distinguishing adenomyosis from leiomyomata. By using the diagnostic criterion of the presence of unencapsulated, heterogeneous, myometrial areas within round anechoic areas 1 to 3 mm in diameter, Fedele and colleagues noted a sensitivity of 80%, a specificity of 74%, a negative predictive value of 81%, and a positive predictive value of 73%. Nevertheless, when transvaginal sonography and MRI have been prospectively compared, the latter has been significantly more accurate in correctly establishing the diagnosis.

Hormone receptor studies have documented the presence of steroid receptors in adenomyotic foci. Estrogen receptors are more consistently present than are progesterone receptors, which are completely absent in 40% of cases evaluated. Progestins or cyclic estrogen-progestin combination preparations offer little aid in treatment, although recent reports indicated that adenomyosis-associated menorrhagia can be controlled with the insertion of a levonorgestrel-releasing intrauterine device or a danazol-loaded intrauterine device. GnRH agonist therapy for 6 months resulted in the disappearance of pain symptoms and a decline in uterine volume in 65% of cases of biopsy-proven adenomyosis, but the dysmenorrhea and menorrhagia recurred at the end of treatment. Nevertheless, extended intermittent use of these agonists can effectively relieve pain symptoms while having the significant advantage of preserving fertility between treatments.

Curettage does not aid in establishing the diagnosis of adenomyosis and is ineffective as treatment, although it may be required because of abnormal bleeding. The need for surgery, therefore, is based on continued menorrhagia and dysmenorrhea rather than on an estimation of uterine size or even the known presence of adenomyosis or leiomyomata. The definitive treatment for abnormal bleeding caused by adenomyosis is hysterectomy. The vaginal route is preferred if the size of the uterus is appropriate and no other pelvic abnormalities are present. Under certain circumstances, as with a younger patient who wishes to retain her reproductive capability, excision of an encapsulated adenomyoma should be considered instead of hysterectomy. Such situations arise infrequently because adenomyosis is generally diffuse and usually occurs in multiparous women who are no longer interested in childbearing. The precise efficacy of hysteroscopic endometrial resection, laparoscopic myometrial reduction, and myometrial excision as conservative surgical procedures for adenomyosis has yet to be proved. Endometrial ablation is ineffective as treatment for deep, subserosal adenomyosis that penetrates more than 2 mm. Attempting to resect deeper myometrial tissue carries the risk of increased bleeding. Thermal balloon and radiofrequency ablation has been used recently to treat excessive bleeding in women with adenomyosis. Ectopic, deeper endometrial glands not resected may persist under the scar and eventually proliferate through the area of ablation or resection to cause symptoms such as dysmenorrhea.

Excisional surgery of adenomyosis is best performed by laparotomy because of the value of palpating the uterus to assess the extent of disease and the greater ease in achieving hemostasis. Fujishita and colleagues described a modified approach called the transverse H technique, where one vertical and two crossing horizontal incisions are made. This allows easier removal of a more limited volume of adenomyotic tissue than classical reduction and resulted in a greater improvement in symptoms.

The use of GnRH analogues postoperatively may reduce the recurrence of symptoms in patients who undergo cytoreductive surgery. Wang et al. followed 165 women treated with surgery alone or surgery followed by a 6-month course of ovarian suppressive therapy with GnRH analogues. They found that the symptom-relapse rates in the surgical-medical group were significantly lower than those in the surgeryalone group (28.1% vs. 49.0%, respectively). There was no significant difference in the clinical pregnancy rates (79.5% vs. 74.1%, respectively) or the delivery rates (72.7% vs. 63.0%) among the 44 women in the surgical-medical group and the 27 patients in the surgery-alone group who tried to conceive upon completion of the course of treatment for adenomyosis.

In a recent series of 104 patients, Osada and colleagues described a technique of radical resection of adenomyomatous tissue along with a triple-flap method for reconstructing the uterine wall. All of the patients in the report had adenomyosis involving more than 80% of the anterior and posterior uterine walls with more than 6 cm of wall thickness as verified by MRI and ultrasound. A supracervical tourniquet was applied, and the uterus was bisected at the midline along the sagittal plane until the uterine cavity was opened. Adenomyotic tissues were excised from surrounding myometrium, leaving a myometrial thickness of 1 cm from serosa to endometrium. The endometrium was reapproximated with suture, and the myometrium was repaired with a triple-flap reconstruction. The serosal surface of the underlying flaps was stripped to ensure that only myometrial tissues apposed each other. Only four cases (3.8%) had recurrence of symptoms after 2 years. Sixteen pregnancies

were reported out of twenty six women who wished to conceive (61%) and three-fourths of these were achieved through IVF. The deliveries occurred through cesarean section.

There have been several reports of uterine rupture in the second and third trimester of women who have undergone cytoreductive surgery, so careful patient counseling and close obstetrical management are necessary if conservative surgery is being contemplated, especially if it entails significant resection of a portion of the myometrium.

Interventional radiologic techniques have been described to selectively embolize the uterine vessels in women with adenomyosis. Although short-term results from Pelage et al. of uterine artery embolization to treat adenomyosis appeared encouraging, midterm results were disappointing, with only 55% of treated patients showing clinical improvement after 2 years. In a review by Popovic et al. of 15 studies in which uterine artery embolization was performed to treat symptomatic adenomyosis in 208 women, 64.9% reported long-term satisfaction. Preliminary trials have suggested that magnetic resonance-guided focused ultrasound surgery may be used in the future to destroy focal adenomyosis.

Hysterectomy should be considered in the severely symptomatic patient when ultrasonography, MRI, or myometrial biopsy demonstrates deep adenomyosis. The surgical procedure may be performed abdominally, vaginally, or laparoscopically. Subtotal hysterectomy should be avoided, as adenomyosis may recur in the cervical stump or the rectovaginal septum.

BEST SURGICAL PRACTICES

- Surgery is indicated for correction of pain, infertility, or other symptoms in patients with extensive pelvic endometriosis or when hormonal manipulation fails to adequately diminish pain symptoms in women with lesser stages of disease. Surgical management of endometriomas has no significant effect on IVF pregnancy rates as compared to no treatment. Resection of large endometriomas (>5 cm in size) allows a histologic confirmation of the etiology of the cyst and may reduce the risk of bacterial seeding of the endometrial cyst during transvaginal aspiration of follicles for IVF.
- Preoperative rectoscopy-sigmoidoscopy and intravenous pyelography are recommended in patients with symptoms suggestive of deeply invasive endometriosis of the posterior cul-de-sac and rectovaginal septum. Preoperative ultrasound and MRI may help to categorize the extent of ovarian involvement and location of deeply infiltrating disease. A bowel prep before surgery may facilitate optimal performance and safety of the surgical procedure, particularly when deep disease is anticipated.
- Laparoscopy can be considered for all cases unless there is difficulty in establishing the appropriate tissue planes of dissection or unless improved access is necessary for atraumatic manipulation of the involved organs. Conservative resection of disease by laparotomy is most valuable in cases of extensive, dense pelvic adhesions or endometriomas greater than 5 cm in diameter. In addition, deep involvement of the rectovaginal septum with fibrotic extension into the perirectal fossa, invasion of the bowel muscularis, and endometriotic infiltration in the region of the uterine vessels and

ureter are generally best approached through the open abdomen for all but advanced endoscopic surgeons.

- The philosophy of gentle manipulation of tissue in an attempt to avoid trauma is the major tenet of pelvic reconstruction. Adhesion formation can be reduced by magnification of the surgical site, avoidance of suture unless clearly indicated, reconstruction with fine nonreactive suture, precise hemostasis, and frequent irrigation of tissues with warmed solution.
- Less tissue damage is achieved with bipolar than with monopolar cautery. Ablation of deep disease by monopolar microdiathermy or CO_2 laser vaporization rather than excision of the disease may result in inadequate resection and a greater amount of ischemic damage to the tissue, heightening the propensity toward adhesion formation. Deep lesions or more extensive peritoneal disease must be excised with a tissue margin of at least 2 to 4 mm, because microscopic lesions are commonly present in tissue adjacent to visible implants. Twenty-five percent of patients have lesions greater than 5 mm in depth.
- Coagulation or vaporization of disease in the ovarian fossa or near the uterosacral ligament should be undertaken only after clear identification of the ureter. Resection of deep posterior cul-de-sac nodules requires great endoscopic expertise. A combined laparoscopic-vaginal approach may be necessary.
- Inability to elevate the ovary is usually a sign of adhesions and endometriotic implants of the inferolateral surface of the ovary and the peritoneum of the ovarian fossa. When removing an endometrioma, the cortical incision should be made in a way that will preserve the normal anatomic relations of the ovary with the uteroovarian ligament and fimbria ovarica. Suture on or extruding through the surface should be avoided when possible because of its adhesiogenic properties. With larger endometriomas, the normal ovarian cortex is stabilized with atraumatic forceps, and the cyst wall is grasped with biopsy forceps and stripped from the bed of normal ovarian tissue. The dissection may be facilitated by removing a small circular rim of tissue around the adhesion site to begin the stripping procedure in a clearer field, where the endometrioma wall is less adhered to healthy ovarian tissue. The rate of recurrence of pelvic pain and dysmenorrhea over a 2-year postoperative period is significantly less for those patients who are managed by cystectomy as compared with those undergoing fenestration and coagulation. Moreover, the rate of reoperation is less and the cumulative pregnancy rate is higher in the cystectomy group. Extensive cauterization or resection of ovarian tissue can lead to a decline in follicle number and a rise in FSH levels postoperatively and should be avoided.
- Aggressive and complete excision of deep endometriosis is justified. The recurrence rate of clinically detectable endometriosis is higher when the depth of infiltration is greater than 5 mm at the time of initial surgery, no matter the site of the lesion. A second cytoreductive procedure may benefit some infertile women who have undergone surgery in the past, although assisted reproductive technologies would lead to a higher chance of conceiving for most patients who failed primary surgery. The hypothesis that surgical therapy of endometriosis increases IVF pregnancy rates is not clearly validated by the available evidence.
- Uterine suspension is of unproven efficacy in enhancing fertility or as an adjunct in the treatment of endometriosisassociated pelvic pain.
- Presacral neurectomy, or division of the superior hypogastric plexus, is useful as an adjunctive procedure to eliminate the uterine component of dysmenorrhea that results from endometriosis. Uterine nerve ablation may be effective in reducing dysmenorrhea in the absence of endometriosis, but the addition of this procedure to the surgical treatment of endometriosis has not been associated with a significant difference in any pain outcomes.

