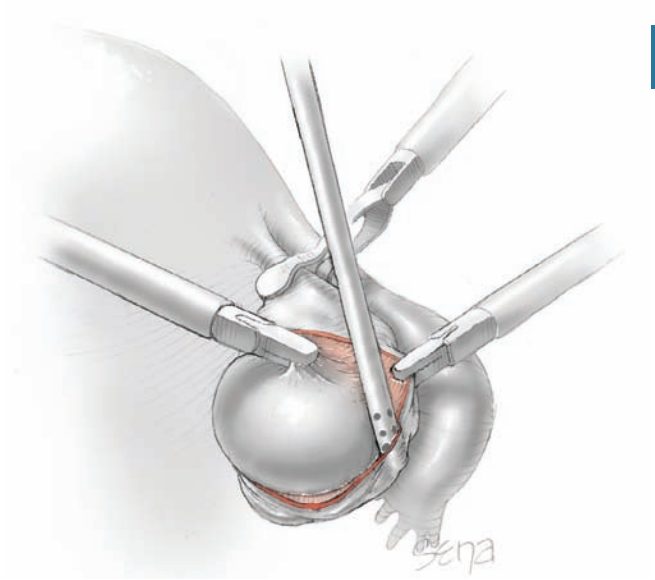


CHAPTER 10

Endometriosis

Endometriosis is a common benign gynecologic disorder defined as the presence of endometrial glands and stroma outside of the normal location. First identified in the mid-nineteenth century (Von Rokitansky, 1860), endometriosis is most commonly found on the pelvic peritoneum but may also be found on the ovaries, rectovaginal septum, ureter, and rarely in the bladder, pericardium, and pleura (Comiter, 2002; Giudice, 2004). Endometriosis is a hormonally dependent disease and as a result is chiefly found in reproductive-aged women. Endometrial tissue located within the myometrium is termed adenomyosis and is discussed in greater detail in Chapter 9 (p. 208).

The incidence of endometriosis is difficult to quantify, as women with the disease are often asymptomatic, and imaging modalities have low sensitivities for diagnosis. Women with endometriosis may be asymptomatic, subfertile, or suffer varying degrees of pelvic pain. The primary method of diagnosis is laparoscopy, with or without biopsy for histologic diagnosis (Kennedy, 2005; Marchino, 2005). Using this standard, investigators have reported the annual incidence of surgically diagnosed endometriosis to be 1.6 cases per 1,000 women aged between 15 and 49 years (Houston, 1987). In asymptomatic women, the prevalence of endometriosis ranges from 2 to 22 percent, depending on the population studied (Eskenazi, 1997; Mahmood, 1991; Moen, 1997). However, because of its link with infertility and pelvic pain, endometriosis is notably more prevalent in subpopulations of women with these complaints. In infertile women, the prevalence has been reported to be between 20 to 50 percent and in those with pelvic pain, 40 to 50 percent (Balasch, 1996; Eskenazi, 2001).

PATHOPHYSIOLOGY

Etiology

Although the definitive cause of endometriosis remains unknown, several theories with supporting evidence have been described.

Retrograde Menstruation

The earliest and most widely accepted theory relates to retrograde menstruation through the fallopian tubes with subsequent dissemination of endometrial tissue within the peritoneal cavity (Sampson, 1927). Refluxed endometrial fragments adhere to and invade the peritoneal mesothelium and develop a blood supply, which leads to continued implant survival and growth (Giudice, 2004).

First proposed in the 1920s, this theory has gained support with the findings of greater volumes of refluxed blood and endometrial tissue in the pelves of women with endometriosis (Halme, 1984). Uterine hyperperistalsis and dysperistalsis have been noted in women with endometriosis and resulted in subsequent increased endometrial reflux (Leyendecker, 2004). Additionally, D'Hooghe (1997) demonstrated that surgical obliteration of the cervical outflow tract in baboons leads to the induction of endometriosis. Women with amenorrhea due to outflow tract obstruction similarly have a high incidence of endometriosis, which is often relieved by correction of the obstruction (Sanfilippo, 1986).

Lymphatic or Vascular Spread

Evidence also supports the concept of endometriosis originating from aberrant lymphatic or vascular spread of endometrial tissue (Ueki, 1991). Findings of endometriosis in unusual locations, such as the perineum or groin, bolster this theory (Mitchell, 1991; Pollack, 1990). The retroperitoneal region has abundant lymphatic circulation. Thus, cases in which no peritoneal implants are found, but solely isolated retroperitoneal lesions are noted, suggest lymphatic spread (Moore, 1988). Additionally, the tendency of endometrial adenocarcinoma to spread via the lymphatic route indicates the ease at which endometrium can be transported by this route (McMeekin, 2003). Although this theory remains attractive, few studies have experimentally evaluated this form of endometriosis transmission.

Coelomic Metaplasia

The theory of coelomic metaplasia suggests that the parietal peritoneum is a pluripotential tissue that can undergo metaplastic transformation to tissue histologically indistinguishable from normal endometrium. Because the ovary and the progenitor of the endometrium, the müllerian ducts, are both derived from coelomic epithelium, metaplasia may explain the development of ovarian endometriosis. In addition, the theory has been extended to include the peritoneum because of the proliferative and differentiation potential of the peritoneal mesothelium. This theory is attractive in instances of endometriosis in the absence of menstruation, such as in premenarchal and postmenopausal women, and in males treated with estrogen and orchiectomy for prostatic carcinoma (Dictor, 1988; Pinkert, 1979). However, the absence of endometriosis in other tissues derived from coelomic epithelium argues against this theory.

Induction Theory

Finally, the induction theory proposes that some hormonal or biologic factor(s) may induce the differentiation of undifferentiated cells into endometrial tissue (Vinatier, 2001). These substances may be exogenous or released directly from the endometrium (Bontis, 1997). In vitro studies have demonstrated the potential for ovarian surface epithelium, in response to estrogens, to undergo transformation to form endometriotic lesions (Matsuura, 1999). Although many putative factors have been identified, their propensity to cause endometriosis in some women but not in others demonstrates the still unidentified etiology of this disease.

Hormonal Dependence

One factor that has been definitively established as having a causative role in the development of endometriosis is estrogen (Gurates, 2003). Although most estrogen in women is produced directly by the ovaries, numerous peripheral tissues are also known to create estrogens through aromatization of ovarian and adrenal androgens. Endometriotic implants have been shown to express aromatase and 17β-hydroxysteroid dehydrogenase type 1, the enzymes responsible for conversion of androstenedione to estrone and of estrone to estradiol, respectively. Implants, however, are deficient in 17β-hydroxysteroid dehydrogenase type 2, which inactivates estrogen (Kitawaki, 1997; Zeitoun, 1998). This enzymatic combination ensures that implants will be exposed to an estrogenic environment. Furthermore, the locally produced estrogens within endometriotic lesions may exert their biologic effect within the same tissue or cell in which they are produced, a process referred to as *intracrinology*.

In contrast, normal endometrium does not express aromatase and has elevated levels of 17β-hydroxysteroid dehydrogenase type 2 in response to progesterone, which ensures that estrogenic effects are attenuated in response to progesterone (Satyaswaroop, 1982). As a result, progesterone antagonizes the estrogen effects in normal endometrium during the luteal phase of the menstrual cycle. Endometriosis, however, manifests a relative progesterone-resistant state, which prevents attenuation of the estrogen stimulation in this tissue (Attia, 2000).

Prostaglandin E_2 (PGE_2) is the most potent inducer of aromatase activity in endometrial stromal cells, acting through the prostaglandin EP_2 receptor subtype (Noble, 1997; Zeitoun, 1999). Estradiol produced in response to the increased aromatase activity subsequently augments PGE_2 production by stimulating cyclooxygenase type 2 (COX-2) enzyme in uterine endothelial cells (Fig. 10-1) (Bulun, 2002; Gurates, 2003). This creates a positive feedback loop and potentiates the estrogenic effects on proliferation of endometriosis. This concept of locally produced estrogens and intracrine estrogen action in endometriosis serves as the basis for pharmacologic inhibition of aromatase activity in cases of endometriosis that are refractory to standard therapy.

Role of the Immune System

Although most women experience retrograde menstruation, which may play a role in the seeding and establishment of implants, few develop endometriosis. Menstrual tissue and endometrium that is refluxed into the peritoneal cavity is usually cleared by immune cells such as macrophages, natural killer (NK) cells, and lymphocytes. For this reason, immune system dysfunction is one likely mechanism for the genesis of

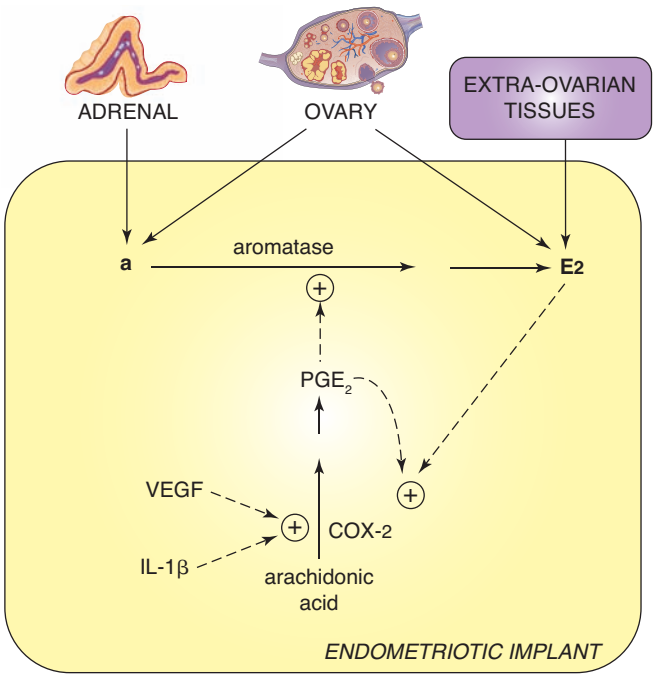


FIGURE 10-1 Activation of COX-2 in endometrial stromal cells results in upregulation of PGE_2, a potent stimulator of aromatase in endometrial stromal cells. Aromatase activity results in intracellular aromatization of androgens to increase intracellular estradiol via an intracrine mechanism. a = androgen; E_2 = estradiol; COX-2 = cyclooxygenase 2; PGE_2 = prostaglandin E2; IL-1β = interleukin 1β; VEGF = vascular endothelial growth factor.

endometriosis in the presence of retrograde menstruation (Seli, 2003). Impaired cellular and humoral immunity and altered growth factor and cytokine signaling have each been identified in endometriotic tissues.

