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Endometriosis and Adenomyosis

Endometriosis and adenomyosis, conditions frequently encountered by the obstetrician-gynecologist as well as the primary care physician, continue to present difficult diagnostic and therapeutic dilemmas. Although each is frequently encountered in everyday practice, they present a contrast in terms of volume and intensity of investigative effort. Both disease entities continue to challenge the practitioner's diagnostic and clinical acumen.

Initially, endometriosis and adenomyosis were thought to be variations of the same disorder. However, we have come to understand that, despite their common feature of ectopic endometrium, they represent distinct pathophysiologic entities. Nevertheless, the two diseases continue to have many features in common. This chapter highlights both the similarities and differences of these proposed endometrium-based abnormalities, as well as differentiating fact from fiction. In so doing, we hope to give the reader a better appreciation of the limitations in current scientific understanding.

ENDOMETRIOSIS

Endometriosis is one of the most commonly encountered diseases in the reproductive-age female. However, despite its prevalence, endometriosis remains one of the most enigmatic disorders encountered by both the generalist and specialist. The wide range of signs, symptoms, and physical appearance of the lesions, combined with the apparent contradictory nature of an extensive scientific literature, has served to create confusion. This confusion has been manifested by widely divergent treatment regimens, each having a paucity of reproducible data to back it up. Indeed, it may well be that to paraphrase Sir William Osler, "he who knows endometriosis knows gynecology."

Established clinical dogma related to endometriosis is now under the close scrutiny of a large group of basic and clinical scientists. These ongoing investigations continue to challenge basic concepts related to the etiology and pathogenesis of the dis-

ease. This scrutiny has forced clinicians to rethink many long-held notions regarding diagnosis and treatment. The rapid evolution in the understanding of endometriosis makes this both a critical and an exciting time in the field. Ongoing analysis of modern advances continues to be paramount in developing a complete and accurate understanding of endometriosis.

Definition

Endometriosis is defined histologically by the presence of endometrial tissue in an ectopic location, exclusive of the myometrium. Traditionally, pathologists have required the presence of both glands and stroma with evidence of menstrual cyclicity (the presence of tissue hemorrhage or hemosiderin-laden macrophages) to firmly establish the diagnosis. The validity of each of these requirements has yet to be established. For the tissue to function as endometrium, there is evidence to indicate that glands and stroma must be present concurrently. However, pathologic function of one or the other of the tissue components (when found alone) has not been adequately assessed. For the purposes of this chapter, we will define endometriosis as the presence of either endometrial glands or stroma, or both, with or without hemosiderin-laden macrophages outside the uterine corpus. Given the fact that the vast majority of endometriosis is found in the pelvis, this is the focus of the discussion unless otherwise specified.

Pathogenesis

More than a century has passed since the original description of endometriosis (Von Rokitansky, 1860), yet we still do not know with certainty why this disease develops. Numerous theories of histogenesis have been proposed by the leading researchers in the field, but three main theories continue to dominate current thinking (Schenken, 1989). The original theory proposed for the origin of ectopic endometriosis was *coelomic metaplasia* arising from the cells that line

the pelvic peritoneum. The basis of this concept derives from the observation that müllerian ducts, germinal epithelium, and pelvic peritoneum all derive from the same source—epithelium of the coelomic wall. This theory, initially advanced by the famous 19th century pathologist Robert Meyer, proposed that continuation of the process of tissue differentiation can occur selectively in certain adult tissues. However, neither he nor subsequent investigators have been able to demonstrate that these differentiated peritoneal cells can maintain a capacity for further differentiation. Several additional issues have arisen that cast doubt concerning the viability of this theory:

1. The disease is not present in males. Only a handful of case reports of endometriosis have been identified in the male; in each case, prostatic carcinoma had been treated with high-dose estrogen (Melicow and Pachter, 1967; Olikier and Harns, 1971; Pinkert et al, 1979; Schrodtt et al, 1980). These few cases probably represent hyperplasia and spread from endometrial rests of the prostatic utricle, a remnant of the müllerian duct in males.
2. The implants lack uniformity within the coelomic membrane, and it is this membrane that covers both the abdominal and thoracic cavities. Although this membrane developmentally contributes to the peritoneum and pleura (Maximow, 1927; Filatow, 1933), endometriosis is seen primarily in the pelvis.
3. In all patients with endometriosis, endometrium is present. Very rarely, endometriosis may be seen in women with müllerian agenesis. However, such women invariably have a focus of endometrium present.
4. The disease occurs primarily in women of reproductive age. If the disease tissue derives from a metaplastic process, then the incidence should increase with advancing age. To explain the observed age distribution, a theory of estrogen-induced metaplasia has been invoked. However, this is not consistent with the low incidence of endometriosis in anovulatory women with chronically elevated estrogen levels.

The theory of coelomic metaplasia persisted unchallenged for many years, despite the lack of scientific evidence. It remains for proponents of this theory to validate its causal role in endometriosis.

The first major challenge to the theory of metaplasia was proposed by Sampson in 1921 when he put forth the concept of *transplantation*. This theory maintains that endometriosis originates from the uterine endometrial tissue that is transported to ectopic locations, then implants and grows. A number of routes of dissemination have been proposed, including lymphatic dissemination, vascular spread, iatrogenic transplantation, and retrograde menstruation.

The idea that "shed" endometriosis could result from lymphatic transport was first advanced by Halban in 1925 with the publication of five cases illus-

trating the concept. Finally, microscopic evidence of endometrial cells within lymphatics and nodes was obtained (Javert, 1949). Considerable research has established that shed endometrial cells are viable in vitro (Geist, 1933; Keettel, 1951). In addition, these cells have been viably maintained in culture for up to 2 months (Mungyer et al, 1987). Early studies done to determine the implantation capacity of such cells in vivo were initially disappointing. However, subsequent experiments involving both monkeys (TeLinde and Scott, 1950) and humans (Ridley and Edwards, 1958; Ridley, 1968) have shown that placement of endometrial tissue into ectopic locations does indeed result in endometriosis.

A second route of spread was proposed by Sampson (1925), when he introduced the concept of hematogenous transport. This was suggested by the demonstration of endometrial tissue within the pelvic veins (Javert, 1952) and reports of endometriosis at a multitude of remote sites (Ridley, 1968). However, the rarity of these cases suggests that they represent a small fraction of the cases of endometriosis.

Iatrogenic transplantation has been suggested experimentally in the subhuman primate and is further endorsed by the finding of endometrial tissue in surgical scars (Ridley, 1968). Yet most women with endometriosis have not experienced prior uterine surgery, negating this as a major cause of the disease.

The major contributing factor of retrograde menstruation in the genesis of endometriosis is now a well-established fact. Retrograde menstruation itself is a well-established phenomenon, with data available in menstruating women undergoing peritoneal dialysis (Blumenkrantz et al, 1981) or laparoscopy at the time of menses (Halme et al, 1984; Liu and Hitchcock, 1986) documenting a 76% to 90% rate of retrograde flow. In addition, it has long been known that there are viable cells within the menstrual flow, clearly demonstrated by supravital staining of endometrial cells within the menstrual discharge (Geist, 1933). Evidence also exists to support the theory that women with endometriosis have a relative hypotonia of the uterotubal junction (Ayers and Friedenstab, 1985), and endometrial tissue is refluxed into the peritoneal cavity in women with endometriosis more frequently than in controls with patent tubes but no endometriosis (Bartosik et al, 1986). Additionally, the presence of endometrial cells within the tubal lumen (Javert, 1949) and in the peritoneal fluid (Beyth et al, 1975) has been clearly established. Finally, in the baboon, intraperitoneal injection of endometrium from the proliferative or luteal phase will only occasionally result in implantation; however, the incidence is drastically higher with the injection of menstrual endometrium (D'Hooghe et al, 1994).