BIBLIOGRAPHY

Abbott JA, Howe J, Clayton RD, et al. The effects and effectiveness of laparoscopic excision of endometriosis: a prospective study with 2-5 year follow-up. *Hum Reprod* 2003;18:1922.

Abbott J, Howe J, Hunter D, et al. Laparoscopic excision of endometriosis: a randomized, placebo-controlled trial. *Fertil Steril* 2004;82:878.

Aboulghar MA, Mansour RT, Serour G, et al. The outcome of *in vitro* fertilization in advanced endometriosis with previous surgery: a case-controlled study. *Am J Obstet Gynecol* 2003;188:371.

Abu Hashim A, El Rakhawy M, Abd Elaal I. Randomized comparison of superovulation with letrozole vs. clomiphene citrate in an IUI program for women with recently surgically treated minimal to mild endometriosis. *Acta Obstet Gynecol Scand* 2012; 91:338.

Adamson GD, Subak LL, Pasta DJ, et al. Comparison of CO_2 laser laparoscopy with laparotomy for the treatment of endometriomata. *Fertil Steril* 1992;57:965.

Adamson GD, Hurd SJ, Pasta DJ, et al. Laparoscopic endometriosis treatment: is it better? *Fertil Steril* 1993;59:35.

Albourzi S, Momtahan M, Parsanezhad M, et al. A prospective, randomized study comparing laparoscopic ovarian cystectomy versus fenestration and coagulation in patients with endometriomas. *Fertil Steril* 2004;82:1633.

Almog B, Shehata F, Sheizaf B, et al. Effects of ovarian endometrioma on the number of oocytes retrieved for in vitro fertilization. *Fertil Steril* 2011;95:525.

American Fertility Society. The classification of endometriosis. *Fertil Steril* 1979;32:633.

American Fertility Society. Revised American Fertility Society classification of endometriosis: 1985. *Fertil Steril* 1985;43:351.

American Society for Reproductive Medicine. Revised American Society for Reproductive Medicine classification of endometriosis: 1996. *Fertil Steril* 1997;67:817.

Andrews WE, Larsen GD. Endometriosis: treatment with hormonal pseudopregnancy and/or operation. *Am J Obstet Gynecol* 1974;118:643.

Ascher SM, Arnold LL, Patt RH, et al. Adenomyosis: prospective comparison of MR imaging and transvaginal sonography. *Radiology* 1994;190:803.

Awadalla SG, Friedman CI, Haq AU, et al. Local peritoneal factors: their role in infertility associated with endometriosis. *Am J Obstet Gynecol* 1987;157:1207.

Ayers JW, Birenbaum DL, Menon KM. Luteal phase dysfunction in endometriosis: elevated progesterone levels in peripheral and ovarian veins during the follicular phase. *Fertil Steril* 1987;47:925.

Badawy SZA, Cuenca V, Kaufman L, et al. The regulation of immunoglobulin production by B cells in patients with endometriosis. *Fertil Steril* 1989;51:770.

Bailey HR, Ott MT, Hartendorp P. Aggressive surgical management for advanced colorectal endometriosis. *Dis Colon Rectum* 1994;37:747.

Ballester M, Mathieu d'Argent E, Morcel K, et al. Cumulative pregnancy rate after ICSI-IVF in patients with colorectal endometriosis: results of a multicentre study. *Hum Reprod* 2012;27:1043.

Barbieri RL. Etiology and epidemiology of endometriosis. *Am J Obstet Gynecol* 1990;162:565.

Barbieri RL. Hormone treatment of endometriosis: the estrogen threshold hypothesis. *Am J Obstet Gynecol* 1992;166:740.

Barbieri RL. Stenosis of the external os: an association with endometriosis in women with chronic pelvic pain. *Fertil Steril* 1998; 70:571.

Barbieri RL, Ryan KJ. Danazol: endocrine pharmacology and therapeutic applications. *Am J Obstet Gynecol* 1981;141:453.

Barbieri RL, Niloff JM, Bast RC Jr, et al. Elevated serum concentrations of CA-125 in patients with advanced endometriosis. *Fertil Steril* 1986;45:630.

Barnhart K, Dunsmoor-Su R, Coutifaris C. Effect of endometriosis on *in vitro* fertilization. *Fertil Steril* 2002;77:1148.

Benschop L, Farquhar C, van der Poel N, et al. Interventions for women with endometrioma prior to assisted reproductive technology. *Cochrane Database Syst Rev* 2010;(11):CD008571. doi: 10.1002/14651858.CD008571.pub2

Beretta P, Franchi M, Ghezzi F, et al. Randomized clinical trial of two laparoscopic treatments of endometriomas: cystectomy versus drainage and coagulation. *Fertil Steril* 1998;70:1176.

Bergqvist A, Theorell T. Changes in quality of life after hormonal treatment of endometriosis. *Acta Obstet Gynecol Scand* 2001;80:628.

Berlanda N, Vercellini P, Fedele L. The outcomes of repeat surgery for recurrent symptomatic endometriosis. *Curr Opin Obstet Gynecol* 2010;22:320.

Biberoglu KO, Behrman SJ. Dosage aspects of danazol therapy in endometriosis: short term and long term effectiveness. *Am J Obstet Gynecol* 1981;138:645.

Bridoux V, Roman H, Kianifard B, et al. Combined transanal and laparoscopic approach for the treatment of deep endometriosis infiltrating the rectum. *Hum Reprod* 2012;27:418.

Brosens IA, Koninckx PR, Corveleyn PA. A study of plasma progesterone, oestradiol-17*β,* prolactin and LH levels and of the luteal phase appearance of the ovaries in patients with endometriosis and infertility. *Br J Obstet Gynaecol* 1978;85:246.

Brosens I, Vasquez G, Gordts S. Scanning electron microscopy study of the pelvic peritoneum in unexplained infertility and endometriosis. *Fertil Steril* 1984;41:215.

Bruner KL, Mastrisian LM, Rodgers WH, et al. Suppression of matrix metalloproteinases inhibits establishment of ectopic lesions by human endometrium in nude mice. *J Clin Invest* 1997;99:2851.

Busacca M, Marana R, Caruana P, et al. Recurrence of ovarian endometriomas after laparoscopic excision. *Am J Obstet Gynecol* 1999;180:519.

Busacca M, Riparini J, Somigliana E, et al. Postsurgical ovarian failure after laparoscopic excision of bilateral endometriomas. *Am J Obstet Gynecol* 2006;195:421.

Buttram VC Jr, Reiter RC, Ward S. Treatment of endometriosis with danazol: report of a 6 year prospective study. *Fertil Steril* 1985;43:353.

Cakmak H, Taylor HS. Molecular mechanisms of treatment resistance in endometriosis: the role of progesterone-hox gene interactions. *Semin Reprod Med* 2010;28:69.

Candiani GB, Vercellini P, Fedele L. Laparoscopic ovarian puncture for correct staging of endometriosis. *Fertil Steril*

1990;53:994.

Candiani GB, Fedele L, Vercellini P, et al. Repetitive conservative surgery for recurrence of endometriosis. *Obstet Gynecol* 1991;77:421.

Candiani GB, Vercellini P, Fedele L, et al. Conservative surgical treatment for severe endometriosis in infertile women: are we making progress? *Obstet Gynecol Surv* 1991;48(suppl 7):490.

Candiani GB, Fedele L, Vercellini P, et al. Presacral neurectomy for the treatment of pelvic pain associated with endometriosis: a controlled study. *Am J Obstet Gynecol* 1992;167:100.