Macrophages act as scavenger cells in various tissues and increased numbers have been found in the peritoneal cavity of women with endometriosis (Haney, 1981; Olive, 1985b). Although this increased population might logically act to suppress endometrial proliferation, macrophages in these women, however, have a stimulatory effect on endometriotic tissue. In one study, circulating monocytes obtained from women with endometriosis enhanced the in vitro proliferation of cultured endometrial cells, whereas the monocytes from women without endometriosis had the opposite effect (Braun, 1994). It appears therefore that impaired function, and not population size, of macrophages allows endometriotic tissue proliferation.

Natural killer cells are immune cells that have cytotoxic activity against foreign cells. Although the number of NK cells is unaltered in the peritoneal fluid of women with endometriosis, decreased NK cell cytotoxicity against endometrium has been demonstrated (Ho, 1995; Wilson, 1994). Specifically, the peritoneal fluid from women with endometriosis has been found to suppress NK cell activity, suggesting that soluble factors may play a role in NK cell suppression (Oosterlynck, 1993).

Cellular immunity may also be disordered in women with endometriosis, and T lymphocytes are implicated. For example, in women with endometriosis compared with unaffected women, total lymphocyte numbers or helper/suppressor subpopulation ratios do not differ in peripheral blood, but peritoneal fluid lymphocyte numbers are increased (Steele, 1984). Also, the cytotoxic activity of T lymphocytes against autologous endometrium in affected women is impaired (Gleicher, 1984).

Humoral immunity has also been shown to be altered in affected women and is suggested to play a role in the development of endometriosis. Endometrial antibodies of the IgG class are more frequently detected in the serum of women with endometriosis (Odukoya, 1995). One study also identified IgG and IgA autoantibodies against endometrial and ovarian tissues in the sera and in cervical and vaginal secretions of affected women (Mathur, 1982). These results suggest that endometriosis may be, in part, an autoimmune disease. This may explain some of the factors influencing lower pregnancy and in vitro fertilization (IVF) implantation rates in women with endometriosis (Dmowski, 1995).

Cytokines are small, soluble immune factors involved in paracrine and autocrine signaling of other immune cells. Numerous cytokines, especially interleukins, have been implicated in the pathogenesis of endometriosis. Increased levels of interleukin-1β (IL-1β) have been identified in the endometrial fluid of those with endometriosis (Mori, 1991). Moreover, IL-6 has been shown to be increased in endometrial stromal cells of affected women (Tseng, 1996). Accordingly, IL-6 serum levels greater than 2 pg/mL and tumor necrosis factor-α (TNF-α) peritoneal fluid levels more than 15 pg/mL may be used to discriminate between those with or without endometriosis (Bedaiwy, 2002). Similarly, IL-8 peritoneal fluid levels are elevated in affected individuals and stimulate proliferation of endometrial stromal cells (Arici, 1996; Arici, 1998; Ryan, 1995).

Other noninterleukin cytokines and growth factors are associated with the pathogenesis of endometriosis. For example, both monocyte chemoattractant protein-1 (MCP-1) and RANTES (regulated on activation, normal T-cell expressed and secreted) are chemoattractant for monocytes. Levels of these cytokines are increased in the peritoneal fluid of those with endometriosis and positively correlate with disease severity (Arici, 1997; Khorram, 1993). In addition, vascular endothelial growth factor (VEGF) is an angiogenic growth factor, which is upregulated by estradiol in endometrial stromal cells and peritoneal fluid macrophages. Levels of this factor are increased in the peritoneal fluid of affected women (McLaren, 1996). Although the exact role of these cytokines is not clear, perturbations in their expression and activity further support an immunologic role in the pathogenesis of endometriosis.

RISK FACTORS

Familial Clustering

There is evidence of a familial inheritance pattern for endometriosis. Although no apparent mendelian genetics inheritance pattern has been identified, the increased incidence in first-degree relatives suggests a polygenic/multifactorial inheritance pattern. For example in a genetic study of women with endometriosis, Simpson and his colleagues (1980) noted that

5.9 percent of female siblings and 8.1 percent of the mothers of affected women had endometriosis compared with 1 percent of the husband's female first-degree relatives. Further research has revealed that women with endometriosis and an affected first-degree relative were more likely to have severe endometriosis (61%) than women without an affected first-degree relative (24 percent) (Malinak, 1980). Moreover, Stefansson and his associates (2002), in their analysis of a large population-based study in Iceland, demonstrated a higher kinship coefficient in women with endometriosis compared with matched controls. In this study, the risk ratios were 5.2 for sisters and 1.56 for cousins. Studies have also demonstrated concordance for endometriosis in monozygotic twin-pairs, suggesting a familial/genetic basis (Hadfield, 1997; Treloar, 1999).

Genetic Mutations and Polymorphisms

Rates of familial clustering noted above suggest polygenic inheritance and several candidate genes have been investigated. Two approaches to identify genes involved with endometriosis include sibling-pair linkage analysis and high-throughput analysis of gene expression patterns using microarray technology.

The largest study to date, examining over 1,000 affected sister-pair families, has identified a region on chromosome 10q26 that demonstrates significant linkage in these sisters affected with endometriosis (Treloar, 2005). This study also revealed a smaller linkage on chromosome 20p13. Two candidate genes within or near this locus have been identified. One such gene is *EMX2*, a transcription factor necessary for reproductive tract development. It has been shown to be aberrantly expressed in the endometrium of women with endometriosis (Daftary, 2004). The second gene is *PTEN*, a tumor suppressor gene implicated in the malignant transformation of ovarian endometriosis (Bischoff, 2000). Studies are currently underway to further determine the role of these genes in endometriosis.

Microarray technology has been used to analyze differences in gene expression in eutopic endometrium (endometrium found normally lining the endometrial cavity) from women without endometriosis compared with that from women with endometriosis (Kao, 2003). Researchers found that several genes were differentially regulated in the eutopic endometrium in women with endometriosis. These include those coding for interleukin 15, glycodelin, Dickkopf-1, semaphorin E, aromatase, progesterone receptor, and various angiogenic factors. Although some of these genes have previously been shown to play a role in endometriosis, others have not been implicated until recently, and their role remains to be elucidated.

Several other genes have been identified, through genetic mutations, polymorphisms, or differential gene expression, to be associated with endometriosis. Although investigations have demonstrated polymorphisms of these genes occur with greater frequency in women suffering with endometriosis, their role in disease causation has not been determined. A more thorough review of candidate genes in the epidemiology of endometriosis can be found at the website http://www.well.ox.ac.uk/~krinaz/genepi_endo.htm.

Anatomic Defects

Reproductive outflow tract obstruction can predispose to development of endometriosis, likely through exacerbation of retrograde menstruation (Breech, 1999). Accordingly, endometriosis has been identified in women with noncommunicating uterine horn, imperforate hymen, and transverse vaginal septum (see Chap. 18, p. 413) (Schattman, 1995). Because of this association, diagnostic laparoscopy to identify and treat endometriosis is suggested at the time of corrective surgery for many of these anomalies. Repair of such anatomic defects is thought to decrease the risk of developing endometriosis (Joki-Erkkila, 2003; Rock, 1982).

Environmental Toxins

There have been numerous studies suggesting that exposure to environmental toxins may play a role in the development of endometriosis. The toxins most commonly implicated are 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and other dioxin-like compounds (Rier, 2003). In binding, TCDD activates the aryl hydrocarbon receptor. This receptor functions as a basic transcription factor, and similarly to the steroid hormone receptor family of proteins, leads to the transcription of various genes. As a result, TCDD and other dioxin-like compounds may stimulate endometriosis through increases in interleukin levels, activation of cytochrome P-450 enzymes such as aromatase, and alterations in tissue remodeling. Moreover, TCDD in conjunction with estrogen appears to stimulate endometriosis formation, and TCDD appears to block the progesterone-induced regression of endometriosis (Rier, 2003).

In the environment, TCDD and dioxin-like compounds are waste by-products of industrial processing. Ingestion of contaminated foods or accidental contact is the most common method of exposure. Although endometriosis and TCDD were initially linked in primates, human studies also note a higher prevalence of endometriosis in women with high breast milk dioxin concentrations (Koninckx, 1994; Rier, 1993). In addition, subsequent studies have demonstrated higher serum dioxin levels in infertile women with endometriosis compared with those in infertile controls (Mayani, 1997).

CLASSIFICATION AND LOCATION OF ENDOMETRIOSIS

Classification System

The primary method of endometriosis diagnosis is visualization of endometriotic lesions by laparoscopy, with or without histologic confirmation. Since the extent of endometriosis can vary widely between individuals, attempts have been made to develop a standardized classification to objectively assess the extent of endometriosis. The initial classification system attempted to provide a scoring system to describe the pathologic extent of disease. Initially created by the American Fertility Society (AFS) 1979, which has been subsequently renamed the American Society for Reproductive Medicine (ASRM), this classification system was subsequently revised by the AFS (American Fertility Society, 1985). This revision

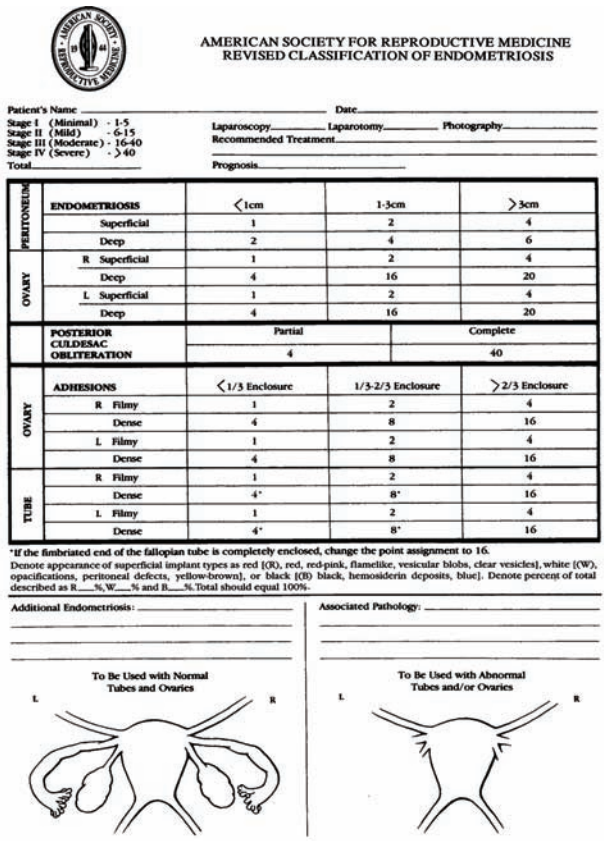
allowed for a three-dimensional view of endometriosis and differentiated between superficial and invasive disease. Unfortunately, studies revealed that both of these classification systems did not provide any prognostic information with respect to subsequent fertility or severity of pelvic pain (Guzick, 1982, 1997). For example, one study has suggested that pain correlates with depth of invasion, which is not a significant factor in the scoring system (Koninckx, 1991).