The anatomic distribution of endometriotic implants offers additional circumstantial evidence in support of the transplantation theory. Jenkins and colleagues (1986) assessed the anatomic distribution of endometriosis (Fig. 30-1) in a laparoscopic study

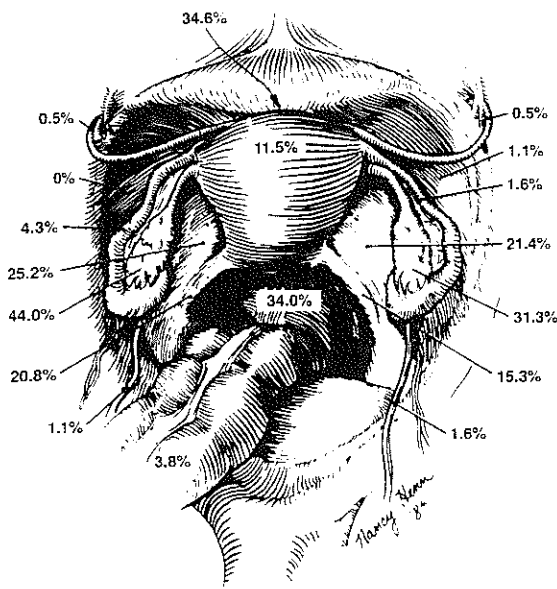


Figure 30-1

Anatomic distribution of endometriotic implants in 182 infertility patients found to have endometriosis at laparoscopy. The rates shown indicate the percentage of all with implants in a given locale. (From Jenkins S, Olive DL, Haney AF: Endometriosis: pathogenetic implications of the anatomic distribution. *Obstet Gynecol* 1986;67:336, with permission of the American College of Obstetricians and Gynecologists.)

of implants, adhesions, and uterine position in 182 patients. The rate of implants in dependent locations supports retrograde menstruation as a mechanism of transport. Implants and adhesions are most common in the anterior and posterior cul-de-sacs of the pelvis, as well as the paracolic gutters. Furthermore, anterior compartment endometriosis was rarely found in women with retroverted uteri, a condition in which the anterior cul-de-sac is no longer a dependent pocket. Taken together, this information confirms the importance of retrograde menstruation in the development of endometriosis. However, not all women (or even a majority of women) have endometriosis, leading one to wonder what other factors are necessary.

The *induction* theory of endometriosis is a combination of the two previously mentioned theories, coelomic metaplasia and endometrial transplantation. It states that unknown substances released from shed endometrium induce undifferentiated mesenchyme to form endometriotic tissue. Animal research in the rabbit model has attempted to validate this theory. Deposition of both fresh and denatured endometrium into the subcutaneous tissue resulted in the formation of endometrial cysts (Lavender and Normal, 1955). The demonstration of glands similar to endometrial structures adjacent to areas of subcutaneous implantation of Millipore chambers in the peritoneal cavity of rabbits supports this theory (Merrill, 1963, 1966). Of note, no endometrial stroma was induced in either of these experiments. Whether

this induction is merely the well-recognized process of stromal induction of adjacent epithelium or, instead, the induction of complete endometrium capable of growth and development is unclear.

The discrepancy between the universality of retrograde menstruation and the minority of patients with endometriosis has led investigators to consider that the intraperitoneal environment in some women may be conducive to the development of the disease. Given this scenario, research has centered on the immune system as a likely instigator. A number of immunologic disorders are associated with the presence of endometriosis (Hill, 1992), any of which could play a role in the successful transplantation of endometrial tissue. In humans most of the research on the immunology of endometriosis is observational and involves studies on the various aspects of immune function in infertile women who have been diagnosed with the disease. A pattern of immune dysfunction can be identified from these studies: women with endometriosis appear to exhibit increased macrophage activation and decreased cell-mediated immunity.

The placement of menstrual debris into the peritoneal cavity with menses elicits a response from the body geared toward its removal, with the prime candidate being cell-mediated cytotoxicity (Dmowski et al, 1981; Steele et al, 1984). Studies have suggested that there exists a deficiency of both T-cell-mediated cytotoxicity and natural killer (NK) cell-mediated cytotoxicity in women with endometriosis. Macrophages, a key component in the function of cell-mediated cytotoxicity, are the major cell type in the peritoneal fluid, and vary throughout the menstrual cycle, being greater in the follicular phase immediately after the menses (Hill, 1988). Infertile women with endometriosis appear to possess a larger number of peritoneal macrophages compared to fertile controls. These cells have all the characteristics of tissue-differentiated mononuclear phagocytes, with the stimulus for differentiation probably being retrograde menstruation (Halme et al, 1982, 1983a, 1983b). There is evidence to suggest that peritoneal macrophages from women with endometriosis possess accentuated activation characteristics resulting in enhanced phagocytic activity and secretion of several soluble substances (e.g., proteolytic enzymes, cytokines, prostaglandins, and/or growth factors) (Halme et al, 1988). Recent investigations have documented that the increased macrophage activation in endometriosis is accompanied by their production of growth factors, including platelet-derived growth factors, epidermal growth factor, and transforming growth factor- β (Ramey and Archer, 1993). It is these growth factors that have been shown to stimulate the proliferation of endometrial stromal cells *in vitro*, and it has been speculated that they enhance the implantation of endometrial cells (Simms et al, 1991; Strowitzki et al, 1991; Surrey and Halme, 1991). Such data suggest that a combination of factors including the hormonal milieu and the number and secretory

capacity of cells residing in the peritoneal cavity might be required to sustain the growth of ectopic endometrium, with the induction of clinical endometriosis.

Several lines of investigation have centered on interleukin-8 (IL-8) and monocyte chemoattractant protein-1 (MCP-1), highly cell-specific chemoattractants in the pathogenesis of endometriosis. IL-8 is a potent angiogenic agent, chemoattractant, and activating cytokine for granulocytes, while MCP-1 is a chemoattractant and activating cytokine for monocytes and macrophages. Sources of these cytokines include endometrium (with retrograde menstrual possibly providing sufficient amounts) and peritoneal mesothelium. The concentrations of MCP-1 and IL-8 are elevated in the peritoneal fluids of women with endometriosis compared to disease-free women, and the levels correlate with the severity of the disease (Arici et al, 1995, 1996). These preliminary data serve to explain the process of endometriosis generation. Retrograde menstruation is a mandatory component, with implantation and growth requiring estrogen in conjunction with growth factors from peritoneal macrophages. In turn, these macrophages are recruited via chemoattractants such as IL-8 and MCP-1, which are produced by endometrium and/or peritoneum. Added to this may be a deficiency in the response by cytotoxic T cells and NK cells, leading to the passive promotion of endometriosis.