Candiani GB, Vercellini P, Fedele L, et al. Conservative surgical treatment of rectovaginal septum endometriosis. *J Gynecol Surg* 1992;8:177.

Canis M, Mage G, Wattiex A, et al. Second-look laparoscopy after laparoscopic cystectomy of large ovarian endometriomas. *Fertil Steril* 1992;58:617.

Carpenter SE, Markham SM, Rock JA. Exercise may reduce side effects of danazol. *Infertility* 1988;2:259.

Cedars MI, Lu JK, Meldrum DR, et al. Treatment of endometriosis with a long-acting gonadotropin releasing hormone agonist plus medroxyprogesterone acetate. *Obstet Gynecol* 1990;75:641.

Chaffkin LM, Nulsen JC, Luciano AA, et al. 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.

Chapron C, Santulli P, de Ziegler D, et al. Ovarian endometrioma: severe pelvic pain is associated with deeply infiltrating endometriosis. *Hum Reprod* 2012;27:702.

Cheesman KL, Ben-Nun I, Chatterton RT Jr, et al. Relationship of luteinizing hormone, pregnanediol-3-glucuronide and estriol-16-glucuronide in urine of infertile women with endometriosis. *Fertil Steril* 1982;38:542.

Cheesman KL, Cheesman SD, Chatterton RT, et al. Alterations in progesterone metabolism and luteal function in infertile women with endometriosis. *Fertil Steril* 1983;40:590.

Chen FP, Soong YK. The efficacy and complications of laparoscopic presacral neurectomy in pelvic pain. *Obstet Gynecol* 1997; 90:974.

Chong AP, Luciano AA, O'Shaughnessy AM. Laser laparoscopy versus laparotomy in the treatment of infertility patients with severe endometriosis. *J Gynecol Surg* 1990;6:179.

Coccia ME, Rizzello F, Mariani G, et al. Ovarian surgery for bilateral endometriomas influences age at menopause. *Hum Reprod* 2011;26:3000.

Coddington CC, Oehninger S, Cunningham DS, et al. Peritoneal fluid from patients with endometriosis decreases sperm binding to the zona pellucida in the hemizona assay: a preliminary report. *Fertil Steril* 1992;57:783.

Confino E, Harlow L, Gleicher N. Peritoneal fluid and serum autoantibody levels in patients with endometriosis. *Fertil Steril* 1990;53:242.

Cook AS, Rock JA. The role of laparoscopy in the treatment of endometriosis. *Fertil Steril* 1991;55:663.

Cornillie FJ, Oosterlynck D, Lauweryns JM, et al. Deeply infiltrating pelvic endometriosis: histology and clinical significance. *Fertil Steril* 1989;53:978.

Coronado C, Franklin RR, Lotze EC, et al. Surgical treatment of symptomatic colorectal endometriosis. *Fertil Steril* 1990;53:411.

Cramer DW, Missmer SA. The epidemiology of endometriosis. *Ann N Y Acad Sci* 2002;955:11.

Cramer DW, Wilson E, Stillman RJ, et al. The relation of endometriosis to menstrual characteristics, smoking, and exercise. *JAMA* 1986;255:1904.

Cullen TS. The distribution of adenomyomata containing uterine mucosa. *Arch Surg* 1919;80:130.

Czernobilsky B, Morris W. A histologic study of ovarian endometriosis with emphasis on hyperplastic and atypical changes. *Obstet Gynecol* 1979;53:318.

Czernobilsky B, Silverstein A. Salpingitis in ovarian endometriosis. *Fertil Steril* 1978;30:45.

Damewood MD, Hesla JS, Schlaff WD, et al. Effect of serum from patients with minimal to mild endometriosis on mouse embryo development in vitro. *Fertil Steril* 1990;54:917.

Daniell JF. Fiberoptic laser laparoscopy. *Baillieres Clin Obstet Gynaecol* 1989;3:545.

Davis GD, Brooks RA. Excision of pelvic endometriosis with the carbon dioxide laser laparoscope. *Obstet Gynecol* 1988;72:816.

Dawood MY. Impact of medical treatment of endometriosis on bone mass. *Am J Obstet Gynecol* 1993;168:674.

Dawood MY, Kahn-Dawood FS, Wilson L Jr. Peritoneal fluid prostaglandins and prostanoids in women with endometriosis, chronic pelvic inflammatory disease, and pelvic pain. *Am J Obstet Gynecol* 1984;148:391.

De Cicco C, Corona R, Schonman R, et al. Bowel resection for deep endometriosis: a systematic review. *Br J Obstet Gynaecol* 2011;118:285.

DeLeon FD, Vijayakumar R, Brown M, et al. Peritoneal fluid volume, estrogen, progesterone, prostaglandin, and epidermal growth factor concentrations in patients with and without endometriosis. *Obstet Gynecol* 1986;68:189.

Diaz I, Navarro J, Blasco L, et al. Impact of stage III-IV endometriosis on recipients of sibling oocytes: matched case-control study. *Fertil Steril* 2000;74:31.

Dicker D, Feldberg D, Goldman JA, et al. 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.

Dickey RP, Olar TT, Taylor SN, et al. Relationship of follicle number, serum estradiol, and other factors to birth rate and multiparity in human menopausal gonadotropin-induced intrauterine insemination cycles. *Fertil Steril* 1991;56:89.

diZerega G, Hodgen G. Endometriosis: role of ovarian steroids in initiation, maintenance, and suppression. *Fertil Steril*

1980; 33:649.

Dlugi AM, Miller JD, Knittle J, et al. Lupron depot (leuprolide acetate for depot suspension) in the treatment of endometriosis: a randomized, placebo-controlled, double-blind study. *Fertil Steril* 1990;54:419.

Dmowski WP, Cohen MR. Treatment of endometriosis with an antigonadotropin, danazol: a laparoscopic and histologic evaluation. *Obstet Gynecol* 1975;46:147.

Dmowski WP, Steele RW, Baker GF. Deficient cellular immunity in endometriosis. *Am J Obstet Gynecol* 1981;141:377.

Dmowski WP, Radwanska E, Binor Z, et al. Mild endometriosis and ovulatory dysfunction: effect of danazol treatment on success of ovulation induction. *Fertil Steril* 1986;46:784.

Döberl A, Berquist A, Jeppson S, et al. Regression of endometriosis following the shorter treatment with, or lower dose of, danazol. *Acta Obstet Gynecol Scand Suppl* 1984;123:51.

Dodin S, Lemay A, Maheux R, et al. Bone mass in endometriosis patients treated with GnRH agonist implant or danazol. *Obstet Gynecol* 1991;77:410.

Dodson WC, Haney AF. Controlled ovarian hyperstimulation and intrauterine insemination for treatment of infertility. *Fertil Steril* 1991;55:457.

Donnez J, Casanas-Roux F, Ferin J, et al. Tubal polyps, epithelial inclusions, and endometriosis after tubal sterilization. *Fertil Steril* 1984;41:56.

Donnez J, Nisolle-Pochet M, Clerckx-Braun F, et al. Administration of nasal buserelin as compared with subcutaneous buserelin implant for endometriosis. *Fertil Steril* 1989;52:25.

Doyle JB. Paracervical uterine denervation by transection of the cervical plexus for the relief of dysmenorrhea. *Am J Obstet Gynecol* 1955;70:11.

Drake TS, O'Brien WF, Ramwell PW, et al. Peritoneal fluid thromboxane B_2 6-keto-prostaglandin F_{1a} in endometriosis. *Am J Obstet Gynecol* 1981;140:401.

Dunselman GA, Dumoulin JC, Land JA, et al. Lack of effect of peritoneal endometriosis on fertility in the rabbit model. *Fertil Steril* 1991;56:340.

Eskenazi B, Warner M, Bonsignore L, et al. Validation study of nonsurgical diagnosis of endometriosis. *Fertil Steril* 2001;76:929.

Evers JL. The second look laparoscopy for evaluation of the results of medical treatment of endometriosis should not be performed during ovarian suppression. *Fertil Steril* 1987;47:502.

Fahaeus L, Larsson-Cohn U, Ljungberg S, et al. Profound alterations of the lipoprotein metabolism during danazol treatment in premenopausal women. *Fertil Steril* 1984;42:52.

Fakih HN, Tamura R, Kesselman A, et al. Endometriosis after tubal ligation. *J Reprod Med* 1985;30:939.

Fakih H, Baggett B, Holtz G, et al. Interleukin-1: a possible role in the infertility associated with endometriosis. *Fertil Steril* 1987;47:218.

Falcone T, Lebovic DI. Clinical management of endometriosis. *Am J Obstet Gynecol* 2011;118:691.

Fayez JA, Collazo LM. Comparison between laparotomy and operative laparoscopy in the treatment of moderate and severe endometriosis. *Int J Fertil* 1990;35:252.

Fayez JA, Vogel MF. Comparison of different treatment methods of endometriomas by laparoscopy. *Obstet Gynecol* 1991;78:660.