In 1996, in an attempt to further correlate surgical findings with clinical outcomes, the ASRM further revised the endometriosis classification system (American Society of Reproductive Medicine, 1997). In this system, endometriosis is classified as stage I (minimal), stage II (mild), stage III (moderate), and stage IV (severe) (Fig. 10-2). Although there was no change in the staging system from the 1985 classification, the revised 1996 classification provided for description of endometriotic lesion morphology as white, red, or black. This modification was prompted by studies demonstrating that some biochemical activities within implants and possibly disease prognosis can be predicted by implant morphology (Vernon, 1986).

Anatomic Sites

Endometriosis may develop anywhere within the pelvis and on other extrapelvic peritoneal surfaces. Most commonly, endometriosis is found in the dependent areas of the pelvis. The ovary, pelvic peritoneum, anterior and posterior cul-de-sac, and uterosacral ligaments are frequently involved (Fig. 10-3). Additionally, the rectovaginal septum, ureter, and rarely the bladder, pericardium, surgical scars, and pleura may be affected. One pathologic review revealed that endometriosis has been identified on all organs except the spleen (Markham, 1989). Rare sites of endometriosis may present with atypical cyclic symptoms. For example, women with urinary tract endometriosis may describe cyclic irritative voiding symptoms and hematuria; those with rectosigmoid involvement may note cyclic rectal bleeding; and pleural lesions have been associated with menstrual pneumothorax or hemoptysis (Price, 1996; Roberts, 2003; Ryu, 2007; Sciume, 2004).

Ovarian endometriomas are a common manifestation of endometriosis. These smooth-walled, dark-brown ovarian cysts are filled with a chocolate-appearing fluid and may be unilocular or when larger, multilocular. Ovarian endometriomas are thought to form through invagination of ovarian cortex and subsequent incorporation of menstrual debris that had been adherent to the ovarian surface (Hughesdon, 1957). Another theory has suggested that endometriomas develop as a result of coelomic metaplasia of invaginated epithelial inclusions (Nisolle, 1997).



AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE
REVISED CLASSIFICATION OF ENDOMETRIOSIS

Patient's Name _____ Date _____

Stage I (Minimal) - 1-5
Stage II (Mild) - 6-15
Stage III (Moderate) - 16-40
Stage IV (Severe) - >40
Total _____

Laparoscopy _____ Laparotomy _____ Photography _____
Recommended Treatment _____
Prognosis _____

	ENDOMETRIOSIS	<1cm	1-3cm	>3cm
PERITONEUM	Superficial	1	2	4
	Deep	2	4	6
OVARY	R Superficial	1	2	4
	Deep	4	16	20
	L Superficial	1	2	4
	Deep	4	16	20

	POSTERIOR CULDESAC OBLITERATION	Partial	Complete
		4	40

	ADHESIONS	<1/3 Enclosure	1/3-2/3 Enclosure	>2/3 Enclosure
OVARY	R Filmy	1	2	4
	Dense	4	8	16
	L Filmy	1	2	4
	Dense	4	8	16
TUBE	R Filmy	1	2	4
	Dense	4*	8*	16
	L Filmy	1	2	4
	Dense	4*	8*	16

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

Denote appearance of superficial implant types as red [(R), red, red-pink, flamelike, vesicular blobs, clear vesicles], white [(W), opacifications, peritoneal defects, yellow-brown], or black [(B) black, hemosiderin deposits, blue]. Denote percent of total described as R____%, W____% and B____%. Total should equal 100%.

Additional Endometriosis: _____

Associated Pathology: _____

To Be Used with Normal Tubes and Ovaries

To Be Used with Abnormal Tubes and/or Ovaries

FIGURE 10-2 American Society for Reproductive Medicine Revised Classification of Endometriosis. Available at: http://www.asrm.org/Literature/classifications/classification_endometriosis.pdf *(From the American Society for Reproductive Medicine, 1997, with permission.)*

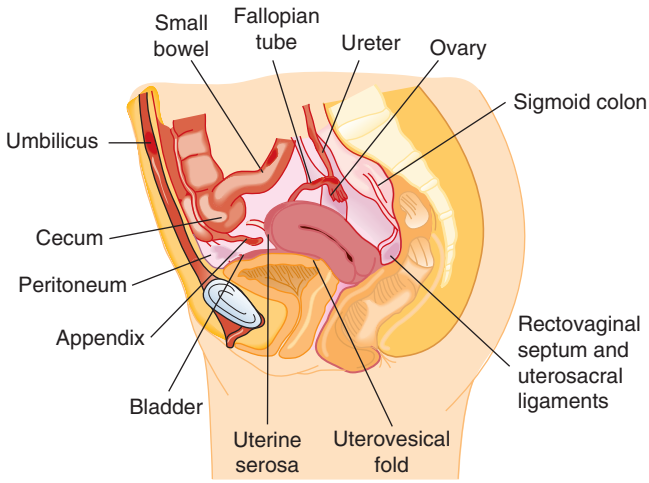


FIGURE 10-3 Common locations of endometriosis within the abdomen and pelvis. *(Redrawn after Olive, 2005.)*

PATIENT SYMPTOMS

Although women with endometriosis may be asymptomatic, symptoms are common and typically include chronic pelvic pain and infertility. As previously stated, the current ASRM classification of endometriosis, which describes the extent of disease bulk, poorly predicts symptoms. Thus clinically, women with extensive disease (stage IV) may note few complaints, whereas those with minimal disease (stage I) may have significant pain or subfertility or both.

Pain

Endometriosis is a common cause of pelvic pain, which in affected women can vary greatly and may be cyclic or

chronic (Mathias, 1996). The underlying cause of this pain is unclear, but proinflammatory cytokines and prostaglandins released by endometriotic implants into the peritoneal fluid may be one source (Giudice, 2004). Additionally, there is also evidence to suggest that pain from endometriosis correlates with depth of invasion and that the site of pain may indicate lesion location (Chapron, 2003; Koninckx, 1991). Recent data suggest that endometriosis pain may result from neuronal invasion of endometriotic implants that subsequently develop a sensory and sympathetic nerve supply, which may undergo central sensitization (see Chapter 11, p. 244). (Berkley, 2005). This leads to persistent hyperexcitability of the neurons and subsequent persistent pain, despite surgical excision. Whatever the cause, clinically women with endometriosis experience different manifestations of pain.

Dysmenorrhea

Cyclic pain with menstruation is noted commonly in women with endometriosis. Typically, endometriosis-associated dysmenorrhea precedes menses by 24 to 48 hours and is less responsive to nonsteroidal anti-inflammatory drugs (NSAIDs) and combination oral contraceptives (COCs). This pain is thought to be more severe in comparison with primary dysmenorrhea. and Cramer and associates (1986) demonstrated a positive correlation between the severity of dysmenorrhea and the risk of endometriosis. Furthermore, deeply infiltrating endometriosis, that is, disease that extends >5 mm under the peritoneal surface, also appears to have positive correlation to the severity of dysmenorrhea (Chapron, 2003).

Dyspareunia

Endometriosis-associated dyspareunia is most often related to rectovaginal septum or uterosacral ligament disease, and is less commonly associated with ovarian involvement (Murphy, 2002; Vercellini, 1996b). During intercourse, tension on diseased uterosacral ligaments may be the trigger of this pain (Fauconnier, 2002). Although some women with endometriosis may describe a history of dyspareunia since coitarche, endometriosis-associated dyspareunia is suspected if pain develops after years of pain-free intercourse (Ferrero, 2005). The degree of discomfort, however, appears to be independent of disease severity (Fedele, 1992).

Dysuria

Although less frequent symptoms of endometriosis, bladder complaints of painful urination as well as cyclic urinary frequency and urgency may be noted in affected women. Endometriosis may be suspected if these symptoms are concurrent with negative urine cultures (Vercellini, 1996a).

Defecatory Pain

Painful defecation develops less commonly than the other manifestations of pelvic pain and typically reflects rectosigmoid involvement with endometriotic implants (Azzena, 1998). Symptoms may be chronic or cyclic, and they may be associated with constipation, diarrhea, or cyclic hematochezia (Remorgida, 2007).

Noncyclical Pelvic Pain

Chronic pelvic pain is the most common symptom associated with endometriosis. Approximately 40 to 60 percent of women with chronic pelvic pain are found to have endometriosis at the time of laparoscopy (Eskenazi, 1997). Some studies have demonstrated a correlation of pain severity with advanced stage disease, whereas other studies have not (Fedele, 1992; Muzii, 1997).

The focus of chronic pain may vary from woman to woman. If the rectovaginal septum or uterosacral ligaments are involved with disease, pain may radiate to the rectum or lower back. Alternatively, pain radiating down the leg and causing cyclic sciatica may reflect posterior peritoneal endometriosis or direct sciatic nerve involvement (Possover, 2007; Vercellini, 2003a; Vilos, 2002).

Infertility

The incidence of endometriosis in women with subfertility is 20 to 30 percent (Waller, 1993). In addition, although there is wide variability reported, patients with infertility appear to have a greater incidence of endometriosis than fertile controls (13 to 33 percent versus 4 to 8 percent) (D'Hooghe, 2003; Strathy, 1982). Furthermore, Matorras and colleagues (2001) noted an increased prevalence of more severe stages of endometriosis in women with infertility. This may result from adhesions which are caused by endometriosis and impair normal oocyte pick-up and transport by the fallopian tube. Beyond mechanical impairment of ovulation and fertilization, more subtle defects also appear to be involved in the pathogenesis of infertility in women with endometriosis. Such defects include perturbations in ovarian and immune function as well as implantation.