Epidemiology

Endometriosis has been estimated to affect between 10% and 15% of premenopausal women (Ranney, 1980). The peak incidence is in the third and fourth decades of life, but diagnosis appears to be in the range of 25 to 29 years. Approximately 4 of 1000 women ages 15 to 64 years are hospitalized annually for endometriosis (Candiani et al, 1991). The typical age at which endometriosis is diagnosed appears to be in the range of 25 to 29 years (Norwood, 1960). One report placed the mean age of symptoms at the age of 20, roughly 5 years before the mean age of diagnosis. Thus, with increased awareness and improved diagnostic capability, a decrease in the average age of diagnosis is anticipated. The latest epidemiologic data suggest that women with short cycle lengths (≤ 27 days) and a longer flow (≥ 1 week) had more than double the risk for endometriosis compared with women with longer cycle lengths and shorter duration of flow (Cramer, 1986). Cramer also found a decreased risk of endometriosis associated with smoking or exercise that was confined to women who began either habit at an early age and were heavier smokers or more strenuous exercisers.

Endometriosis is extremely rare in premenarche, having been reported in only a single autopsy examination of a stillborn (Redwine, 1989b). Its occurrence rate in adolescents is unknown, but it appears

not to be rare in the teenage years. In two studies of women under age 20 with chronic pelvic pain or dysmenorrhea unresponsive to medical therapy, endometriosis was found at surgery in 47% to 65% of cases (Goldstein et al, 1980; Chatman and Ward, 1982). Simply considering the teenage years to be a single entity, however, may be misleading. A disproportionate number of cases in the early teen years are attributable to müllerian anomalies and uterine outflow obstruction (Hanton et al, 1967; Schiffrin et al, 1973), whereas cases in the late teenage years tend to occur in females with otherwise normal genital tracts. Although this may represent selection bias based on when these young women undergo surgery, the fact remains that most documented instances of endometriosis in females under 17 are associated with outflow tract obstruction (Huffman, 1981).

Endometriosis is commonly believed to be rare in menopausal women. However, 2% to 4% of all women requiring laparoscopy for endometriosis are postmenopausal (Kempers et al, 1960; Punnonen et al, 1980). Although most of these women are receiving hormone replacement therapy, this is not true in all reports (Djursing et al, 1981).

Epidemiologic evaluation of the "true" prevalence of endometriosis is difficult because laparoscopy is required to make the diagnosis, but it is not possible to expose a random sample of women to the procedure. The choice of the population studied has been responsible for the large variations in observed frequency of disease. The prevalence has ranged from 2% to 48%, but these figures have been based on the populations studied. The highest rates of endometriosis are found in women undergoing laparoscopy for infertility and pelvic pain, whereas the lowest rates are in those undergoing laparoscopic tubal sterilization (Sangi-Haghpeykar and Poindexter, 1995).

The impact of selection bias is evident in a study by the Baylor Gynecologic Collaborative Group, which found a prevalence of 0.7% in women undergoing tubal anastomosis, 1.6% at laparoscopic tubal ligation, 11.3% at the time of abdominal hysterectomy, and 31% at operative laparoscopy (Wheeler, 1989). Using vaginal hysterectomy as a reference procedure by which to determine the true prevalence in the reproductive-age population, Wheeler estimated an overall prevalence of approximately 10%.

The demography of endometriosis has a highly controversial history. It was classically thought to be a disease of white middle-aged women belonging to the upper socioeconomic class, with Meigs (1949) documenting endometriosis in 28% of white women undergoing laparotomy versus only 5.8% of blacks. Numerous epidemiologic studies have disputed this myth (Chatman, 1976; Chatman and Ward, 1982; Kirshon et al, 1989), with endometriosis noted to be present in all ages, races, and socioeconomic groups. Meigs' study was limited by not controlling for confounding variables such as availability of health care, access to contraception, cultural differences regard-

ing childbearing patterns, and attitudes toward men- ses and pain. Later studies demonstrated that the ap- parently higher endometriosis rates in whites were the result of socioeconomic factors rather than race, and controlling for such factors resulted in similar rates among the races (Scott and TeLinde, 1950; Lloyd, 1964). Investigations undertaken more re- cently have noted an increased rate of endometriosis among Asians in comparison to other ethnic groups (Sangi-Haghpeykar and Poindexter, 1995). They noted a higher probability of disease among Asian women (odds ratio = 8.6) compared with white women after controlling for the effect of age, number of live births, and income. When other socioeco- nomic factors were controlled for (i.e., marital status, income level, and education), no association with en- dometriosis was noted.

The possibility of a familial tendency for endo- metriosis was first suggested by Goodall (1943). Al- though initially there were few data to support this concept, Ranney (1971b) demonstrated, by retrospec- tive analysis, what appeared to be hereditary ten- dencies in 53 family groups having the disease. More recently, Simpson et al (1980) and Malinak and co- workers (1980) have demonstrated a high probability of genetic influences, with the most probable mode being polygenic and multifactorial. A current search is ongoing for the endometriosis gene. The OXE- GENE project has targeted sister-sister pairs with ad- vanced, documented endometriosis as a source to identify a gene variant unique to this population. Re- sults will be forthcoming.

Symptoms

Endometriosis, although associated with a large va- riety of symptoms, primarily produces pain and in- fertility. Despite the strong correlation with these dis- orders, however, the pathophysiology of the associations is not well understood. Appearance, lo- cation, depth of invasion, and other factors may all influence symptoms, as well as a number of individ- ualized confounding variables.

When one is examining the relationship between infertility and endometriosis, two questions must be asked. First, what is the incidence of infertility in women with endometriosis? This question remains unanswered because selection bias limits the appli- cability of any published figures. The second ques- tion is the reverse: What is the rate of endometriosis in the infertile patient? The published range is 4.5% to 33%, with a mean of 14% (Pauerstein, 1989). One investigation demonstrated a 21% incidence of en- dometriosis in infertile women, whereas only 2% of fertile controls were found to have the disease (Stra- thy et al, 1982). Thus endometriosis is not a random finding but, rather, is well associated with infertility.

Endometriosis has been linked to aberrations in every step of the reproductive process. Moderate to severe disease can lead to marked anatomic altera-

tions and subsequent changes in the tubo-ovarian relationship. Disturbances in ovulation caused by intermittent anovulation, abnormal follicular devel- opment, and/or luteal-phase defects have been sug- gested as possible mechanisms (Olive and Ham- mond, 1985; Surrey and Halme, 1989). However, more recent studies have suggested that such abnor- malities are present no more often in patients with endometriosis than in other fertile or infertile women. The role of endometriosis-associated inflam- matory changes in the local peritoneal fluid environ- ment as a cause of infertility is now an active area of investigation. Several reports have demonstrated that inflammatory cytokines within the peritoneal fluid of women with endometriosis affect sperm mo- tility and survival, sperm-oocyte interactions, ovum pickup by the fimbria, and early embryonic devel- opment (Eisermann et al, 1988; Halme, 1989; Hill et al, 1987).