Fedele L, Parazzini F, Bianchi S, et al. Stage and localization of pelvic endometriosis and pain. *Fertil Steril* 1990;53:155.

Fedele L, Bianchi S, Bocciolone L, et al. Pain symptoms associated with endometriosis. *Obstet Gynecol* 1992;79:767.

Fedele L, Bianchi S, Dorta M, et al. Transvaginal ultrasonography in the differential diagnosis of adenomyoma versus leiomyoma. *Am J Obstet Gynecol* 1992;167:603.

Fedele L, Bianchi S, Marchini M, et al. 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.

Fedele L, Bianchi S, Zanconato G, et al. Long-term follow-up after conservative surgery for bladder endometriosis. *Fertil Steril* 2005;83:1729.

Fedele L, Bianchi S, Zanconato G, et al. Laparoscopic excision of recurrent endometriomas: long-term outcome and comparison with primary surgery. *Fertil Steril* 2006;85:694.

Ferrero S, Anserini P, Abbamonte LH, et al. Fertility after bowel resection for endometriosis. *Fertil Steril* 2009;92:41.

Ferrero S, Venturini PL, Gillott DJ, et al. Hemostasis by bipolar coagulation versus suture after surgical stripping of bilateral ovarian endometriomas: a randomized controlled trial. *J Minim Invasive Gynecol* 2012;19:722.

Foster DC, Stern JL, Buscema J, et al. Pleural and parenchymal pulmonary endometriosis. *Obstet Gynecol* 1981;58:552.

Franssen AM, Kaver FM, Chadha DR, et al. Endometriosis: treatment with gonadotropin-releasing hormone agonist buserelin. *Fertil Steril* 1989;51:401.

Fujishita A, Masuzaki H, Khan KN, et al. Modified reduction surgery for adenomyosis. A preliminary report of the transverse H incision technique. *Gynecol Obstet Invest* 2004;57:132.

Gambone JC, Reiter RC, Lerich JB, et al. The impact of a quality assurance process in the frequency and confirmation rate of hysterectomy. *Am J Obstet Gynecol* 1990;163:545.

Gant NF. Infertility and endometriosis: comparison of pregnancy outcomes with laparotomy versus laparoscopic techniques. *Am J Obstet Gynecol* 1992;166:1072.

Garcia-Velasco JA, Mahutte NG, Corona J, et al. Removal of endometriomas before in vitro fertilization does not improve fertility outcomes: a matched, case-control study. *Fertil Steril* 2004;81:1194.

Glatt AE, Zinner SH, McCormack WM. The prevalence of dyspareunia. *Obstet Gynecol* 1990;75:433.

Goksever Celik H, Dogan E, Okyay E, et al. Effect of laparoscopic excision of endometriomas on ovarian reserve: serial changes in the serum antimullerian hormone levels. *Fertil Steril* 2012;97:1472.

Gould SF, Shannon JM, Cunha GR. Nuclear estrogen binding sites in human endometriosis. *Fertil Steril* 1983;39:520.

Granberg S, Wikland M, Jansson I. Macroscopic characterization of ovarian tumors and the relation to the histologic diagnosis: criteria to be used for ultrasound evaluation. *Gynecol Oncol* 1989;35:139.

Greenblatt RB, Dmowski WP, Mahesh VB, et al. Clinical studies with an antigonadotropin danazol. *Fertil Steril* 1971;22:102.

Grow DR, Filer RB. Treatment of adenomyosis with long-term GnRH analogues: a case report. *Obstet Gynecol* 1991;78:538.

Gruenwald P. Origin of endometriosis from the mesenchyme of the coelomic walls. *Am J Obstet Gynecol* 1942;44:470.

Guzick DS. Clinical epidemiology of endometriosis and infertility. *Obstet Gynecol Clin North Am* 1989;16:43.

Haas D, Oppelt P, Shebl O, et al. Enzian classification: does it correlate with clinical symptoms and the rASRM score? *Acta Obstet Gynecol Scand* 2013;92:962.

Habuchi T, Okagaki T, Miyakawa M. Endometriosis of bladder after menopause. *J Urol* 1991;145:361.

Halme J, Hammond MG, Hulka JK, et al. Retrograde menstruation in healthy women and in patients with endometriosis. *Obstet Gynecol* 1984;64:151.

Halme J, White C, Kauma S, et al. Peritoneal macrophages from patients with endometriosis release growth factor activity in vitro. *J Clin Endocrinol Metab* 1988;66:1044.

Haney AF, Jenkins S, Weinberg JB. The stimulus responsible for the peritoneal fluid inflammation observed in infertile women with endometriosis. *Fertil Steril* 1991;56:408.

Harada T, Momoeda M, Taketani Y, et al. Low-dose oral contraceptive pill for dysmenorrhea associated with endometriosis: a placebo-controlled, double-blind, randomized trial. *Fertil Steril* 2008;90:1583.

Hart RJ, Hickey M, Maouris P, et al. Excisional surgery versus ablative surgery for ovarian endometriomata. *Cochrane Database System Rev* 2011(5):CD004992. doi: 10.1002/14651858. CD004992.pub3

Heaps JM, Nieberg RK, Berek JS. Malignant neoplasms arising in endometriosis. *Obstet Gynecol* 1990;75:1023.

Heilier JF, Nackers F, Verougstraete V, et al. Increased dioxin-like compounds in the serum of women with peritoneal endometriosis and deep endometriotic (adenomyotic) nodules. *Fertil Steril* 2005;84:305.

Henzl MR. Gonadotropin-releasing hormone analogs: update on new findings. *Am J Obstet Gynecol* 1992;166:757.

Henzl MR, Corson SL, Moghissi K, et al. Administration of nasal nafarelin as compared with oral danazol for endometriosis. *N Engl J Med* 1988;318:485.

Hickman TN, Namnoum AB, Hinton EL, et al. Timing of estrogen replacement therapy following hysterectomy with oophorectomy for endometriosis. *Obstet Gynecol* 1998;91:673.

Hill JA, Faris HM, Schiff I, et al. Characterization of leukocyte subpopulations in the peritoneal fluid of women with endometriosis. *Fertil Steril* 1988;50:216.

Hornstein MD, Hemmings R, Yuzpe AA, et al. Use of nafarelin versus placebo after reductive laparoscopic surgery for endometriosis. *Fertil Steril* 1997;68:860.

Hornstein MD, Surrey ES, Weisberg GW, et al. Leuprolide acetate depot and hormonal add-back in endometriosis: a 12-month study. *Obstet Gynecol* 1998;91:16.

Houston DE, Noller RL, Melton LJ III, et al. Incidence of pelvic endometriosis in Rochester, Minnesota 1970-1979. *Am J Epidemiol* 1987;125:959.

Hsu AL, Sinaii N, Segars J, et al. Relating pelvic pain location to surgical findings of endometriosis. *Obstet Gynecol* 2011;188:223.

Hughes E, Brown J, Collins JJ, et al. Ovulation suppression for endometriosis. *Cochrane Database Syst Rev* 2007;18:CD000155.

Hull ME, Moghissi KS, Magyar DF, et al. Comparison of different treatment modalities of endometriosis in infertile women. *Fertil Steril* 1987;47:40.

Igarashi M, Abe Y, Fukuda M, et al. Novel conservative medical therapy for uterine adenomyosis with a danazol-loaded intrauterine device. *Fertil Steril* 2000;74:412.

Ishimaru T, Masuzaki H. Peritoneal endometriosis: endometrial tissue implantation as its primary etiologic mechanism. *Am J Obstet Gynecol* 1991;165:210.

Jacobson TZ, Duffy JM, Barlow D, et al. Laparoscopic surgery for subfertility associated with endometriosis. *Cochrane Database Syst Rev* 2009;4:CD001398.doi: 10.1002/14651858.CD001398.pub2

Jacobson TZ, Duffy JM, Barlow D, et al. Laparoscopic surgery for pelvic pain associated with endometriosis. *Cochrane Database Syst Rev* 2010;(11):CD001300.

Jadoul P, Kitajima M, Donnez O, et al. Surgical treatment of ovarian endometriomas: state of the art? *Fertil Steril* 2012;98:556.

Jänne O, Kauppila A, Kukko E, et al. Estrogen and progestin receptors in endometriosis lesions: comparison with endometrial tissue. *Am J Obstet Gynecol* 1981;141:562.

Jansen RP, Russell P. Nonpigmented endometriosis: clinical, laparoscopic, and pathologic definition. *Am J Obstet Gynecol* 1986;155:1154.

Javert CT. Pathogenesis of endometriosis based on endometrial homeoplasia direct extension, exfoliation and implantation, lymphatic and hematogenous metastasis. *Cancer* 1949;2:399.

Jenkins S, Olive DL, Haney AF. Endometriosis: pathogenetic implications of the anatomic distribution. *Obstet Gynecol* 1986;67:335.

Johnson JV, Roxek MM, Moreno AC, et al. Surgically induced endometriosis does not alter peritoneal factors in the rabbit

model. *Fertil Steril* 1991;56:343.