Minimal or Mild Disease

Although evidence from animal studies suggest that severe forms of endometriosis are associated with infertility, support for an association and causation of infertility by milder forms of endometriosis is less abundant (D'Hooghe, 1996; Schenken, 1980). Primate studies have shown that surgically-induced endometriosis resulted in a 35-percent pregnancy rate in animals with minimal endometriosis, a 12 percent rate with advanced endometriosis, and no pregnancies if ovarian adhesions were present. These rates compared poorly with a 42-percent pregnancy rate in control animals (Schenken, 1984).

Human studies demonstrating a causation of subfertility by endometriosis are lacking, but an association is suggested by the differing prevalence of endometriosis between infertile patients and fertile women.

Evaluating women with minimal disease, Rodriguez-Escudero and colleagues (1988) reported that women with minimal endometriosis had a monthly fecundity rate of 6 percent and a 12-month cumulative pregnancy rate of 47 percent. Although this is much lower than normal fertile women, participation bias likely exists in such studies. Furthermore, a prospective cohort study demonstrated that women with minimal or mild endometriosis had a similar fecundity compared

with those with unexplained infertility. Well-designed, prospective randomized controlled trials (RCTs) have found conflicting evidence as to whether surgical treatment of endometriosis improves fecundity rates and cumulative pregnancy rates in these women. One of these studies demonstrated improved fertility, but a trial with fewer women noted no improvement (Marcoux, 1997; Parazzini, 1999).

Moderate or Severe Disease

In moderate to severe endometriosis (stage III to IV), tubal and ovarian architecture are often distorted. As a result, impaired fertility would be expected. Unfortunately, few studies report fecundity rates in women with severe endometriosis. One investigation comparing mild, moderate, and severe endometriosis revealed a monthly fecundity rate of 8.7 percent in those with mild disease, 3.2 percent with moderate disease, and no pregnancies with severe disease (Olive, 1985a). There are no well-designed studies examining the effectiveness of surgical therapy in patients with severe endometriosis, but cumulative pregnancy rates have reached 30 percent after surgical excision (Adamson, 1993; Osuga, 2002). This rate appears to be greater than that of women who undergo expectant management.

Folliculogenesis and Embryogenesis Effects

Some researchers have suggested that folliculogenesis is impaired in women with endometriosis. Embryo development and quality in women with endometriosis undergoing IVF was compared with that of embryos originating from women with tubal factor infertility (Pellicer, 1995). There were significantly fewer blastomeres per embryo and a significantly greater rate of embryonic developmental arrest in the endometriosis group. This suggests a possible decreased developmental competence of oocytes originating from the ovaries of women with endometriosis. Another investigation found that oocyte number may be decreased in women with endometriosis (Suzuki, 2005). In addition, researchers have attempted to determine if the follicular environment is different in women with endometriosis. Specifically, studies demonstrating qualitative and quantitative changes in steroidogenesis, however, have found conflicting results (Garrido, 2002; Harlow, 1996; Pellicer, 1998). Apoptosis is another attractive theory for decreased oocyte competence in women with endometriosis, but well-designed studies are lacking.

Endometrical Changes

Abnormalities in endometrial development in women with endometriosis support the possibility that implantation defects may be responsible for subfertility associated with endometriosis. For example, researchers have revealed abnormalities in gene expression profiles in the eutopic endometrium from women with endometriosis compared with that from women without endometriosis (Kao, 2003). Specifically, deficient $\alpha_v\beta_3$ integrin expression in the peri-implantation endometrium of women with endometriosis has been demonstrated, and this may be associated with decreased uterine receptivity (Lessey, 1994). The role of apoptosis on peri-implantation endometrium is another area of study that still remains largely unexplored.

Other Factors

Abnormalities in inflammation and cytokine activity in women with endometriosis may play a role in endometriosis-associated infertility. Sperm function may be affected in women with endometriosis. Studies have demonstrated increased phagocytosis of spermatozoa by macrophages from women with endometriosis (Haney, 1981; Muscato, 1982). Moreover, sperm binding to the zona pellucida appears to be adversely affected (Qiao, 1998). However, investigations of the effects of endometriosis on sperm motility and the acrosome reaction reveal conflicting results (Bielfeld, 1993; Curtis, 1993; Tasdemir, 1995).

Intestinal Obstruction

Endometriosis may involve the small bowel, cecum, appendix, or rectosigmoid colon and lead to intestinal obstruction in some cases (Cameron, 1995; Varras, 2002; Wickramasekera, 1999). Although endometriosis of the gastrointestinal tract is usually confined to the subserosa and muscularis propria, more severe cases may involve the bowel wall transmurally and lead to a clinical and radiologic picture consistent with malignancy (Decker, 2004). Accurate preoperative diagnosis and management are difficult due to the atypical presentation. Laparoscopy typically provides the definitive diagnosis. Treatment is often surgical, with resection and primary anastomosis of the affected intestinal segment. In women without obstructing symptoms, however, conservative management with hormonal therapy may be considered.

DIFFERENTIAL DIAGNOSIS

The symptoms of endometriosis are nonspecific and may mimic many disease processes. Because endometriosis is a surgical diagnosis, several other diagnoses may be considered prior to surgical exploration (Table 10-1).

TABLE 10-1 Differential Diagnosis of Endometriosis

Gynecologic
Pelvic inflammatory disease
Tubo-ovarian abscess
Salpingitis
Endometritis
Hemorrhagic ovarian cyst
Ovarian torsion
Primary dysmenorrhea
Degenerating leiomyoma
Nongynecologic
Interstitial cystitis
Chronic urinary tract infection
Renal calculi
Inflammatory bowel disease
Irritable bowel syndrome
Diverticulitis
Mesenteric lymphadenitis
Musculoskeletal disorders

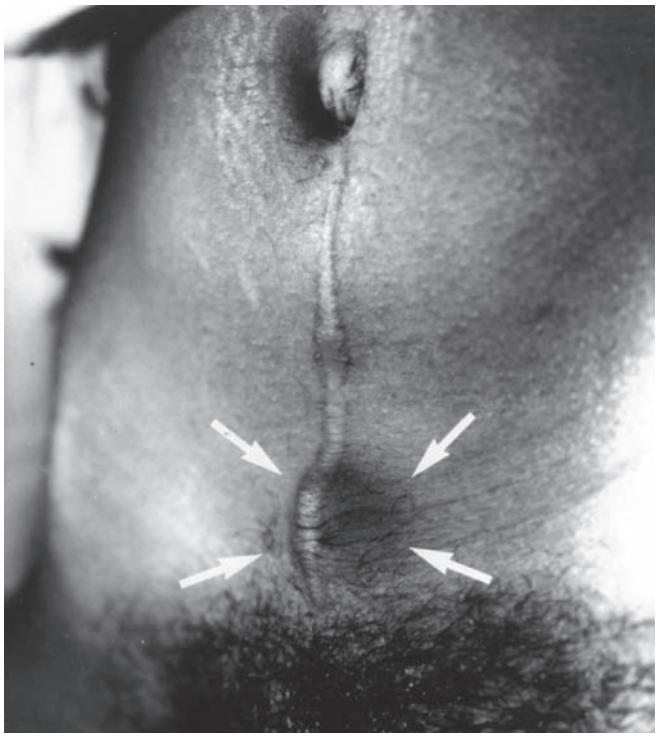


FIGURE 10-4 Endometriosis within a lower vertical midline incision scar (**arrows**).

DIAGNOSIS

Physical Examination

Visual Inspection

For the most part, endometriosis is a disease confined to the pelvis. Accordingly, there are often no abnormalities on visual inspection. Some exceptions include endometriosis within an episiotomy scar or surgical scar, most often within a Pfannenstiel incision (Fig. 10-4) (Koger, 1993; Zhu, 2002). Rarely, endometriosis may develop spontaneously within the perineum or perianal region (Watanabe, 2003).

Speculum Examination

Examination of the vagina and cervix by speculum examination often reveals no signs of endometriosis. Occasionally, bluish or red powder-burn lesions may be seen on the cervix or the posterior fornix of the vagina. These lesions may be tender or bleed with contact. One recent study found that speculum examination displayed endometriosis in 14 percent of patients diagnosed with deeply infiltrating endometriosis (Chapron, 2002).

Bimanual Examination

Pelvic organ palpation often reveals anatomic abnormalities suggestive of endometriosis. Uterosacral ligament nodularity and tenderness may reflect active disease or scarring along the ligament. In addition, an enlarged cystic adnexal mass may represent an ovarian endometrioma, which may be mobile or adherent to other pelvic structures. Bimanual examination may reveal a retroverted, fixed, tender uterus, or a firm, fixed posterior cul-de-sac.

Although pelvic organ palpation may assist in the diagnosis, the sensitivity and specificity of focal pelvic tenderness in detecting endometriosis displays wide variation and ranges from 36 to 90 percent and 32 to 92 percent, respectively (Chapron, 2002; Eskenazi, 2001; Koninckx, 1996; Ripps, 1992). For example, Chapron and co-workers (2002) palpated a painful nodule in 43 percent of patients with deeply infiltrating endometriosis. In another study of 91 women with chronic pelvic pain and surgically confirmed endometriosis, the bimanual examination was normal 47 percent of the time (Nezhat, 1994). One study suggested that pelvic nodularities secondary to endometriosis may be more easily detected by bimanual examination during menses (Koninckx, 1996).

Laboratory Testing

To exclude other causes of pelvic pain, laboratory investigations are often undertaken. Initially, a complete blood count (CBC), urinalysis and urine cultures, vaginal cultures, and cervical swabs may be obtained to exclude infections or sexually transmitted infections that may cause pelvic inflammatory disease (see Chap. 3, p. 73).

Serum CA125

Numerous serum markers have been studied as possible adjuncts in the diagnosis of endometriosis. No serum marker has been studied in greater detail than CA125 (cancer antigen 125). Found as an antigenic determinant on a glycoprotein, CA125 has been identified in several adult tissues such as the epithelium of the fallopian tubes, the endometrium, the endocervix, the pleura, and the peritoneum (see Chap. 35, p. 722). Recognized by monoclonal antibody assays, elevated CA125 levels have been shown to positively correlate with the severity of endometriosis (Hornstein, 1995a). Unfortunately, although demonstrating adequate specificity, the assay has poor sensitivity in detecting mild endometriosis. A meta-analysis of studies evaluating CA125 in the diagnosis of endometriosis revealed a sensitivity of only 28 percent and a specificity of 90 percent (Mol, 1998). This marker appeared to be a better test in diagnosing stage III and IV endometriosis. Although the role of this test in clinical practice is uncertain, it may be useful in the presence of a sonographically detected ovarian cyst suggestive of an endometrioma.