Clinical investigators also have addressed this is- sue. Jansen (1986) prospectively analyzed 91 women undergoing artificial insemination with donor sperm who had no apparent infertility factor. All had hus- bands with azospermia or severe oligospermia. Of the 91, 7 had endometriosis upon screening laparos- copy. Subsequent fertility was significantly lower in the women with endometriosis. However, the study was limited by the number of endometriosis pa- tients, the lack of uniform criteria regarding laparo- scopic diagnosis of endometriosis, and a 4% monthly conception rate among women with endometriosis (a figure far lower than that seen in most studies of endometriosis-associated infertility). A compre- hensive multivariate investigation into potential patho- genic factors affecting fertility in 731 infertile women determined that endometriosis without adhesions did not alter the cumulative conception rate (Dun- phy, 1989). Data on 207 couples undergoing donor insemination were analyzed by Chauhan and asso- ciates (1989); they found that recipients with no in- fertility problems whose partners were azospermic had the highest pregnancy rates, while rates were lowest for normal women with oligospermic part- ners. In addition, donor insemination recipients with treated endometriosis had higher pregnancy rates than women with other infertility factors.

Pelvic pain may well be the most common symp- tom of endometriosis. This particular expression of the disease may take on many forms. Dysmenorrhea is reported in 25% to 67% of women with endome- triosis, with the rate clearly dependent on selection bias in the study group (Olive and Haney, 1986). Good evidence of the disease is the onset of second- ary dysmenorrhea. In patients with a history of pri- mary dysmenorrhea, increasing severity may also be a clue to the presence of endometriosis. Dyspareunia is also common, generally reported in approximately 25% in patients with documented endometriosis (Olive and Haney, 1986). The greatest incidence of dyspareunia is seen in association with uterosacral involvement. Other types of pain are also reported:

noncyclic lower abdominal pain in 25% to 39% and backaches in 25% to 31% (Olive and Haney, 1986).

Numerous investigators have attempted to explain the pathophysiology of endometriosis associated pain. The heterogeneity of the disease process, however, suggests that a range of pathophysiologic processes are involved. Different types of lesions cause pain via different routes. Atypical papular lesions may produce more prostaglandins than older lesions. These lesions may be responsible for functional pain symptoms, such as dysmenorrhea (Vercellini et al, 1991). Classical-appearing lesions are thought to be older or burnt out endometriosis (Koninckx et al, 1991). It is these lesions that might be more likely to provoke organic-type pain from mechanical pressure of cystic nodules and from stimulation of pain fibers by scars and stretching of areas of fibrotic infiltration, as could occur during intercourse upon deep penetration (Vercellini et al, 1991).

The depth of infiltration of endometriosis has been recognized to correlate with pelvic pain (Koninckx et al, 1991; Martin et al, 1989). Because depth cannot be easily evaluated by visual inspection alone, surgical excision is required to make an accurate evaluation. Very deep implants appear to be more active and may be found exclusively in patients with pain. Cornillie and co-workers (1990) found that nearly all women with lesions deeper than 1 cm suffer from severe pain. In this study, women with superficial (<1 mm), intermediate (2 to 4 mm), or deep (5 to 10 mm) infiltration had pain in 17%, 53%, and 37% of cases, respectively. Total lesion volume, however, has not been found to be directly related to patient symptoms. Most recently, Vercellini and co-workers (1996) found that the frequency and severity of deep dyspareunia and the frequency of dysmenorrhea were less in the patients with only ovarian endometriosis than in those with lesions at other sites. The presence of vaginal endometriosis was associated with more frequent and severe deep dyspareunia.

Adhesion formation is common in patients with endometriosis, and may be related to the degree of pain. Adhesions may cause pain by direct nerve damage, from tissue destruction and scar formation, or by devitalization and ischemia of parts of the internal pelvic organs, secondary to damage to the blood supply. Organs such as bowel or adnexa may also be adherent in abnormal areas and cause any movement to place traction on their nerve supply. Over time, scarring of the posterior uterine surface may become extensive enough to produce a fixed retroflexion possibly resulting in sacral pain caused by direct pressure. In addition, the pain may be referred to the back, lower abdomen, rectum, and thighs because of the proximity of lumbar and sacral nerves.

Dysfunctional uterine bleeding is often linked with endometriosis. Scott and TeLinde (1950) first noted the association, reporting 44% incidence of abnormal bleeding among their patients with endometriosis. However, virtually all cases were attrib-

uted to associated pathology, with few women exhibiting true dysfunctional bleeding with the disease. Similar results were later reported by Ranney (1971a). Anovulation rates in women with endometriosis are reported to be 9% to 17% (Soules et al, 1976; Radwanska et al, 1984). However, such studies lack control groups, utilize inconsistent criteria for the diagnosis of anovulation, and have not evaluated the frequency of repetitive anovulatory cycles. Thus there is not good evidence to implicate endometriosis as a cause of dysfunctional uterine bleeding.

Additionally, a diverse array of symptoms may result from implantation of endometrium on the pelvic viscera. Thus endometriosis may result in bowel-related symptoms, such as tenesmus or dyschezia, or urinary tract symptoms, such as dysuria, frequency, or urgency. Finally, endometriosis at remote sites may produce unusual site-specific complaints; examples include pleuritic pain caused by pulmonary involvement and seizures secondary to brain lesions.

Physical Findings

Physical findings associated with endometriosis are variable and dependent on the severity and location of disease as well as the character of the population under study. Common findings include nodularity or tenderness of the cul-de-sac, parametrial thickening, and adnexal masses. A retrodisplaced uterus, often fixed, has been frequently noted. Cutaneous lesions may even be present, with likely sites being the vagina, perineum, and umbilicus and within surgical scars. Rarely, significant ascites may be observed (Jenks et al, 1984).

Physical exam is of limited value in these patients because women with extensive disease often have minimal findings. Because disease manifestations often become more pronounced and areas of ectopic endometrial implantation more tender during the menses, it is often useful to examine the patient during the perimenstrual period. Deep endometriosis may be underdiagnosed clinically and, during surgery, the diagnosis can be difficult and deep endometriosis may remain undetected. Koninckx and colleagues (1996) confirmed that clinical examination during menstruation is a simple and reliable test to diagnose deep endometriosis and to decide which women should be prepared preoperatively for bowel surgery. They prospectively documented a 77% sensitivity rate for identification of deep endometriosis during menstruation, whereas there was a 36% sensitivity rate by routine clinical examination during the follicular or luteal phase.

Diagnostic Methods

Three classes of techniques have been used to diagnose and observe women with endometriosis: serum

immunology, radiologic imaging, and laparoscopic examination of the peritoneal cavity. The monoclonal antibody OC-125 identifies the antigenic determinant CA-125, originally found in an ovarian epithelial tumor. This antigen has subsequently been found in the endocervix, endometrium, fallopian tube, peritoneum, pleura, and pericardium. An elevated peripheral blood concentration of CA-125 has been described in many women with endometriosis (Barbieri et al, 1986; Pittaway and Favez, 1986). Although this discovery raised the hope of a possible blood test for endometriosis, subsequent evaluation has shown the test to be insufficiently sensitive or specific to be useful in screening (Malkasian et al, 1986; Patton et al, 1986). Furthermore, a placebo-controlled trial has questioned the value of following serum CA-125 levels to monitor treatment effect (Kauppila et al, 1988).

Development of a second-generation CA-125 assay has increased interest in its use. Hornstein and colleagues (1995) have compared the serum CA-125 concentrations in women with and without endometriosis using both the older assay and the new CA-125 assay in an effort to determine if the newer assay has improved clinical utility. They found that the sensitivity and specificity of the newer assay was slightly improved; however, they found no increase in the rate of detection of endometriosis over the old assay.