Johnson NP, Farquhar CM, Crossley S, et al. A double-blinded randomized controlled trial of laparoscopic uterine nerve ablation for women with chronic pelvic pain. *Br J Obstet Gynaecol* 2004;111:950.

Killick S, Elstein M. Pharmacologic production of luteinized unruptured follicles by prostaglandin synthetase inhibitors. *Fertil Steril* 1987;47:773.

Kim CH, Cho YK, Mok JE. Simplified ultralong protocol of gonadotrophin-releasing hormone agonist for ovulation induction with intrauterine insemination in patients with endometriosis. *Hum Reprod* 1996;11:398.

Koninckx PR, Martin DC. Deep endometriosis: a consequence of infiltration or retraction or possibly adenomyosis externa? *Fertil Steril* 1992;58:924.

Koninckx P, Ide P, Vandenbroucke W, et al. New aspects of the pathophysiology of endometriosis and associated infertility. *J Reprod Med* 1980;24:257.

Koninckx PR, Mueleman C, Demeyere S, et al. Suggestive evidence that pelvic endometriosis is a progressive disease, whereas deeply infiltrating endometriosis is associated with pelvic pain. *Fertil Steril* 1991;55:759.

Koninckx PR, Rittinen L, Seppälä M, et al. CA-125 and placental protein 14 concentrations in plasma and peritoneal fluid of women with deeply infiltrating pelvic endometriosis. *Fertil Steril* 1992;57:523.

Koninckx PR, Braet P, Kennedy SH, et al. Dioxin pollution and endometriosis in Belgium. *Hum Reprod* 1994;9:1001.

Koninckx PR, Ussia A, Adamyan L, et al. Deep endometriosis: definition, diagnosis, and treatment. *Fertil Steril* 2012;98:564.

Kuivasaari P, Hippeläinen M, Anttila M, et al. Effect of endometriosis on IVF/ICSI outcome: stage III/IV endometriosis worsens cumulative pregnancy and live-born rates. *Hum Reprod* 2005;20:3130.

Lamb K, Hoffman RG, Nichols TR. Family trait analysis: a case-control study of 43 women with endometriosis and their best friends. *Am J Obstet Gynecol* 1986;154:596.

Laufer MR. Identification of clear vesicular lesions of atypical endometriosis: a new technique. *Fertil Steril* 1997;68:739.

Laufer MR, Goitein L, Bush M, et al. Prevalence of endometriosis in adolescent girls with chronic pelvic pain not responding to conventional therapy. *J Pediatr Adolesc Gynecol* 1997;10:199.

Leach RE, Arneson BW, Ball GD, et al. Absence of antisperm antibodies and factors influencing sperm motility in the cul-del-sac fluid of women with endometriosis. *Fertil Steril* 1990;53:351.

Lee NC, Dicker RC, Rubin GL, et al. Confirmation of the preoperative diagnoses for hysterectomy. *Am J Obstet Gynecol* 1984;150:283.

Lee RB, Stone K, Magelssen D, et al. Presacral neurectomy for chronic pelvic pain. *Obstet Gynecol* 1986;69:517.

Leibson CL, Good AE, Hass SL, et al. Incidence and characterization of diagnosed endometriosis in a geographically defined population. *Fertil Steril* 2004;82:314.

Lemay A, Maheux R, Faure N, et al. Reversible hypogonadism induced by a luteinizing hormone-releasing hormone (LH-RH) agonist (buserelin) as a new therapeutic approach for endometriosis. *Fertil Steril* 1984;41:863.

Lessey BA, Castelbaum AJ, Sawin SW, et al. Aberrant integrin expression in the endometrium of women with endometriosis. *J Clin Endocrinol Metab* 1994;79:643.

Lichten EM, Bombard J. Surgical treatment of primary dysmenorrhea with laparoscopic uterine nerve ablation. *J Reprod Med* 1987;32:37.

Lockhat FB, Emembolu JO, Konje JC. The efficacy, side-effects and continuation rates in women with symptomatic endometriosis undergoing treatment with an intra-uterine administered progestogen (levonorgestrel): a 3 year follow-up. *Hum Reprod* 2005;20:789.

Loh FH, Tan AT, Kumar J, et al. Ovarian response after laparoscopic ovarian cystectomy for endometriotic cysts in 132 monitored cycles. *Fertil Steril* 1999;72:316.

Luciano AA, Hauser KS, Chapler FK, et al. Effects of danazol on plasma lipids and lipoprotein levels in healthy woman and in women with endometriosis. *Am J Obstet Gynecol* 1983;145:422.

Luciano AA, Turksoy RN, Carleo J. Evaluation of oral medroxyprogesterone acetate in the treatment of endometriosis. *Obstet Gynecol* 1988;72:323.

Mahmood TA, Templeton A. Pathophysiology of mild endometriosis: review of literature. *Hum Reprod* 1990;5:765.

Mahmood TA, Templeton A. Folliculogenesis and ovulation in infertile women with mild endometriosis. *Hum Reprod* 1991;6:225.

Mahmood TA, Templeton A. Peritoneal fluid volume and sex steroids in the preovulatory period in mild endometriosis. *Br J Obstet Gynaecol* 1991;98:179.

Mahmood TA, Arumugam K, Templeton AA. Oocyte and follicular fluid characteristics in women with mild endometriosis. *Br J Obstet Gynaecol* 1991;98:573.

Makarainen L, Ronnberg L, Kauppila A. Medroxyprogesterone acetate supplementation diminishes the hypoestrogenic side effects of gonadotropin-releasing hormone agonist without changing its efficacy in endometriosis. *Fertil Steril* 1996;65:29.

Marcoux S, Maheux R, Bérubé S, et al. Laparoscopic surgery in infertile women with minimal or mild endometriosis. *N Engl J Med* 1997;337:217.

Marrs RP. The use of potassium-titanyl-phosphate laser for laparoscopic removal of ovarian endometriomas. *Am J Obstet Gynecol* 1991;164:1622.

Martin D. Laparoscopic treatment of ovarian endometriomas. *Clin Obstet Gynecol* 1991;34:452.

Martin DC, Hubert GD, Levy BS. Depth of infiltration of endometriosis. *J Gynecol Surg* 1989;5:55.

Martin DC, Hubert GD, Vander Zwaag R, et al. Laparoscopic appearances of peritoneal endometriosis. *Fertil Steril* 1989;51:63.

Matorras R, Elorriaga MA, Pijoan JI, et al. Recurrence of endometriosis in women with bilateral adnexectomy (with or without total hysterectomy) who received hormone replacement therapy. *Fertil Steril* 2002;77:303.

Max E, Sweeney WB, Bailey HR, et al. Results of 1,000 single-layer continuous polypropylene intestinal anastomoses. *Am J Surg* 1991;162:461.

McArthur JW, Ulfelder H. The effect of pregnancy upon endometriosis. *Obstet Gynecol Surv* 1965;20:709.

McCausland AM. Hysteroscopic myometrial biopsy: its use in diagnosing adenomyosis and its clinical application. *Am J Obstet Gynecol* 1992;166:1619.

Meldrum DR, Chang RJ, Lu J, et al. "Medical oophorectomy" using a long-acting GnRH agonist: a possible new approach to the treatment of endometriosis. *J Clin Endocrinol Metab* 1982;54:1081.

Melin AS, Lundholm C, Malki N, et al. Hormonal and surgical treatments for endometriosis and risk of epithelial ovarian cancer. *Acta Obstet Gynecol Scand* 2013;92:546.

Meresman GF, Auge L, Baranao RI, et al. Oral contraceptives suppress cell proliferation and enhance apoptosis of eutopic endometrial tissue from patients with endometriosis. *Fertil Steril* 2002;77:1141.

Metzger DA, Olive DL, Stohs GF, et al. Association of endometriosis and spontaneous abortion: effect of control group selection. *Fertil Steril* 1986;45:18.

Meyer R. Über Stand der Frage der Adenomyositis und Adenomyome im Allgemeinen und ins Besondere über Adenomyositis seroepithelialis und Adenomyometritis sarcomatosa. *Zentralbl Gynakol* 1919;36:745.

Mio Y, Toda T, Harada T, et al. Pathophysiology of infertility associated with endometriosis: luteinized unruptured follicle in the early stages of endometriosis as a cause of unexplained infertility. *Am J Obstet Gynecol* 1992;167:251.

Missmer SA, Hankinson SE, Spiegelman D, et al. Reproductive history and endometriosis among premenopausal women. *Obstet Gynecol* 2004;104:965.

Missmer SA, Hankinson SE, Speigelman D, et al. Incidence of laparoscopically confirmed endometriosis by demographic, anthropometric, and lifestyle factors. *Am J Epidemiol* 2004;160:784.

Mittal KR, Barwick KW. Endometrial adenocarcinoma involving adenomyosis without true myometrial invasion is characterized by frequent preceding estrogen therapy, low histologic grades, and excellent prognosis. *Gynecol Oncol* 1993;49:197.