Other Serum Markers

Cancer antigen19-9 (CA 19-9), another antigenic glycoprotein, is a serum marker that has also been shown to positively correlate with the severity of endometriosis (Harada, 2002). Serum placental protein 14 (PP14; glycodelin-A) was initially shown to have adequate sensitivity (59 percent), but this has not been confirmed by other studies (Telimaa, 1989). Interleukin-6 (IL-6) serum levels above 2 pg/mL (90-percent sensitivity and 67-percent specificity) and tumor necrosis factor-α (TNF-α) peritoneal fluid levels above 15 pg/mL (100-percent sensitivity and 89-percent specificity) may be used to discriminate between those with or without endometriosis (Bedaiwy, 2002). Several other serum markers have been studied, with limited diagnostic accuracy (Bedaiwy, 2004). Most of these tests are rarely used outside of research settings.

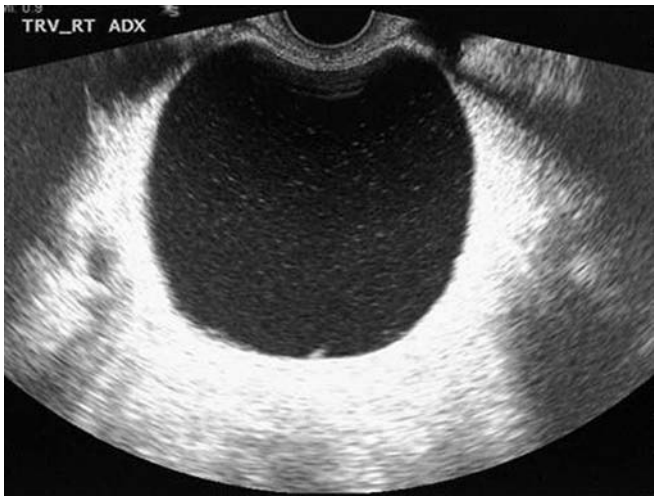
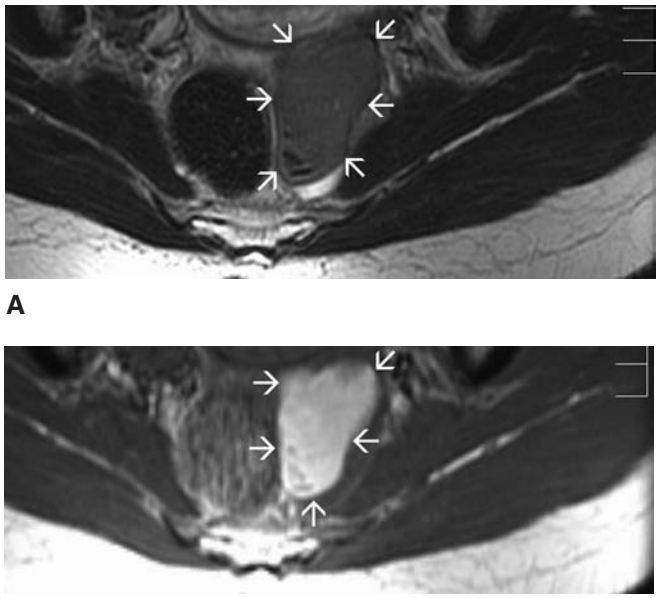


FIGURE 10-5 Transvaginal sonogram demonstrating ovarian endometrioma. A cyst with diffuse internal low-level echoes is seen. *(Courtesy of Dr. Elysia Moschos.)*



A

B

FIGURE 10-6 Magnetic resonance images of an endometrioma. T2- (**A**) and T1-weighted (**B**) images reveal an endometrioma (**arrows**) just lateral to the rectum. The findings are consistent with subacute blood, based on the bright signal on T-1 and the relatively low signal intensity on T-2 of the lesion. *(Courtesy of Dr. Diane Twickler.)*

Diagnostic Imaging

Sonography

Both transabdominal and the more sensitive transvaginal (TVS) sonographic approaches have been used extensively in the diagnosis of endometriosis (see Chap. 2, p. 25). Although TVS is the mainstay in evaluating symptoms associated with endometriosis and is accurate in detecting endometriomas, imaging of superficial endometriosis or endometriotic adhesions is inadequate. Small endometriotic plaques or nodules may occasionally be seen, but these findings are inconsistent (Carbognin, 2004).

More recently, sonovaginography, a technique involving vaginal saline instillation to more accurately localize rectovaginal endometriosis, and transrectal sonography have assisted in the diagnosis and evaluation of endometriosis (Brosens, 2003). Transvaginal sonography appears to be as effective as a transrectal approach in identifying posterior pelvic endometriosis, but the latter may delineate rectal involvement more accurately and may be more appropriate when planning surgery (Bazot, 2003).

Endometriomas can be diagnosed by TVS with adequate sensitivity in most settings if they are 20 mm in diameter or greater (Fig. 10-5). Specifically, sensitivity and specificity of TVS to diagnose endometriomas range from 64 to 90 percent and from 22 to 100 percent, respectively (Moore, 2002). Endometriomas often present as cystic structures with low-level internal echoes, and occasional thick septations, thickened walls, and echogenic wall foci (Athey, 1989; Patel, 1999). Color Doppler transvaginal sonography often demonstrates pericystic, but not intracystic, flow (Carbognin, 2004).

Magnetic Resonance Imaging

Magnetic resonance imaging has been increasingly used as a noninvasive method for diagnosis of endometriosis. Small nodules may be recognized as hyperintense lesions on T1-weighted sequences, and plaque lesions have a similar appearance, with a variable signal on T2-weighted sequences (Carbognin, 2004). An endometrioma appears as a hyperintense mass on T1-weighted sequences, with a tendency towards hypointensity in T2-weighted sequences. A hypointense ring is often seen surrounding the endometrioma, which is enhanced after contrast administration (Fig. 10-6).

Diagnostic Laparoscopy

Diagnostic laparoscopy is the primary method used for diagnosing endometriosis (see Section 41-28, p. 929) (Kennedy, 2005). Laparoscopic findings are variable and may include discrete endometriotic lesions, endometrioma, and adhesion formation.

Endometriotic Lesions

The pelvic organs and pelvic peritoneum are typical locations for endometriosis. The appearance of these lesions by laparoscopy is varied and colors may include red (red, red-pink, or clear), white (white or yellow-brown), and black (black or black-blue) (Fig. 10-7). Dark lesions are pigmented by hemosiderin deposition from trapped menstrual debris. White and red lesions most commonly correlate with the histologic findings of endometriosis (Jansen, 1986). In addition to color differences, endometriotic lesions may differ morphologically. They can appear as smooth blebs on peritoneal surfaces, as holes or defects within the peritoneum, or as flat stellate lesions whose points are formed by surrounding scar tissue. Endometriotic lesions may be superficial or may deeply invade the peritoneum or pelvic organs. Although

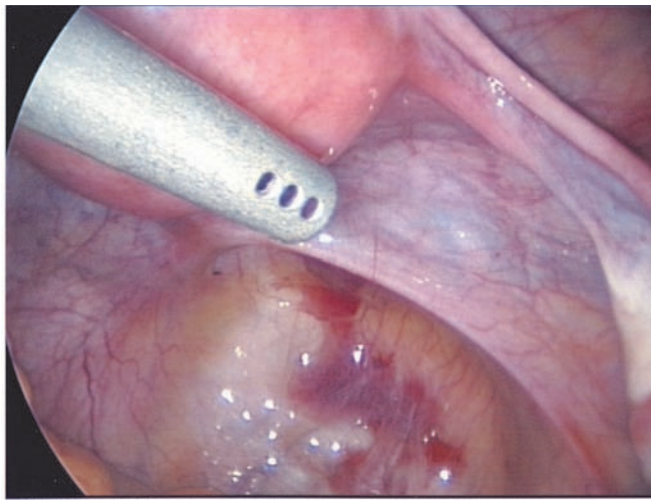


FIGURE 10-7 Below the irrigator tip, a red and white endometriotic lesion is seen on the pelvic peritoneum during laparoscopy. *(Courtesy of Dr. Karen Bradshaw.)*

these findings may allow endometriosis to be diagnosed with accuracy, pain symptoms correlate poorly with findings at laparoscopy (Kennedy, 2005).

Endometriomas

Endometriomas are cystic endometrial lesions contained within the ovary. Typically, they have the appearance of smooth-walled, brown cysts filled with thick, chocolate-appearing liquid (Fig. 10-8). These ovarian masses may be unilocular, but are often multilocular when >3 cm in diameter (Nezhat, 1992b).

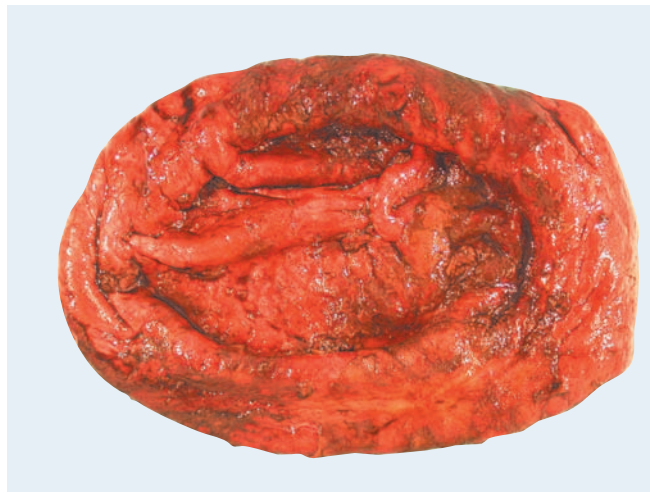
Laparoscopic visualization of ovarian endometriomas has a sensitivity and specificity of 97 percent and 95 percent, respectively (Vercellini, 1991). Because of this, ovarian biopsy is rarely required for diagnosis.