Screening for other serum proteins, such as placental protein 14 (PP-14) and antibodies to endometrial tissue, are currently being investigated. PP-14 is produced in secretory endometrium, and its concentration in the serum varies with the menstrual cycle. Active endometriosis has been shown to elevate the serum levels (Telimaa et al, 1989a). More recently, it has been shown that superficial endometriosis secreted both PP-14 and CA-125 into the peritoneal cavity and that more deeply infiltrating lesions secreted these substances into the blood (Koninckx et al, 1992). Although endometrial antibodies are detected in the serum in a high percentage of patients with endometriosis, these levels do not correlate with the severity of the disease (Wild and Shivers, 1985).

Imaging techniques have been used periodically in an attempt to diagnose endometriosis. Ultrasonography has proven to be of value in the identification of ovarian endometriomas, although the appearance of an echogenic cystic structure is not pathognomonic (Schwartz and Seifer, 1992). Guerriero and colleagues (1996) prospectively evaluated the use of transvaginal ultrasonography combined with CA-125 plasma levels to differentiate endometriomas from nonendometriotic cysts. They found that the addition of CA-125 did not improve the quality of the test. Ultrasonography is not currently useful in identifying focal implants because its sensitivity is as low as 11% (Friedman et al, 1985). In addition, Pauerstein (1989) has noted a high false-positive diagnostic rate for the identification of diffuse disease.

Magnetic resonance imaging (MRI) has now demonstrated its value in the diagnosis of endometriosis (Arrive et al, 1989; Zawin et al, 1989; Togashi et al, 1991). Some of these early studies proved disappointing, with a sensitivity of only 64%, a specificity of 60%, and predictive accuracy of 63%. When Togashi and colleagues (1991) limited their investigation to women with adnexal masses, however, the sensitivity, specificity, and predictive accuracy of the identification of endometriomas by MRI were 90%, 98%, and 96%, respectively. MRI does exhibit several limitations. The appearance of endometriosis is not pathognomonic. Although the imaging of diffuse pelvic lesions is more readily accomplished by MRI than by ultrasonography, the sensitivity remains low.

The refinement of MRI detection of diffuse endometriosis with the inclusion of both fat-suppression and fat-saturation techniques has greatly enhanced its diagnostic accuracy. Diagnosis of endometriosis by MRI using the fat-saturation technique revealed an overall sensitivity of 89%, a specificity of 71%, a positive predictive value of 95%, and a negative predictive value of 50% when compared to conventional MRI and confirmed surgically (Takahashi et al, 1994). Use of the fat-suppression technique increased the diagnostic accuracy to 77% versus 55% with conventional MRI, while overall sensitivity was increased to 61% versus 27% (Ha et al, 1994). In both studies, the detection rates were based on endometrial implants greater than 4 mm in size.

Two potential roles for MRI can be readily identified. One is the identification of endometriosis obscured by pelvic adhesions, which may prove an important screening tool prior to surgery and extensive lysis of adhesions (Zawin et al, 1989). Additionally, pelvic MRI has now been shown to be effective in the evaluation of response to medical treatment of endometriomas (Takahashi et al, 1996).

Laparoscopy remains the optimal diagnostic method for endometriosis. However, the value of this modality is directly dependent on the ability of the surgeon to recognize the lesion when visualized. Difficulty in identifying the more subtle manifestations of endometriosis may have resulted in underestimation of the prevalence of the disease among young women. Additionally, the great variety in the appearance of these lesions contributes to the potential diagnostic confusion (Table 30-1) (Jansen and Russell, 1986; Stripling et al, 1988). A recognition of

Table 30-1. MULTIPLE APPEARANCES OF ENDOMETRIOTIC IMPLANTS

Brownish, discolored peritoneum
Superficial peritoneal ecchymoses
Raised, reddish, superficial nodules
Reddish-blue invasive nodules
Fibrotic, whitish nodules
Raised, glossy, translucent blobs
Patchy, white opacified peritoneum
Reddish or bluish ovarian cysts

these "nontraditional" appearances can result in a significant increase in the frequency of diagnosis (Martin et al, 1989). The effect of this protean appearance of the disease may have resulted in a significant underestimation of endometriosis in young adults, because a pattern of evolution has been identified from more subtle-appearing lesions in the teenage years to the traditional red or black foci a decade later (Table 30-2) (Redwine, 1987). D'Hooghe et al (1996) demonstrated that endometriosis in captive baboons undergoing repeated laparoscopies is a dynamic and moderately progressive disease with periods of development, regression, and active remodeling. These fluctuations eventually led to disease progression as scored by increase in American Fertility Society (AFS) score and in both number and surface area of lesions after 9 to 13 months and after 19 to 24 months.

Given this wide variation in appearance, simple visualization cannot be relied on to rule out the disease. To this end, excision of any suspect lesions at laparoscopy, with pathologic confirmation, is essential to assess questionable aspects of the disorder (Martin and Zwaag, 1987). Still, some colorless manifestations are extremely subtle. One technique that can assist the surgeon in the identification of these subtle manifestations is the "painting" of peritoneal surfaces with bloody peritoneal fluid. By allowing the fluid to flow across the peritoneal surface, colorless endometrial lesions will be highlighted by erythrocytes as the red blood cells stream around them (Redwine, 1989a). Additionally, some have advocated the use of a "bubble test" of peritoneal surfaces utilizing bursts of saline and subsequent observation of excessive soap-like bubbling. Gleicher and colleagues (1995) demonstrated a sensitivity of 100% and a specificity of 88% for this technique, with positive and negative predictive values of 94% and 100%, respectively.

Pathology

Endometriotic implants have traditionally been described as bluish-gray "powder burns." The color is attributed to the menstrual cyclicality of the ectopic endometrium, with hemolysis and encapsulation of the debris by scarring. Frequently, the distinctive coloration is lost during surgical excision because of incision of the surrounding scar and escape of the encapsulated debris. As mentioned earlier, endometriotic implants may appear in a wide variety of presentations, including nonpigmented, clear vesicles; white plaques; and reddish petechiae or flame-like areas. These implants range from several millimeters to 2 cm in diameter. They can be superficial or invasive, with the latter often involving subperitoneal structures.

Endometriotic cysts are frequently encountered, primarily involving the ovary. At the time of menstruation, cyclic hemorrhage is retained by the sur-

rounding cell wall, with slow reabsorption of the debris. Fresh episodes of bleeding replenish the cyst contents with each menses. Cyst fluid is often a dark, tarry, "chocolate" brown, but may also appear clear or bright red.

Fibrous adhesions often form as a response to chronic irritation of the peritoneal surfaces by the endometriotic implant and its secretory products. Foci of endometriosis are often found at the base of such adhesions.

Peritoneal pockets in the pelvis were first described in association with endometriosis by Sampson (1927). These pockets are found in roughly 18% of women with endometriosis, and two thirds of the structures have endometriotic implants either around the rim or inside the defect (Redwine, 1989b). Such pockets are thought to represent a primary developmental formation defect of the pelvic peritoneum; the ontologic relationship between these pockets and endometriosis, if any, has yet to be delineated.