Modugno F, Ness RB, Allen GO, et al. Oral contraceptive use, reproductive history, and risk of epithelial ovarian cancer in women with and without endometriosis. *Am J Obstet Gynecol* 2004;191:733.

Moen M, Bratlie A, Moen T. Distribution of HLA antigens among patients with endometriosis. *Acta Obstet Gynecol Scand Suppl* 1984;123:25.

Moghissi KS, Boyce CR. Management of endometriosis with oral medroxyprogesterone acetate. *Obstet Gynecol* 1976;47:265.

Moore JG, Hibbard LT, Growdon WA, et al. Urinary tract endometriosis: enigmas in diagnosis and management. *Am J Obstet Gynecol* 1979;134:162.

Moore EE, Harger JH, Rock JA, et al. Management of pelvic endometriosis with low-dose danazol. *Fertil Steril* 1981;36:15.

Moore JG, Binstock MA, Growdon WA. The clinical implications of retroperitoneal endometriosis. *Am J Obstet Gynecol* 1988;158:1291.

Morcos RN, Gibbons WE, Findlay WE. Effect of peritoneal fluid on in vitro cleavage of 2-cell mouse embryos: possible role in infertility associated with endometriosis. *Fertil Steril* 1985;44:678.

Murphy AA, Green WR, Bobbie D, et al. Unsuspected endometriosis documented by scanning electron microscopy in visually normal peritoneum. *Fertil Steril* 1986;46:522.

Murphy AA, Schlaff WD, Hassiakos D, et al. Laparoscopic cautery in the treatment of endometriosis-related infertility. *Fertil Steril* 1991;55:246.

Muscato JJ, Haney AF, Weinberg JB. Sperm phagocytosis by human peritoneal macrophages: a possible cause of infertility in endometriosis. *Am J Obstet Gynecol* 1982;144:503.

Muzii L, Marana R, Caruana P, et al. The impact of preoperative gonadotropin-releasing hormone agonist treatment on laparoscopic excision of ovarian endometriotic cysts. *Fertil Steril* 1996;65:1235.

Muzii L, Marana R, Pedulla S, et al. Correlation between endometriosis-associated dysmenorrhea and the presence of typical and atypical lesions. *Fertil Steril* 1997;68:19.

Muzii L, Marana R, Caruana P, et al. Postoperative administration of monophasic combined oral contraceptives after laparoscopic treatment of ovarian endometriomas: a prospective, randomized trial. *Am J Obstet Gynecol* 2000;183:588.

Muzii L, Bellati F, Palaia I, et al. Laparoscopic stripping of endometriomas: a randomized trial on different surgical techniques. Part I: clinical results. *Hum Reprod* 2005;20:1981.

Namnoum AB, Hickman TN, Goodman SB, et al. Incidence of symptom recurrence after hysterectomy for endometriosis. *Fertil Steril* 1995;64:898.

Naples JD, Batt RE, Sadigh A. Spontaneous abortion rate in patients with endometriosis. *Obstet Gynecol* 1981;57:509.

Nezhat C, Nezhat F, Pennington E. Laparoscopic treatment of infiltrative rectosigmoid colon and rectovaginal septum endometriosis by the technique of video laparoscopy and the CO_2 laser. *Br J Obstet Gynaecol* 1992;99:664.

Nezhat C, Seidman DS, Nezhat F, et al. Laparoscopic surgical management of diaphragmatic endometriosis. *Fertil Steril* 1998;69:1048.

Nezhat CH, Seidman DS, Nezhat FR, et al. Long-term outcome of laparoscopic presacral neurectomy for the treatment of central pelvic pain attributed to endometriosis. *Obstet Gynecol* 1998; 91:701.

Nishida M. Relationship between the onset of dysmenorrhea and histologic findings in adenomyosis. *Am J Obstet Gynecol* 1991;165:229.

Noble LS, Simpson ER, John A, et al. Aromatase expression in endometriosis. *J Clin Endocrinol Metab* 1996;81:174.

Nuoja-Huttunen S, Tomas C, Bloigu R, et al. Intrauterine insemination treatment in subfertility: an analysis of factors

affecting outcome. *Hum Reprod* 1999;14:698.

Oak MK, Chantler EN, Williams CA, et al. Sperm survival studies in peritoneal fluid from infertile women with endometriosis and unexplained infertility. *Clin Reprod Fertil* 1985;3:297.

Olive DL, Henderson DY. Endometriosis and müllerian anomalies. *Obstet Gynecol* 1987;69:412.

Olive DL, Lee KL. Analysis of sequential treatment protocols for endometriosis-associated infertility. *Am J Obstet Gynecol* 1986;154:613.

Olive DL, Martin DC. Treatment of endometriosis-associated infertility with CO_2 laser laparoscopy: the use of one- and two-parameter exponential models. *Fertil Steril* 1987;48:18.

Olive DL, Montoya I, Riehl RM, et al. Macrophage-conditioned media enhance endometrial stromal cell proliferation in vitro. *Am J Obstet Gynecol* 1991;164:953.

Oosterlynck DJ, Cornillie FJ, Waer M, et al. Women with endometriosis show a defect in natural killer cell activity resulting in a decreased cytotoxicity to autologous endometrium. *Fertil Steril* 1991;56:45.

Osada H, Silber S, Kakinuma T, et al. Surgical procedure to conserve the uterus for future pregnancy in patients suffering from massive adenomyosis. *Reprod Biomed Online* 2011;22:94.

Pagidas K, Falcone T, Hemmings R, et al. 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.

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.

Parazzini F, Fedele L, Busacca M, et al. Postsurgical medical treatment of advanced endometriosis: results of a randomized clinical trial. *Am J Obstet Gynecol* 1994;171:1205.

Parker JD, Leondires M, Sinaii N. Persistence of dysmenorrhea and nonmenstrual pain after optimal endometriosis surgery may indicate adenomyosis. *Fertil Steril* 2006;86:711.

Paull T, Tedeschi LG. Perineal endometriosis at the site of episiotomy scar. *Obstet Gynecol* 1972;40:28.

Pelage JP, Jacob D, Fazel A, et al. Midterm results of uterine artery embolization for symptomatic adenomyosis: initial experience. *Radiology* 2005;234:948.

Pellegrini C, Gori I, Achtari C, et al. The expression of estrogen receptors as well as GREB1, c-MYC, and cyclin D1, estrogen-regulated genes implicated in proliferation, is increased in peritoneal endometriosis. *Fertil Steril* 2012;98:1200.

Pinkert T, Catlow C, Straus R. Endometriosis of the urinary bladder in a man with prostatic carcinoma. *Cancer* 1979;43:1562.

Pittaway DE, Douglas JW. Serum CA-125 in women with endometriosis and chronic pelvic pain. *Fertil Steril* 1989;51:68.

Pittaway DE, Daniell JF, Maxson WS. Ovarian surgery in an infertility patient as an indication for a short-interval second-look laparoscopy: a preliminary study. *Fertil Steril* 1985;44:611.

Pittaway DE, Vernon C, Fayez JA. Spontaneous abortions in women with endometriosis. *Fertil Steril* 1988;50:711.

Pokras R, Hufnagel VG. Hysterectomy in the United States, 1965-84. *Am J Public Health* 1988;78:852.

Polan ML, DeCherney A. Presacral neurectomy for pelvic pain in infertility. *Fertil Steril* 1980;34:557.

Popovic M, Puchner S, Berzaczy D, et al. Uterine artery embolization for the treatment of adenomyosis: a review. *J Vasc Interv Radiol* 2011;22:901.

Prystowsky JB, Stryker SJ, Ujiki GT, et al. Gastrointestinal endometriosis: incidence and indications for resection. *Arch Surg* 1988;123:855.

Punnonen R, Soderstrom P, Alanen A. Isthmic tubal occlusion: etiology and histology. *Acta Eur Fertil* 1984;15:39.

Ranney B. Endometriosis IV: hereditary tendency. *Obstet Gynecol* 1971;37:734.

Redwine DB. The distribution of endometriosis in the pelvis by age groups and fertility. *Fertil Steril* 1987;47:173.

Redwine DB. Peritoneal blood painting: an aid in the diagnosis of endometriosis. *Am J Obstet Gynecol* 1989;161:865.

Redwine DB. Endometriosis persisting after castration: clinical characteristics and results of surgical management. *Obstet Gynecol* 1994;83:405.

Redwine DB. Ovarian endometriosis: a marker for more extensive pelvic and intestinal disease. *Fertil Steril* 1999;72:310.

Ret Davalos ML, De Cicco C, D'Hoore A, et al. Outcome after rectum resection: a review for gynecologists. *J Minim Invasive Gynecol* 2007;12:33.

Rezai N, Ghodgaonkar RB, Zacur HA, et al. Cul-de-sac fluid in women with endometriosis: fluid volume, protein and prostanoid concentration during the periovulatory period—days 13 to 18. *Fertil Steril* 1987;48:29.