Pathologic Analysis

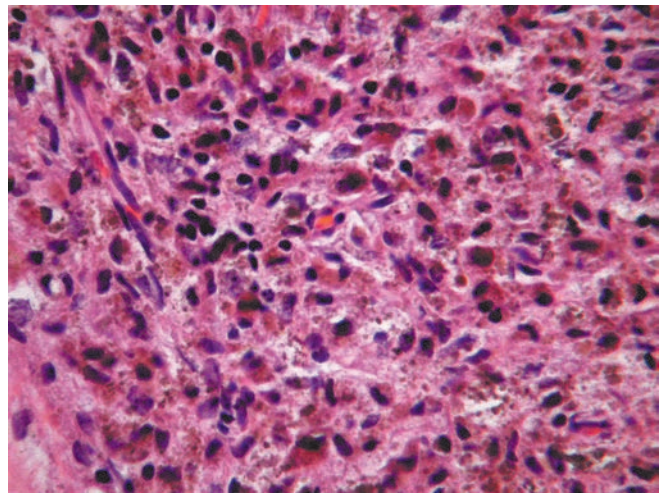
Although current guidelines do not require histologic evaluation for the diagnosis of endometriosis, some suggest that relying solely on laparoscopic findings in the absence of histologic confirmation often results in overdiagnosis (American Society for Reproductive Medicine, 1997). Specifically, the greatest discordance between laparoscopic and histologic findings is noted in scarred lesions (Marchino, 2005a; Walter, 2001). Histologic diagnosis requires the presence of both endometrial glands and stroma found outside the uterine cavity (Fig. 10-9). Additionally, hemosiderin deposition and fibromuscular metaplasia are frequently noted (Murphy, 2002). The gross appearance of endometriotic lesions often suggests certain microscopic findings. For example, when examined microscopically, red lesions are frequently vascularized, whereas white lesions more often display fibrosis and few vessels (Nisolle, 1997).

Diagnostic Algorithm

The approach to diagnosis and treatment of endometriosis depends on the presenting symptoms and goals of therapy



A



B

FIGURE 10-8 Photographs of an endometrioma. **A.** A bisected endometrioma showing a shaggy hemorrhagic lining. **B.** Microscopic image of an endometrioma showing predominantly hemosiderin-laden macrophages resulting in the brown discoloration. *(Courtesy of Dr. Raheela Ashfaq.)*

(Fig. 10-10). If infertility is the presenting symptom, then fertility-preserving treatment without ovulation suppression will be required. In contrast, if the patient has severe, recalcitrant pain symptoms and has completed childbearing, definitive surgery may be warranted.

TREATMENT

Treatment for endometriosis depends on the woman's specific symptoms, severity of symptoms, location of endometriotic lesions, goals for treatment, and desire to conserve future fertility. The most important factor when determining the most appropriate management is whether a patient is seeking treatment for infertility or pain, as the treatment will differ based on the symptom (Olive, 2001).

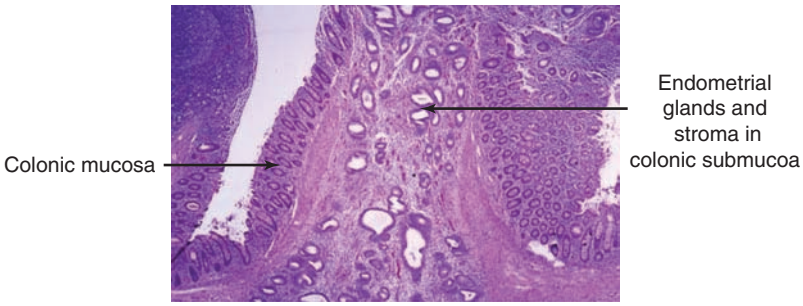


FIGURE 10-9 Colonic endometriosis. Note the benign endometrial glands and endometrial stroma in the colonic submucosa. *(Courtesy of Dr. Raheela Ashfaq.)*

Expectant Management

For many women, symptoms will preclude them from choosing expectant management. However, for those with mild symptoms or for asymptomatic women diagnosed incidentally, expectant management may be appropriate. For example, Sutton and associates (1997) expectantly managed patients initially diagnosed by laparoscopy with minimal to moderate endometriosis. At second-look laparoscopy after 1 year, 29 percent of women had disease regression, 42 percent remained unchanged, and 29 percent had disease progression. Other investigations have shown similar rates of disease regression with expectant management (Thomas, 1987). However, studies evaluating infertile women have demonstrated lower fecundity rates after expectant management than following surgical treatment (Milingos, 2002; Marcoux, 1997). These studies are confined to patients with minimal to moderate endometriosis, and there are no well-designed trials examining the effect of expectant management on severe endometriosis.

Medical Treatment of Endometriosis-Related Pain

Nonsteroidal Anti-Inflammatory Drugs

These agents nonselectively inhibit the cyclooxygenase isoenzymes 1 and 2 (COX-1 and COX-2), and within this group, the selective COX-2 inhibitors selectively inhibit the COX-2 isoenzyme. These enzymes are responsible for the synthesis of prostaglandins involved

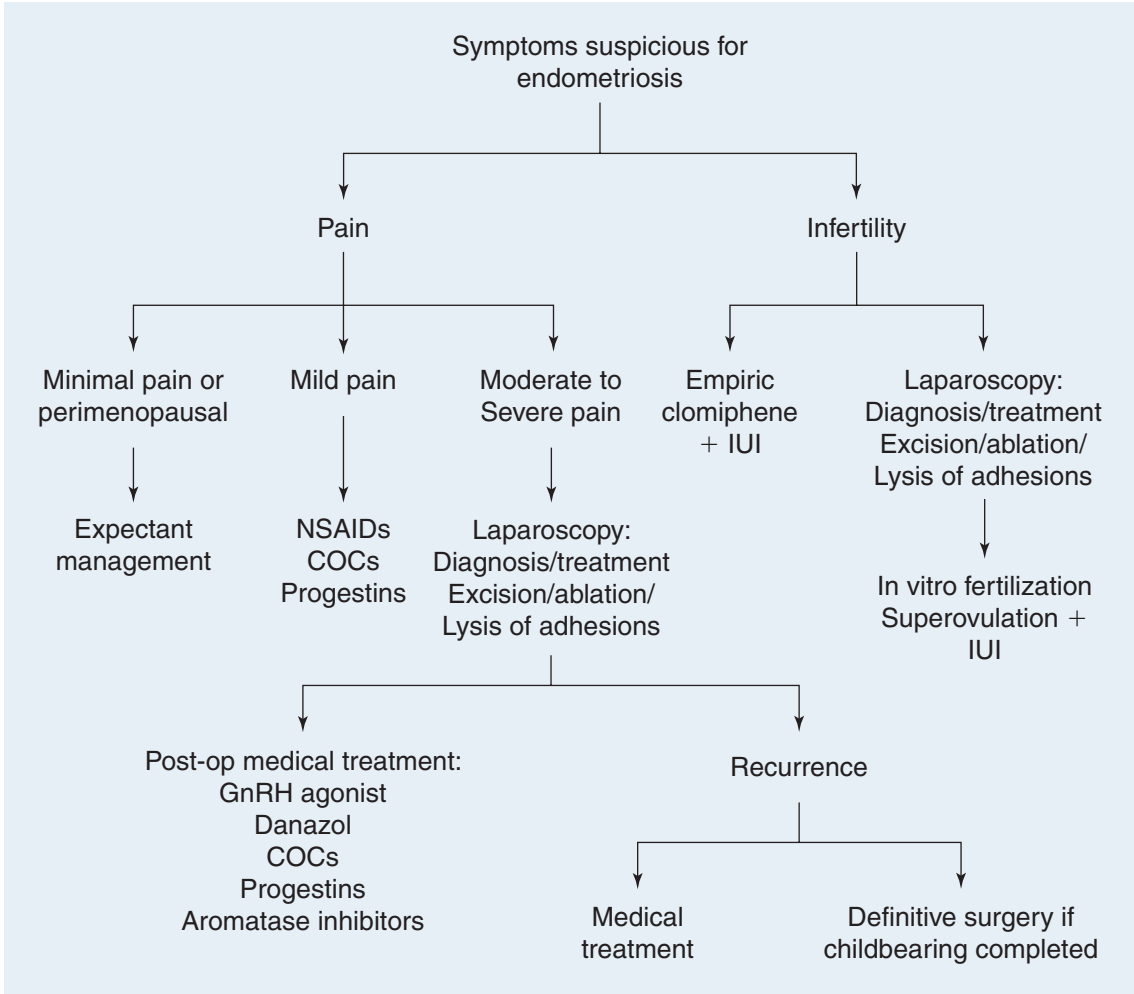


FIGURE 10-10 Diagnostic and treatment algorithm for women with presumptive or proven endometriosis. COCs = combination oral contraceptives; GnRH = gonadotropin-releasing hormone; IUI = intrauterine insemination; NSAIDs = nonsteroidal anti-inflammatory drugs.

in the pain and inflammation associated with endometriosis. For example, endometriotic tissue has been shown to express COX-2 at greater levels than eutopic endometrium (Ota, 2001). Therefore, therapy aimed at lowering these prostaglandin levels may play a role in alleviating endometriosis-associated pain.

Nonsteroidal anti-inflammatory drugs are often first-line therapy in women with primary dysmenorrhea or pelvic pain prior to laparoscopic confirmation of endometriosis, and in women with minimal or mild pain symptoms associated with known endometriosis. Although animal models have demonstrated disease regression with NSAID treatment, few studies have critically evaluated their effectiveness in disease regression in surgically-confirmed endometriosis (Efstathiou, 2005). However, evidence exists for their efficacy in patients with dysmenorrhea and pelvic pain (Table 10-2) (Nasir, 2004). Due to the cardiovascular risks with long-term use of COX-2 inhibitors, these medications should be used at the lowest possible dose and for the shortest duration necessary (Jones, 2005).

Combination Oral Contraceptives

These agents have been a mainstay for the treatment of pain associated with endometriosis. Although no randomized controlled trials have compared COCs with placebo, abundant observational evidence supports the role of COCs in the relief of endometriosis-related pain (Vercellini, 1993; Vessey, 1993). These drugs appear to act by inhibiting gonadotropin release, decreasing menstrual flow, and decidualizing implants. In addition, COCs have the added benefit of contraception, suppression of ovulation, and other noncontraceptive benefits (see Table 5-6, p. 112).

These drugs can be used conventionally in a cyclic regimen or may be used continuously, without a break for withdrawal menses. The continuous regimen may be preferable for its decreased frequency of menses for women who fail to achieve pain relief with cyclic COC therapy (Vercellini, 2003b; Wiegratz, 2004). Traditionally, monophasic COCs have been used in the treatment of endometriosis, but no evidence supports their clinical superiority to multiphasic COCs. Additionally, low-dose COCs (containing 20 µg ethinyl estradiol) have not proved superior to conventional-dose COCs for the treatment of endometriosis and may lead to higher rates of abnormal bleeding (Gallo, 2005).