Although endometriosis is often easily visualized, the disease may be missed completely by the surgeon because microscopic lesions may be present in visually normal peritoneum (Murphy et al, 1986). This phenomenon has been seen in up to 6% of women and endometriosis when biopsies were done of visually normal peritoneum and/or uterosacral ligaments (Nisolle et al, 1990b). This finding, however, has been disputed by others who claim that the original finding was secondary to "unrecognized" rather than "microscopic" disease (Redwine, 1988a).

Microscopically, endometriosis contains four major components: endometrial glands, endometrial stroma, fibrosis, and hemorrhage (Fig. 30-2). It is generally accepted that at least two of these components must be present before the lesion can be classified as endometriosis, because no individual component is itself pathognomonic.

Implants are often thought to undergo cyclic histologic changes in synchrony with normal endometrium as determined by the gonadal steroids. When carefully evaluated, however, the vast majority of implants do not demonstrate the typical cyclic histology observed within the uterus, and those that do are often asynchronous with active tissue (Metzger et al, 1988). Nisolle et al. (1994) evaluated estrogen and progesterone receptor content in both normal endometrium and peritoneal endometriotic implants; the estrogen receptor content was found to be lower in the endometriotic tissue when compared with endometrium, but the cyclic pattern was similar in both tissues. Progesterone receptor content was similar in both tissues, except during the late secretory phase in ectopic glandular epithelium, in which high persistent progesterone receptor content was observed. It is unclear whether this is due to abnormal hormonal responsiveness because of altered steroid receptor populations, an altered epithelial-stromal relationship, an aberrant blood supply, or the presence of an associated inflammatory reaction.

Table 30-2. EVOLUTION OF COLOR APPEARANCE OF ENDOMETRIOSIS WITH AGE

COLOR APPEARANCE	NO. OF PATIENTS	MEAN AGE (yr) \pm SD	AGE RANGE (yr)
Clear papules only	6	21.5 \pm 3.5	17-26
Clear papules plus other clear lesions	8	23.0 \pm 4.0	17-28
Clear plus any others	14	23.4 \pm 4.7	17-31
Red only	16	26.3 \pm 5.4	16-38
Red plus any others	22	26.9 \pm 5.7	17-43
All nonblack	55	27.9 \pm 7.2	17-42
White plus any others	24	28.3 \pm 6.9	17-43
Black plus any others	34	28.4 \pm 5.8	17-43
White only	8	29.5 \pm 5.9	20-39
Black only	48	31.9 \pm 7.5	20-52

From Redwine DB: Age-related evolution in color appearance of endometriosis. *Fertil Steril* 1987;48:1063, with permission of the American Fertility Society.

The histology of the ovarian endometrioma often lacks the usual findings characteristic of the disease. The cyst wall is often nondescript, with simple cuboidal epithelium and little histologic evidence of menstrual cyclicality. Fibrous tissue often lines the cyst wall (Fig. 30-3).

Specific cycle-dependent changes in the ultrastructural appearance of normal endometrium have been described for both normal glands and stroma (Ferenczy, 1976a, 1976b). These include giant mitochondria and the appearance of nuclear channel systems coinciding with ovulation. Conversely, ectopic endometrium often fails to demonstrate these ultrastructural characteristics (Lox et al, 1984). Frequently, collagen fibrils surround the implant. Because the scarring may obliterate standard histologic features, the ultrastructural appearance may be the best means of identifying the tissue as endometriotic.



Figure 30-2
Photomicrograph of implant of endometriosis, exhibiting both glands and stroma. (Courtesy of Philip T. Valente, MD, Department of Pathology, University of Texas Health Science Center at San Antonio.)

Staging Systems

A variety of classification schemes have been proposed over the years. Early attempts centered around descriptive stages derived from surgical and histopathologic findings (Table 30-3). In 1962, Riva and associates were the first to attempt a classification of endometriosis based on scalar criteria. They grouped patients based on the cumulative count of pelvic structures involved, but found their scores correlated poorly with clinical status. This attempt was the forerunner of modern classification schemes.

More recent staging systems have focused not merely on the physical manifestations but also on the prognosis (Table 30-4). Acosta and associates (1973) were the first to correlate extent of disease with pregnancy rates following conservative surgery. Their scheme was based on an anatomic description of in-

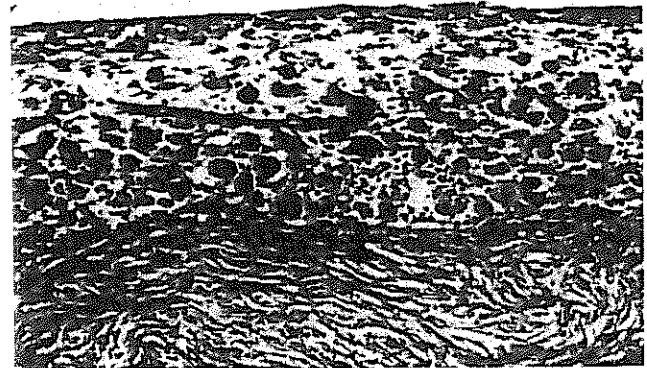


Figure 30-3
Photomicrograph of endometrioma cyst wall with numerous macrophages. (Courtesy of Philip T. Valente, MD, Department of Pathology, University of Texas Health Science Center at San Antonio.)

Table 30-3. EARLY ENDOMETRIOSIS CLASSIFICATION SCHEMES

Sampson (1921)	Staged by adhesions
Wicks and Larson (1949)	Histology alone
Huffman (1951)	Amount of invasion, location, pregnancy rates
Norwood (1960)	Clinical-anatomic-histologic
Riva et al (1962)	Attempted scalar criteria
Beecham (1966)	Intraoperative findings, for record keeping only
Mitchell and Farber (1974)	Similar to malignant staging

volved pelvic areas. Unfortunately, the staging was entirely arbitrary and unsupported by data; nevertheless, a rough correlation existed between severity of disease and inability to conceive. Although other related schemes were published in subsequent years, none enjoyed the widespread popularity of the "Acosta Classification."

Nevertheless, because of the lack of agreement among leading researchers in the field, the AFS convened a panel in 1978 to arrive at a consensus. The result was an innovative scheme based on the natural progression of the disease, with allowances for unilateral involvement (AFS, 1979). The stage of endometriosis was based on a cumulative score of a weighted value system related to the involvement of the peritoneum, ovaries, and fallopian tubes. In addition, an anatomic drawing was provided to depict surgical findings, including extragenital implants. In 1985, the AFS introduced a revision of this classification scheme because of numerous shortcomings that had been identified over the ensuing years. In contrast to the original scale, strong emphasis was placed upon the presence of adnexal adhesions and deep endometriotic invasion (Fig. 30-4).

The basic premise for categorization protocols is that similar stages of a disease will respond predictably to specific treatment plans, resulting in a reproducible outcome. Despite the wide range of attempts at staging the disease, all classification schemes developed to date have a number of inherent problems in fulfilling this theoretical framework:

1. None of the modern schemes attempts to correlate extent of disease with pain or risk of recurrence; only the relationship between extent of disease and fertility prognosis has been attempted.
2. All schemes are based on clinical opinion rather than any type of sophisticated statistical analysis.
3. Each classification category is arbitrarily assigned a point score that may not reflect the true relative risk of each disease locus.