Rier SE, Martin DC, Bowman RE, et al. Endometriosis in rhesus monkeys (*Macaca mulatta*) following chronic exposure to 2,3, 7,8-tetrachloro-dibenzo-p-dioxin. *Fundam Appl Toxicol* 1993; 21:433.

Riva HL, Kawasaki DM, Messinger AJ. Further experience with norethynodrel in treatment of endometriosis. *Obstet Gynecol* 1962;19:111.

Rivlin ME, Miller JD, Krueger RP, et al. Leuprolide acetate in the management of ureteral obstruction caused by endometriosis. *Obstet Gynecol* 1990;75:532.

Rock JA, Guzick DS, Jones HW Jr. The efficacy of accessory surgical intervention in conjunction with resection and fulguration of endometriosis. *Infertility* 1981;4:193.

Rock JA, Guzick DS, Sengos C, et al. Evaluation of pregnancy success with respect to extent of disease as categorized using contemporary classification systems. *Fertil Steril* 1981;35:131.

Rock JA, Parmley TH, King TM, et al. Endometriosis and the development of tuboperitoneal fistulas after tubal ligation. *Fertil Steril* 1981;35:16.

Rock JA, Dubin NH, Ghodgaonkar RB, et al. Cul-de-sac fluid in women with endometriosis: fluid volume and prostanoid concentration during the proliferative phase of the cycle—days 8-12. *Fertil Steril* 1982;37:747.

Romualdi D, Franco Zannoni G, Lanzone A, et al. Follicular loss in endoscopic surgery for ovarian endometriosis: quantitative and qualitative observations. *Fertil Steril* 2011;96:374.

Rown J, Pan A, Hart RJ. Gonadotrophin-releasing hormone analogues for pain associated with endometriosis. *Cochrane Database Syst Rev* 2010;(12):CD008475.

Ruggi G. Della sympatectamia al collo ed ale adome. *Policlinico* 1899;1:193.

Sakamoto A. Subserosal adenomyosis: a possible variant of pelvic endometriosis. *Am J Obstet Gynecol* 1991;165:198.

Saleh A, Tulandi T. Reoperation after laparoscopic treatment of ovarian endometriomas by excision and by fenestration. *Fertil Steril* 1999;72:322.

Sallam HN, Garcia-Velasco JA, Dias S, et al. Long-term pituitary down-regulation before in vitro fertilization (IVF) for women with endometriosis. *Cochrane Database Syst Rev* 2006;(1):CD004635. doi: 10.1002/14651858.CD004635.pub2

Sampson JA. Benign and malignant endometrial implants in peritoneal cavity, and their relation to certain ovarian tumors. *Surg Gynecol Obstet* 1924;38:287.

Sampson JA. Peritoneal endometriosis due to menstrual dissemination of endometrial tissue into the peritoneal cavity. *Am J Obstet Gynecol* 1925;14:422.

Sangi-Haghpeykar H, Poindexter AN. Epidemiology of endometriosis among parous women. *Obstet Gynecol* 1995;85:983.

Schenken RS, Asch RH, Williams RF, et al. Etiology of infertility in monkeys with endometriosis: luteinized unruptured follicles, luteal phase defects, pelvic adhesions and spontaneous abortions. *Fertil Steril* 1984;41:122.

Schenken RS, Williams RF, Hodgen GD. Effect of pregnancy on surgically induced endometriosis in cynomolgus monkeys. *Am J Obstet Gynecol* 1987;157:1392.

Schlaff WD, Dugoff L, Damewood MD, et al. Megestrol acetate for treatment of endometriosis. *Obstet Gynecol* 1990;75:646.

Schmidt CL. Endometriosis: a reappraisal of pathogenesis and treatment. *Fertil Steril* 1985;44:157.

Schneider VL, Schneider A, Reed KL, et al. Comparison of Doppler with two-dimensional sonography and CA-125 for prediction of malignancy of pelvic masses. *Obstet Gynecol* 1993;81:983.

Schweppe KW, Wynn RM. Ultrastructural changes in endometriotic implants during the menstrual cycle. *Obstet Gynecol* 1981;58:465.

Schweppe KW, Wynn RM, Beller FK. Ultrastructural comparison of endometriotic implants and eutopic endometrium. *Am J Obstet Gynecol* 1984;148:1024.

Seibel MM, Berger MJ, Weinstein FG, et al. The effectiveness of danazol on subsequent fertility in minimal endometriosis. *Fertil Steril* 1982;38:534.

Sekiba K, Obstetrics and Gynecology Adhesion Prevention Committee. Use of Interceed (TC7) absorbable adhesion barrier to reduce postoperative adhesion reformation in infertility and endometriosis surgery. *Obstet Gynecol* 1992;79:518.

Serta RT, Rufo S, Seibel MM. Minimal endometriosis and intrauterine insemination: does controlled ovarian hyperstimulation improve pregnancy rates? *Obstet Gynecol* 1992;80:37.

Shakiba K, Bena JF, McGill KM, et al. Surgical treatment of endometriosis: a 7-year follow up on the requirement for further surgery. *Obstet Gynecol* 2008;111:1285.

Shook TE, Nyberg LM. Endometriosis of the urinary tract. *Urology* 1988;31:1.

Simpson JL, Elias S, Malinak LR, et al. Heritable aspects of endometriosis. I. Genetic studies. *Am J Obstet Gynecol* 1980;137:325.

Simpson JL, Malinak LR, Elias S, et al. HLA associations in endometriosis. *Am J Obstet Gynecol* 1984;148:395.

Somigliana E, Vercellini P, Viganc P, et al. Should endometriomas be treated before IVF-ICSI cycles? *Hum Reprod Update* 2006;12:57.

Somigliana E, Vercellini P, Vigano P, et al. Non-invasive diagnosis of endometriosis: the goal or own goal? *Hum Reprod* 2010;25:1863.

Steele RW, Dmowski WP, Marmer DJ. Immunologic aspects of human endometriosis. *Am J Reprod Immunol* 1984;6:33.

Stephansson O, Kieler H, Granath F, et al. Endometriosis, assisted reproduction technology, and risk of adverse pregnancy outcome. *Hum Reprod* 2009;24:2341.

Stock RJ. Postsalpingectomy endometriosis: a reassessment. *Obstet Gynecol* 1982;60:560.

Stovall TG, Ling FW, Crawford DA. Hysterectomy for chronic pelvic pain of presumed uterine etiology. *Obstet Gynecol* 1990;75:676.

Strathy JH, Molgaard CA, Coulam CB, et al. Endometriosis and infertility: a laparoscopic study of endometriosis among fertile and infertile women. *Fertil Steril* 1982;38:667.

Stripling MC, Martin DC, Chatman DL, et al. Subtle appearance of pelvic endometriosis. *Fertil Steril* 1988;49:425.

Sueldo CE, Lambert H, Steinleitner A, et al. The effect of peritoneal fluid from patients with endometriosis on murine sperm-oocyte interaction. *Fertil Steril* 1987;48:697.

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.

Surgical Membrane Study Group. Prophylaxis of pelvic sidewall adhesions with Gore-Tex surgical membrane: a multicenter clinical investigation. *Fertil Steril* 1992;57:921.

Surrey ES, Halme J. Effect of platelet-derived growth factor on endometrial stromal cell proliferation in vitro: a model for endometriosis? *Fertil Steril* 1991;56:672.

Surrey ES, Gambone JC, Lu JK, et al. The effects of combining norethindrone with a gonadotropin-releasing hormone agonist in the treatment of symptomatic endometriosis. *Fertil Steril* 1990;53:620.

Surrey ES, Voigt B, Fournet N, et al. Prolonged gonadotropin-releasing hormone agonist treatment of symptomatic endometriosis: the role of cyclic sodium etidronate and low-dose norethindrone “addback” therapy. *Fertil Steril* 1995;63:747.

Sutton CJ, Ewen SP, Whitelaw N, et al. 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.

Suzuki T, Ixumi S, Matsubayashi H, et al. Impact of ovarian endometrioma on oocytes and pregnancy outcome in in vitro fertilization. *Fertil Steril* 2005;83:908.

Takahashi K, Okada S, Ozaki T, et al. Diagnosis of pelvic endometriosis by “fat-saturation” technique. *Fertil Steril* 1994;62:973.

Tamaya T, Motoyama T, Ohono Y, et al. Steroid receptor levels and histology of endometriosis and adenomyosis. *Fertil Steril* 1979;31:396.

Tanmahasamut P, Rattanachaiyanont M, Angsuwathana S, et al. Postoperative levonorgestrel-releasing intrauterine system for pelvic endometriosis-related pain. *Obstet Gynecol* 2012;119:519.

Te Linde RW, Scott RB. Experimental endometriosis. *Obstet Gynecol* 1978;130:569.

Telimaa S. Danazol and medroxyprogesterone acetate inefficacious in the treatment of infertility in endometriosis. *Fertil Steril* 1988;50:872.

Thomas EJ, Lenton EA, Cooke ID. Follicle growth patterns and endocrinological abnormalities in infertile women with minor degrees of endometriosis. *Br J Obstet Gynaecol* 1986;93:852.