Progestins

Progestational agents have long been used in the treatment of endometriosis. Progestins are known to antagonize estrogenic effects on the endometrium, causing initial decidualization and subsequent endometrial atrophy. Progestins have been administered for the treatment of endometriosis in numerous ways and include oral progestins, depot medroxyprogesterone acetate (DMPA), a levonorgestrel-releasing intrauterine device (IUD), and the newer selective progesterone-receptor modulators (SPRMs).

Although progestin-based therapy is commonly used to effectively treat symptoms, there has been only one well-designed, randomized controlled trial comparing the effect of placebo with medroxyprogesterone acetate (MPA), 100 mg orally daily, given for 6 months. At second-look laparoscopy, partial or total resolution of peritoneal implants in 60 percent of women was noted, compared with 18 percent in the placebo group. Furthermore, pelvic pain and defecatory pain were significantly reduced (Telimaa, 1987). Side effects of high-dose MPA included acne, edema, weight gain, and irregular menstrual bleeding. In practice, MPA is prescribed in dosages ranging from 20 to 100 mg daily. Alternatively, MPA may be given intramuscularly in depot form in a dosage of 150 mg every 3 months. In depot form, MPA may delay resumption of normal menses and ovulation and should not be used in women contemplating imminent pregnancy.

Norethindrone acetate (NETA) is a 19-nortestosterone synthetic progestin that has been used in the treatment of endometriosis. In one study, investigators administered an initial oral dosage of NETA, 5 mg daily, with increases of 2.5 mg daily until amenorrhea or a maximal dosage of 20 mg daily was reached. They found an approximately 90-percent reduction in dysmenorrhea and pelvic pain (Muneyyirci-Delale, 1998). Additionally, NETA has been shown to be effective in conjunction with long-term gonadotropin-releasing hormone (GnRH) agonist therapy for endometriosis. In this fashion, NETA, 5 mg administered orally daily, in conjunction with prolonged GnRH agonist therapy, results in significant resolution of symptoms while protecting against bone loss (Hornstein, 1998; Surrey, 2002).

TABLE 10-2 Commonly Used Oral Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) in the Treatment of Endometriosis-Associated Dysmenorrhea

Generic Name	Trade Name	Dosage	Adverse Effects
Ibuprofen	Motrin, Advil, Nuprin	400 mg every 4–6 h	Nausea; epigastric pain; anorexia; constipation; gastrointestinal bleeding
Naproxen	Naprosyn, Aleve	500 mg initially, then 250 mg every 6–8 h	Same as above
Naproxen sodium	Anaprox	550 mg initially, then 275 mg every 6–8 h	Same as above
Mefenamic acid	Ponstel	500 mg initially, then 250 mg every 6 h, starting with menses and continued for 3 days	Same as above
Ketoprofen	Orudis, Oruvail	50 mg q6–8 h	Same as above

The levonorgestrel-releasing intrauterine system (LNG-IUS) (Mirena, Berlex, Montville, NJ) has traditionally been used for contraception and dysfunctional uterine bleeding (see Fig. 5-5, p. 119). Recently, the LNG-IUS, however, has been used for the treatment of endometriosis. This IUD delivers levonorgestrel directly to the endometrium and is effective for up to 5 years. An observational trial revealed symptomatic improvement in patients with endometriosis using the LNG-IUS, with symptom improvement continuing up to 30 months (Lockhat, 2005). The continuation rate at 3 years, however, was only 56 percent, mostly due to intolerable bleeding, persistent pain, and weight gain. A randomized controlled trial comparing LNG-IUS with GnRH agonist therapy showed equivalent improvement in pain symptoms, without the concomitant hypoestrogenism that accompanies GnRH agonist treatment (Petta, 2005). Accordingly, these recent findings make the LNG-IUS an attractive option in treating women with endometriosis.

Selective Progesterone Receptor Modulators

A new and novel option in the treatment of endometriosis has been the use of selective progesterone-receptor modulators (SPRMs). These are progesterone-receptor ligands (molecules that bind and activate or inactivate the progesterone receptor) and have both progesterone antagonist and antagonist activities (Elger, 2000). One common SPRM, mifepristone (RU486), is a controversial abortifacient that predominantly possesses antiprogestational activity. It has also been studied in women with endometriosis and was found to reduce pelvic pain and extent of endometriosis, when used for 6 months at oral dosages of 50 mg daily (Kettel, 1996). Asoprisnil (J867) is a SPRM that induces endometrial atrophy and amenorrhea. Currently in Phase III trials for the treatment of leiomyomas and endometriosis, asoprisnil in Phase II studies improved dysmenorrhea and pelvic pain symptoms, whereas amenorrhea was dose dependent (Chwalisz, 2005). These novel agents hold promise for future treatment of endometriosis.

Androgens

The first medication approved for the treatment of endometriosis in the United States was the androgen danazol. This agent is a synthetic androgen that is an isoxazole derivative of 17-α-ethinyl testosterone. The predominant mechanism of action appears to be suppression of midcycle luteinizing hormone (LH) surge, creating a chronic anovulatory state (Floyd, 1980). Danazol occupies receptor sites on sex-hormone binding globulin (SHBG) to increase serum free testosterone levels and also binds directly to androgen and progesterone receptors. As a result, danazol creates a hypoestrogenic, hyperandrogenic state, inducing endometrial atrophy in endometriotic implants (Fedele, 1990).

Danazol at dosages of 200 mg given orally three times daily proved superior to placebo for the reduction of endometriotic implants and pelvic pain symptoms after 6 months of therapy (Telimaa, 1987). The recommended dosage of danazol is 600 to 800 mg daily. Unfortunately, significant androgenic side effects develop at this dosage and include acne, hot flashes, hirsutism, adverse serum lipid profiles, voice deepening (possibly irreversible), elevation of liver enzymes, and mood changes. Moreover, due to possible teratogenicity, this medication should be taken in conjunction with effective contraception. Because of this adverse side-effect profile, danazol is prescribed less frequently, and when administered, its duration should be limited.

Gestrinone (ethylnorgestrienone; R2323) is an antiprogestational agent prescribed in Europe for the treatment of endometriosis. Although it has antiprogestational, antiestrogenic, and androgenic effects, it predominantly induces a progesterone withdrawal effect and decreases the number of estrogen and progesterone receptors. Endocrinologic changes during therapy with gestrinone show that basal concentrations of gonadotropin levels remain unchanged, estradiol concentrations vary, and free testosterone levels increase, with concomitant androgenic side effects (Forbes, 1993).

Gestrinone equals the effectiveness of danazol and of GnRH agonists for relief of endometriosis-related pain (Prentice, 2000a). Furthermore, during 6 months of treatment, gestrinone was not associated with the bone density loss commonly seen with GnRH agonist use and was more effective in persistently decreasing moderate to severe pelvic pain (Gestrinone Italian Study Group, 1996). Unfortunately, gestrinone appears to lower high-density lipoprotein (HDL) levels. Gestrinone is administered orally, 2.5 to 10 mg weekly, given daily or three times weekly.

GnRH Agonists

Endogenous pulsatile release of GnRH leads to pulsatile secretory activity of the gonadotropes within the anterior pituitary. This pulsatile release results in pituitary release of gonadotropins, with subsequent ovarian steroidogenesis and ovulation. Continuous, nonpulsatile GnRH administration, however, results in pituitary desensitization and subsequent loss of ovarian steroidogenesis (Rabin, 1980). These features allow pharmacologic use of GnRH agonists for the treatment of endometriosis. With loss of ovarian estradiol production, the hypoestrogenic environment removes the stimulation normally provided to the endometriotic implants and creates a pseudomenopausal state during treatment.

Pain Improvement. Agonists may be used prior to laparoscopy in women with chronic pelvic pain and clinical suspicion of endometriosis. A list of clinically used GnRH agonists is found in Table 9-3 (p. 204). After 3 months of GnRH agonist treatment (depot leuprolide acetate; Lupron Depot, TAP Pharmaceutical Products, Lake Forest, IL), pain scores were significantly reduced compared with placebo (Ling, 1999). Subsequent laparoscopy revealed that 93 percent of these women had surgically-diagnosed endometriosis. Accordingly, many suggest that in similar patients, depot leuprolide acetate may be used empirically in lieu of laparoscopy, for satisfactory improvement in symptoms.

Numerous studies have demonstrated the effectiveness of GnRH agonist therapy to improve pain symptoms in women with surgically-confirmed endometriosis. For example, in their randomized controlled trial, Dlugi and co-workers (1990) compared depot leuprolide acetate with placebo and found significant decreases in the severity of pelvic pain. Similar findings

were obtained comparing buserelin, another GnRH agonist, with expectant management during a 6-month period (Fedele, 1993). The GnRH agonists seem to provide greater relief when administered for 6 months compared with 3 months (Hornstein, 1995b).

In trials with other drugs for the treatment of endometriosis, GnRH agonists compared favorably. Vercellini and associates (1993), in their randomized controlled trial found equal degrees of pain improvement when comparing GnRH agonist therapy with a low-dose cyclic COC regimen. Dyspareunia, however, was less in the GnRH agonist–treated group. In addition, a meta-analysis revealed that GnRH agonists were equally effective in improving pain scores and decreasing endometriotic implants compared with danazol (Prentice, 2000b).

Add-back Therapy. Concerns about the long-term effects of prolonged hypoestrogenism preclude extended treatment with GnRH agonists. Hypoestrogenic symptoms include hot flushes, insomnia, reduced libido, vaginal dryness, and headaches. Of particular concern is the effect of the hypoestrogenic state on bone mineral density (BMD). Evidence indicates that there are decreases in spine and hip BMD at 3 and 6 months of GnRH agonist therapy, with only partial recovery at 12 to 15 months after treatment (Orwoll, 1994). Because of the increased risk of osteoporosis, therapy is usually limited to the shortest possible duration (usually no greater than 6 months). Additionally, estrogen in the form of COCs may be added to GnRH agonist therapy to counteract the bone loss and is termed *add-back therapy* (Fig. 10-11) (Carr, 1995). Occasionally a GnRH agonist may be used for longer periods, with hormonal add-back therapy in the form of norethindrone acetate, 5 mg orally given daily, with or without conjugated equine estrogen (Premarin, Wyeth, Madison, NJ) 0.625 mg daily for 12 months. This regimen has been shown to provide extended pain relief beyond the duration of treatment and preservation of bone density (Surrey, 2002).