4. The cutoff thresholds for each of the severity categories were chosen arbitrarily.
5. The accuracy of laparoscopic staging using these staging systems has never been assessed.

Given these shortcomings, it is of limited utility to report treatment data in terms of disease severity according to any of the published classification methods. Only more recently has scientific rigor been applied to basic and clinical investigation into endometriosis, as anecdotal reports and retrospective surveys appeared in an attempt to pass for treatment trials. The reproducibility of the revised AFS classification scheme for endometriosis has been called into question. Hornstein and colleagues (1993) found that the comparison of intraobserver and interobserver scores resulted in a change in endometriosis staging in 38% and 52% of patients, respectively. The variability was found to be high for ovarian endometriosis and cul-de-sac subscores when the revised classification was utilized.

To define adequately the relationship of various locations and extent of endometriotic lesions to the successful treatment of infertility and pelvic pain, a large, prospective study utilizing multivariate logistic regression analysis is required. Palmisano and colleagues (1993) undertook just such a study in a cohort of infertile women in whom they retrospectively evaluated the use of endometriosis staging systems to predict pregnancy rates. Pregnancy rates were analyzed using life table and cluster analyses, with combinations of endometriosis site and infertility type being evaluated with Cox's regression model. Their results showed that no anatomic site or type significantly affected prognosis, and staging systems based solely on anatomic site and the type of lesion are insufficient for predicting fertility. The relationship of pelvic pain to the stage and type of endometriotic lesions requires a different scheme, which is best illustrated by the surgical trial undertaken by Sutton and colleagues (1994). In their study

Table 30-4. MODERN ENDOMETRIOSIS CLASSIFICATION SCHEMES

Acosta et al (1973)	Correlates extent with pregnancy after surgery
Ingersoll (1977)	Modification of Acosta scheme
Kistner et al (1977)	Based on geographic dissemination
Buttram (1978)	Designed to select most appropriate mode of therapy
Cohen (1979)	Based on laparoscopic findings
American Fertility Society (1979)	Scalar scheme selected by committee
American Fertility Society (1985)	Revision of 1979 method

Patient's Name _____ Date _____
 Stage I (Minimal) - 1-5 Laparoscopy _____ Laparotomy _____ Photography _____
 Stage II (Mild) - 6-15 Recommended Treatment _____
 Stage III (Moderate) - 16-40
 Stage IV (Severe) - >40
 Total _____ Prognosis _____

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

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

Additional Endometriosis: _____

Associated Pathology: _____

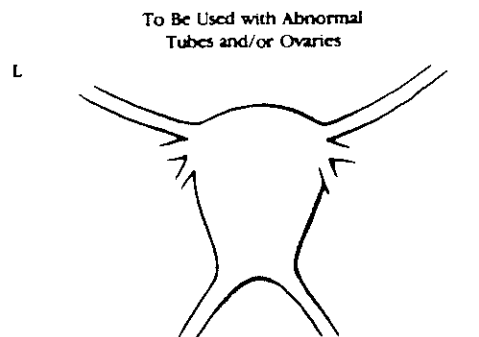
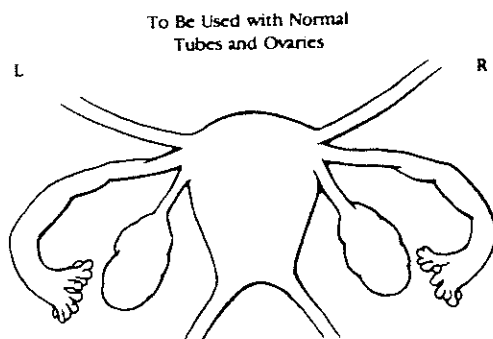


Figure 30-4 American Fertility Society revised classification, 1985. (From American Fertility Society: Research classification of endometriosis. Fertil Steril 1985;43:351, with permission of the American Fertility Society.)

assessing the efficacy of laser laparoscopic surgery in the treatment of pain associated with minimal, mild, and moderate endometriosis, they observed the poorest results in those patients with stage I disease. Conversely, patients with stage II and stage III disease experienced marked and prolonged relief of symptoms. Clearly, the standard classification of endometriosis as it relates to pelvic pain had no bearing on the severity of symptoms or surgical outcome.

Treatment

A variety of treatment options have been developed over the years in an attempt to combat endometriosis. Recommendations have included expectant management, medical therapy with a number of drugs, and surgical excision or destruction of the endometriotic lesions. It is clear that the key to developing a rational approach to the treatment of en-

ometriosis is a thorough understanding of the pathogenesis and mechanism of adverse effects of the disease. In the absence of a general agreement on the issues, it should be no surprise that therapeutic approaches have been so diverse.

Evaluation of Treatment Options

In order to assess the relative merits of the therapeutic alternatives, it is paramount to identify outcome measures for comparison. For endometriosis, such measurable outcomes include extent of disease, pelvic pain, and infertility. Today, given the large amount of data accumulated regarding the outcomes of various treatments, rigorous adherence to a treatment regimen based solely on the scientific approach allows institution of only a few interventions of proven efficacy.

OUTCOME MEASURES

Extent of Disease. It is widely believed that endometriosis is a relentlessly progressive disease. However, longitudinal data in untreated women tend to dispute this concept. In 17 such patients observed for 6 months, 29% showed a decrease in the extent of the endometriosis (based on the revised AFS score), 24% demonstrated no change, and 47% showed a worsening of disease (Cooke and Thomas, 1989). When the patients were followed out to 12 months, progression was found in 64%, with improvement found in 27% in that time period (Mahmood and Templeton, 1990). Given the paucity of data with regard to human subjects, D'Hooghe and colleagues (1996) demonstrated that endometriosis in baboons followed with serial laparoscopies over 32 months was a dynamic and moderately progressive disease. There was a significant increase in the number of lesions and the endometriosis score, based on the revised AFS criteria. Specifically, the total number of endometriotic lesions after 24 months consisted of 69% new implants, 10% remodeled lesions, and 21% unchanged implants. However, this progression or regression must be assessed relative to a control group in order to draw useful conclusions about the natural history of endometriosis (D'Hooghe et al, 1996).

Because determination of extent of disease is by nature subjective, it can be subject to ascertainment bias on the part of the investigator. This is evidenced by one treatment trial demonstrating a decrease in adhesions as assessed by the surgeon at laparoscopy following medical therapy (Henzl et al, 1988). This effect was not present when photographic documentation was used in a similar trial (Steingold et al, 1987). Thus ascertainment bias can play a significant role in subjective study results and must be accounted for.

Pelvic Pain. Pain is a truly subjective phenomenon that is dependent on a complex interaction of pathophysiologic and psychological factors. Pain is difficult

to quantify, and it is even more difficult to evaluate the results of treatment because the types of pain are heterogeneous and an effective classification of endometriosis-related pain has yet to be established.

Two other factors are critical to evaluating pain-related treatment trials. First, relief of pain symptoms may be time dependent. Although pain relief may be substantial at the conclusion of the therapeutic intervention, once treatment is discontinued, a recurrence rate is inevitable. Evaluation of the recurrence is essential to proper evaluation of the therapeutic agent.