Tinkanen H, Kujansuu E. In vitro fertilization in patients with ovarian endometriomas. *Acta Obstet Gynecol Scand* 2000;79:119.

Tjaden B, Schlaff WD, Kimball A, et al. The efficacy of presacral neurectomy for the relief of midline dysmenorrhea. *Obstet Gynecol* 1990;76:89.

Togashi K, Ozasa H, Konishi I, et al. Enlarged uterus: differentiation between adenomyosis and leiomyoma with MR imaging. *Radiology* 1989;171:531.

Tseng JF, Ryan IP, Milam TD, et al. Interleukin-6 secretion in vitro is upregulated in ectopic and eutopic endometrial stromal cells from women with endometriosis. *J Clin Endocrinol Metab* 1996;81:1118.

Tulandi T, Al-Took S. Reproductive outcome after treatment of mild endometriosis with laparoscopic excision and electrocoagulation. *Fertil Steril* 1998;69:229.

Tulandi T, Mouchawar M. Treatment-dependent and treatment-independent pregnancy in women with minimal and mild endometriosis. *Fertil Steril* 1991;56:790.

Tummon IS, Maclin VM, Radwanska E, et al. Occult ovulatory dysfunction in women with minimal endometriosis and unexplained infertility. *Fertil Steril* 1988;50:716.

Tummon IS, Colwell KA, MacKinnoa CJ, et al. Abbreviated endometriosis-associated infertility correlates with in vitro fertilization success. *J In Vitro Fert Embryo Transf* 1991;8:149.

Tummon IS, Asher LJ, Martin JS, et al. Randomized controlled trial of superovulation and insemination for infertility associated with minimal or mild endometriosis. *Fertil Steril* 1997;68:8.

Uchima FD, Edery M, Iguchi T, et al. Growth of mouse endometrial luminal epithelial cells in vitro: functional integrity of the oestrogen receptor system and failure of oestrogen to induce proliferation. *J Endocrinol* 1991;128:115.

Uohara JK, Kovara TY. Endometriosis of the appendix: report of 12 cases and review of the literature. *Am J Obstet Gynecol* 1975;121:423.

Vaughan Williams CA, Oak MK, Elstein M. Cyclical gonadotrophin and progesterone secretion in women with minimal endometriosis. *Clin Reprod Fertil* 1986;4:259.

Vercellini P, Fedele L, Bianchi S, et al. Pelvic denervation for chronic pain associated with endometriosis: fact or fancy? *Am J Obstet Gynecol* 1991;165:745.

Vercellini P, Vendola N, Bocciolone L, et al. Reliability of visual diagnosis of ovarian endometriosis. *Fertil Steril* 1991;56:1198.

Vercellini P, De Giorgi O, Oldani S, et al. Depot medroxyprogesterone acetate versus an oral contraceptive combined with very-lowdose danazol for long-term treatment of pelvic pain associated with endometriosis. *Am J Obstet Gynecol* 1996;175:396.

Vercellini P, Chapron C, Fedele L, et al. Evidence for asymmetric distribution of sciatic nerve endometriosis. *Obstet Gynecol* 2003;102:383.

Vercellini P, Frontino G, De Giorgi O. Continuous use of an oral contraceptive for endometriosis-associated recurrent dysmenorrhea that does not respond to a cyclic pill regimen. *Fertil Steril* 2003;80:560.

Vercellini P, Chapron C, Fedele L, et al. Evidence for asymmetric distribution of lower intestinal endometriosis. *Br J Obstet Gynaecol* 2004; 111:1213.

Vercellini P, Pietropaolo G, De Giorgi O, et al. Treatment of symptomatic rectovaginal endometriosis with an estrogen-progestogen combination versus low-dose norethindrone acetate. *Fertil Steril* 2005;84:1375.

Vercellini P, Fedele L, Aimi G, et al. Reproductive performance, pain recurrence and disease relapse after conservative surgical treatment for endometriosis: the predictive value of the current classification system. *Hum Reprod* 2006;21:2679.

Vercellini P, Pietropaolo G, De Giorgi O, et al. Reproductive performance in infertile women with rectovaginal endometriosis: is surgery worthwhile? *Am J Obstet Gynecol* 2006;195:1303.

Vercellini P, Abbiati A, Vigano' P, et al. Asymmetry in distribution of diaphragmatic endometriosis lesions: evidence in favour of the menstrual reflux theory. *Hum Reprod* 2007;22:2359.

Vercellini P, Barbara G, Buggio L, et al. Effect of patient selection on estimate of reproductive success after surgery for rectovaginal endometriosis: literature review. *Reprod Biomed Online* 2012;24:389.

Vercellini P, Somigliana E, Consonni D, et al. Surgical versus medical treatment for endometriosis-associated deep dyspareunia: I. Effect on pain during intercourse and patient satisfaction. *Hum Reprod* 2012;27:3450.

Vercellini P, De Matteis S, Somigliana E, et al. Long-term adjuvant therapy for the prevention of postoperative endometrioma recurrence: a systematic review and meta-analysis. *Acta Obstet Gynecol Scand* 2013;92:8.

Verkauf BS. The incidence, symptoms, and signs of endometriosis in fertile and infertile women. *J Fla Med Assoc* 1987;74:671.

Vernon MW, Beard JS, Graves K, et al. Classification of endometriotic implants by morphologic appearance and capacity to synthesize prostaglandin F. *Fertil Steril* 1986;46:801.

Vigano P, Vercellini P, Di Blasio AM, et al. Deficient antiendometrium lymphocyte-mediated cytotoxicity in patient with endometriosis. *Fertil Steril* 1991;56:894.

von Rokitansky C. Ueber Uterusdrusen-Neubildung im Uterus und Varialsarcomen. *Zkk Gesellsch d Aerzte zu Wien* 1860;37:577.

Wang PH, Liu WM, Fuh JL, et al. Comparison of surgery alone and combined surgical-medical treatment in the management of symptomatic uterine adenomyoma. *Fertil Steril* 2009;92:876.

Wardle PG, Hull MG. Is endometriosis a disease? *Baillieres Clin Obstet Gynaecol* 1993;7:673.

Weed JC, Arquembourg PC. Endometriosis: can it produce an autoimmune response resulting in infertility? *Clin Obstet Gynecol* 1980;23:885.

Wentz AC. Premenstrual spotting: its association with endometriosis but not luteal phase inadequacy. *Fertil Steril* 1980;33:605.

Werbrouck E, Spiessens C, Meuleman C, et al. 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.

Wespi HJ, Kletzhändler M. Uber Narbenendometriosen. *Mschr Geburtsh Gynakol* 1940;111:169.

Wheeler JM, Malinak LR. Recurrent endometriosis: incidence, management, and prognosis. *Am J Obstet Gynecol* 1983;146:247.

Wheeler JM, Johnston BM, Malinak LR. The relationship of endometriosis to spontaneous abortion. *Fertil Steril* 1983;39:656.

Wihemsson L, Lindblom B, Wiqvist N. The human uterotubal junction: contractile patterns of different smooth muscle layers and the influence of prostaglandin E_2, prostaglandin $F_{2\alpha}$ and prostaglandin I_2 in vitro. *Fertil Steril* 1979;32:303.

Wilcox LS, Koonin LM, Pokras R, et al. Hysterectomy in the United States, 1988-1990. *Obstet Gynecol* 1994;83:549.

Wood C, Maher P, Hill D. Biopsy diagnosis and conservative surgical treatment of adenomyosis. *Aust N Z J Obstet Gynaecol* 1993;33:319.

Wright J, Lotfallah H, Jones K, et al. A randomized trial of excision versus ablation for mild endometriosis. *Fertil Steril*

2005;83:1830.

Yanushpolsky EH, Best CL, Jackson KV, et al. Effects of endometriomas on oocyte quality, embryo quality, and pregnancy rates in in vitro fertilization cycles: a prospective, case-controlled study. *J Assist Reprod Genet* 1998;15:193.

Yaron Y, Peyser MR, Samuel D, et al. Infected endometriotic cysts secondary to oocyte aspiration for in-vitro fertilization. *Hum Reprod* 1994;9:1759.

Ylikorkla O, Koskimies A, Laathainen T, et al. Peritoneal fluid prostaglandins in endometriosis, tubal disorders, and unexplained infertility. *Obstet Gynecol* 1984;63:616.

Young MD, Blackmore WP. The use of danazol in the management of endometriosis. *J Int Med Res* 1977;5(suppl 3):86.

Zanagnolo VL, Beck R, Schlaff WD, et al. Time-related effects of gonadotropin-releasing hormone analog treatment in experimentally induced endometriosis in the rat. *Fertil Steril* 1991;55:411.

Zullo F, Palomba S, Zupi E, et al. Effectiveness of presacral neurectomy in women with severe dysmenorrhea caused by endometriosis who were treated with laparoscopic conservative surgery: a 1-year prospective randomized double-blind controlled trial. *Am J Obstet Gynecol* 2003;189:5.