Aromatase Inhibitors

As previously mentioned, endometrial tissue locally produces aromatase, the enzyme responsible for estrogen synthesis. In endometriotic tissue, estrogen may be produced locally through aromatization of circulating androgens. This may be the reason for postmenopausal endometriosis and for intractable symptoms in some women despite treatment. An aromatase inhibitor was first used for endometriosis treatment in a woman with postmenopausal endometriosis after total hysterectomy and bilateral salpingo-oophorectomy (Takayama, 1998). The patient experienced significant pain relief, significant endometriotic lesion size reduction, and a 6-percent reduction in lumbar spine BMD after 9 months of treatment. Subsequently, further study has examined aromatase inhibitors in conjunction with low-dose, continuous COC add-back therapy for 6 months. This small Phase II trial revealed a significant pain reduction in 14 of 15 women with previously intractable pain from endometriosis (Amsterdam, 2005). Aromatase inhibitors have similar hypoestrogenic side-effect profiles as GnRH agonists, but hold promise in severe, refractory cases of endometriosis.

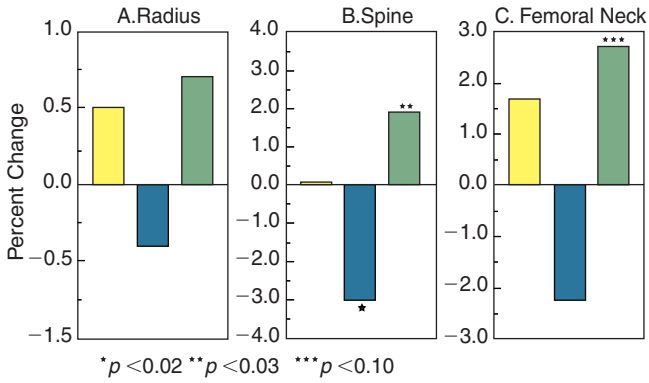


FIGURE 10-11 Changes in bone mineral density in the radius, spine, and femoral neck in women treated for 6 months with oral contraceptive pills (**yellow**), gonadotropin-releasing hormone agonist (**blue**), or gonadotropin-releasing hormone agonist plus oral contraceptive pills (**green**). *(From Carr, 1995, with permission).*

Surgical Treatment of Endometriosis-Related Pain

Lesion Removal and Adhesiolysis

Because the primary method for diagnosis of endometriosis is laparoscopy, surgical treatment of endometriosis at the time of diagnosis is an attractive option. There are numerous studies examining removal of endometriotic lesions, either through excision or ablation. Unfortunately, many of these studies are uncontrolled or retrospective. However, a single randomized controlled trial comparing laparoscopic ablation of endometriotic lesions and laparoscopic uterine nerve ablation with diagnostic laparoscopy performed alone revealed significant symptom relief in 63 percent of women in the ablation group, compared with 23 percent in the expectant management group. Unfortunately, recurrence is common following surgical excision. Jones (2001) demonstrated pain recurrence in 74 percent of patients at a mean time following surgery of 73 months. The median time for recurrence was 20 months.

The optimal method of endometriotic implant ablation for maximal symptom relief is controversial. Laser ablation does not appear to be more effective than conventional electrosurgical ablation of endometriosis (Blackwell, 1991). A randomized controlled trial comparing ablation with excision of endometriotic lesions in women with stage I or II endometriosis revealed similar reductions in pain scores at 6 months (Wright, 2005). For deeply infiltrative endometriosis, some authors have advocated radical surgical excision, although well-designed trials are lacking (Chapron, 2004).

Adhesiolysis is postulated to effectively treat pain symptoms in women with endometriosis by restoring normal anatomy. Unfortunately, most studies are poorly designed and retrospective. As a result, a definitive link between adhesions and pelvic pain is unclear (Hammoud, 2004). For example, one randomized controlled trial demonstrated no overall pain relief from adhesiolysis compared with expectant management (Peters, 1992). However, within this study, one woman with severe, dense vascularized bowel adhesions experienced pain relief following adhesiolysis.

Endometrioma Resection

Endometriomas are often treated surgically, as ovarian masses often prompt surgical investigation, and their associated symptoms may lead to more aggressive therapy (see Chap. 9, p. 211). Historically, endometriomas have been treated by total ovarian cystectomy or by aspiration coupled with ablation of the cyst capsule (see Section 41-33, p. 946). One randomized controlled trial has compared cystectomy with surgical drainage and bipolar coagulation of the endometrioma's inner lining (Beretta, 1998). Cystectomy lead to lower rates of pelvic pain compared with drainage and coagulation (10 percent versus 53 percent). Additionally, cumulative pregnancy rates were higher following cystectomy during 24-month surveillance (67 percent versus 24 percent). Endometriomas may recur. Liu and coworkers (2007) found an approximately 15-percent rate of recurrence at 2 years following initial surgery.

Presacral Neurectomy

For some women, transection of presacral nerves lying within the interiliac triangle may provide relief of chronic pelvic pain. Results from a recent randomized controlled trial revealed significantly greater pain relief at 12 months postoperatively in women treated with presacral neurectomy (PSN) and endometriotic excision compared with endometriotic excision alone (86 percent versus 57 percent) (Zullo, 2003). However, all of these women had midline pain, and an earlier meta-analysis demonstrated a significant decrease in pelvic pain after PSN compared with that following more conservative procedures, but only in those with midline pain (Wilson, 2000). Neurectomy may be performed laparoscopically, but it is technically challenging. For these reasons, PSN is used in a limited manner and not recommended routinely for management of endometriosis-related pain.

Abdominal versus Laparoscopic Approach

All of the surgical procedures listed above can be approached either through laparotomy or laparoscopy. Operative laparoscopy has been used for treatment of ovarian endometriomas for over 20 years, and strong evidence supports laparoscopy over laparotomy in managing benign ovarian masses (see Chap 9, p. 211) (Mais, 1995; Reich, 1986; Yuen, 1997). Unfortunately, a large number of endometriomas are still treated by laparotomy, with 50 percent of physicians surveyed in the United Kingdom still treating endometriomas in this manner (Jones, 2002). Although laparoscopic treatment of endometrioma carries an associated 5 percent risk for conversion to laparotomy, because of its efficacy and low rates of postoperative morbidity, laparoscopy should be the primary procedure of choice (Canis, 2003).

Studies also demonstrate the effectiveness and low morbidity rates in laparoscopic excision of endometriotic implants, and laparoscopic presacral neurectomy appears to be as effective as laparotomy (Nezhat, 1992a; Redwine, 1991). Moreover, adhesiolysis should be performed by laparoscopy when safe, and laparoscopy leads to less de novo adhesion formation than laparotomy (Gutt, 2004).

Hysterectomy with Bilateral Oophorectomy

Hysterectomy with bilateral oophorectomy is the definitive and most effective therapy for women with endometriosis who do not wish to retain their reproductive function. Women who forego bilateral oophorectomy during hysterectomy for endometriosis have a sixfold greater risk of recurrent chronic pelvic pain (CPP) and an eightfold greater risk of requiring additional surgery compared with women who undergo concomitant bilateral oophorectomy (Namnoum, 1995). For this reason, hysterectomy alone has no role in the treatment of CPP secondary to endometriosis.

Despite its effectiveness in the treatment of endometriosis, limitations of hysterectomy with bilateral oophorectomy include surgical risks, pain recurrence, and the effects of hypoestrogenism. Of women who undergo hysterectomy and bilateral oophorectomy for CPP, 10 percent have recurrent symptoms and 3.7 percent required additional pelvic surgery. Accordingly, a consensus conference recommendation from an expert panel of gynecologists in the United States stated that hysterectomy with bilateral oophorectomy should be reserved for women with symptomatic endometriosis who have completed childbearing and recognize the risk of premature hypoestrogenism, including possible osteoporosis and decreased libido (Gambone, 2002).

Approach to Hysterectomy with Oophorectomy

There is no single correct procedure for hysterectomy and bilateral oophorectomy for patients with endometriosis, and surgery may be completed laparoscopically, abdominally, or vaginally (see Section 41-19, p. 905). However, adhesions and distorted anatomy secondary to endometriosis often makes a laparoscopic or vaginal approach more difficult. In addition, the need to remove ovaries may make a vaginal approach less feasible. Accordingly, the choice of procedure will depend on equipment availability, operator experience, and extent of disease.

Postoperative Hormone Replacement

In response to concerns of increased risk of cardiovascular disease and breast cancer with the use of postmenopausal hormone therapy (HT), attention has been directed toward indiscriminant HT use (Anderson, 2004; Rossouw, 2002). Women with endometriosis who undergo hysterectomy with oophorectomy, however, represent a subset of menopausal women who may be better candidates for HT than women who go through natural menopause. First, women who undergo surgical menopause are usually younger and would likely benefit from replacement of estrogen that is lost by removal of functional ovaries. Estrogen replacement should be considered in women with a surgical menopause for prevention of hypoestrogenic side effects such as hot flashes, osteoporosis, or decreased libido. It has been suggested to treat these women until the time of expected natural menopause, although evidence is lacking.

Although unopposed estrogen may be used in postmenopausal women in the absence of a uterus, disease recurrence has been reported with this therapy in women with severe endometriosis first treated with hysterectomy and oophorectomy

(Taylor, 1999). Symptoms required repeat surgery, and did not recur with combined estrogen and a progestin. Additionally, cases of endometrial carcinoma have been reported in women with endometriosis treated with unopposed estrogen after hysterectomy and oophorectomy (Reimnitz, 1988; Soliman, 2004). This is a rare phenomenon and may arise from incompletely resected pelvic endometriosis. Therefore, adding a progestin to the estrogen replacement therapy may be considered in women with severe endometriosis treated surgically.

Treatment of Endometriosis-Related Infertility

Medical therapy used for treatment of endometriosis-related pain has not been shown to be effective in increasing fecundity in women with endometriosis (Hughes, 2003). Surgical ablation has been suggested to be beneficial for women with infertility and minimal to mild endometriosis, although the effect was minimal (Marcoux, 1997). Moderate to severe endometriosis may be treated with surgery to restore normal anatomy and tubal function. However, there are no well-designed trials examining the role of surgery for subfertility in women with severe endometriosis. Alternatively, patients with endometriosis and infertility are candidates for fertility treatments such as controlled ovarian hyperstimulation, intrauterine insemination, and in vitro fertilization (see Chap. 20, p. 447).

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