Second, there is generally a substantial placebo effect in the treatment of pain. Most types of pain symptoms respond to placebo, at least temporarily, at a rate of roughly 30%. However, placebo treatment of endometriosis-associated pain has shown a partial response in up to 55% of those affected (Kauppila et al, 1979). Proper evaluation of treatment of pelvic pain related to endometriosis must take the placebo response into consideration, and this can only be done by comparison to an appropriate control group.

Infertility. In regard to evaluation of the clinical response to infertility treatment, there are numerous ways to report data. Most commonly, the crude or simple pregnancy rate is used:

$$\frac{\text{Number of pregnancies}}{\text{Number of patients treated}}$$

Although simple to calculate, this figure is of little value in that pregnancy is a time-dependent phenomenon, with an increasing rate seen with longer follow-up. Two methods of correcting for this have been devised: the monthly fecundity rate (MFR) and cumulative pregnancy curve. The MFR is also simply calculated:

$$\frac{\text{Number of pregnancies}}{\text{Number of months of follow-up}}$$

Cumulative pregnancy curves are graphic constructs of the data as a function of time of follow-up and are amenable to statistical analysis by life table methodology. Both of these methods are preferable to simple pregnancy rates and should be the minimum requirement for a therapeutic trial to be considered of value. When more complex analysis is desired, a wide variety of additional statistical approaches exists. A thorough review of the advantages and disadvantages of these techniques is beyond the scope of this chapter; the reader is referred to an extensive review for further information (Olive, 1986).

Although infertility has been associated with endometriosis, except in extreme cases of extensive pelvic adhesions with tubal obstruction, the association is not absolute. In the majority of such women, there is a relative decrease in fertility reflected in a lower (but finite) rate of conception than that seen in the general population. Numerous uncontrolled trials have demonstrated pregnancy rates in untreated patients ranging from approximately 30% to 70% in

early stage disease, with MRFs ranging from 5% to 11%. Similarly, women with moderate disease undergoing expectant management demonstrate an MFR of 2.9% (Olive and Lee, 1986); however, in those with severe disease, no pregnancies were noted with expectant management alone. Thus, when one is designing clinical trials to assess the efficacy of a therapeutic intervention upon fertility enhancement, the background conception rate must be considered.

STUDY DESIGN

Given the nature of the above outcome measures, it is readily apparent that uncontrolled or poorly controlled trials are of limited value. To generate meaningful information, randomized prospective trials are optimal with a controlled comparative design a minimum requirement.

A wide variety of study designs exist for treatment trials of endometriosis. Studies may be controlled or uncontrolled; if controlled, they may be controlled with historical data, concurrent nonrandomized patients, or by randomization. They may also be either retrospectively performed or carried out in a prospective manner. In endometriosis treatment trials, the vast majority of available data are derived from retrospective, uncontrolled trials. Given today's understanding of the disease, however, such studies are of little value when extent of disease, pain relief, or fertility enhancement is being evaluated. Clearly, randomized, controlled, prospective trials are required to generate significant information regarding these end points.

Additionally, the trial must be constructed and analyzed to ensure the maximal information is derived from the data generated. Objective and validated assessments of the extent of endometriosis and pain must be performed. Fertility rates must be calculated and compared in a statistically sound manner. Care must be taken to avoid the biases inherent in this type of investigation and alluded to above.

Medical Treatment

Medical therapy of endometriosis originated as a result of several distinct observations. The first was that pregnancy appeared to have a beneficial effect on the development of the disease. Although early epidemiologic data appeared to support this, it has subsequently become apparent that this effect is somewhat variable (McArthur and Ulfelder, 1965; Walton, 1977).

A second observation was the apparently hormonally dependent nature of the implants. Data in the rat and monkey conclusively demonstrated a requirement for ovarian sex steroids to maintain ectopically transplanted endometrium (DiZerega et al, 1980; Vernon et al, 1984). However, inconsistent effects of sex steroids have been noted on human endometriotic implants (Novak, 1960; Bergquist et al, 1981; Schweppe and Wynn, 1981).

Further insights have been gained by observing a number of naturally occurring states that appear to delay the onset of the disease process. Women who are at risk for endometriosis all share the common facet of altered cyclic ovulation. Thus medical strategies have been designed to create a chronic anovulatory pattern (danazol), a pseudopregnancy (continuous oral contraceptives), or a postmenopausal state (gonadotropin-releasing hormone [GnRH] analog).

Danazol

Danazol is an isoxazol derivative of 17 α -ethinyl testosterone (ethisterone). The drug is well absorbed orally and has more than 60 metabolites, many of which are hormonally active. Danazol was originally thought to produce a "pseudomenopause" by lowering gonadotropins, but subsequent studies have shown this concept to be in error. In premenopausal women, danazol does not alter basal levels of gonadotropins, but rather diminishes the midcycle luteinizing hormone and follicle-stimulating hormone surge (Goebel and Rjosk, 1977; Floyd, 1980). Thus the drug creates a chronic anovulatory state to inhibit the growth and development of endometriosis.

Danazol is noted to have a number of other hormonal effects. The drug binds well to the androgen receptor (Chamness et al, 1980), less effectively to the progesterone receptor (Tamaya et al, 1978), and poorly to the estrogen receptor (Tamaya et al, 1984). These binding characteristics suggest that the capacity of the drug has a direct effect on the implants. In addition, danazol displaces testosterone and estradiol from sex hormone-binding globulin (SHBG) as well as progesterone and cortisol from corticosteroid-binding globulin; this action increases free hormone levels in the circulation, especially that of testosterone (McGinley and Casey, 1979). Finally, danazol inhibits multiple enzymes of the steroidogenic pathway (Barbieri et al, 1977).

The dosage of danazol recommended for the treatment of endometriosis has ranged from 100 to 800 mg/day and remains controversial. Originally, it was generally agreed that, to be effective, danazol must result in amenorrhea. To this end, Young and Blackmore (1977) demonstrated that 90% to 100% of women were amenorrheic at 600 to 800 mg/day, whereas 80% were amenorrheic at 400 mg/day; at 200 mg/day, only 44% ceased having menses. More recently, Vercellini and colleagues (1994) treated endometriosis patients with moderate to severe pelvic pain with very-low-dose danazol, 50 mg/day for 9 months, or depot leupron for 3 months followed by very-low-dose danazol at 50 mg/day for 6 months. They noted a significant improvement in dysmenorrhea, deep dyspareunia, and nonmenstrual pain in both treatment groups.

A number of side effects have been attributed to danazol (Table 30-5) (Buttram et al, 1982). Most result from androgenic effects of the drug, and some,

Table 30-5. SIDE EFFECTS OF DANAZOL THERAPY

SIDE EFFECTS	INCIDENCE (%)
Weight gain	85*
Muscle cramps	52
Decreased breast size	48
Flushing	42
Mood change	38
Oily skin	37
Depression	32
Sweating	32
Edema	28
Change in appetite	28
Acne	27
Fatigue	25
Hirsutism	21
Decreased libido	20
Nausea	17
Headache	17
Dizziness	10
Rash	8
Increased libido	8
Deepening of voice	7

*0-1 pound, 15%; 1-5 pounds, 22%; 6-10 pounds, 32%; 11-15 pounds, 18%; 16-20 pounds, 11%.
From Buttram VC Jr, Belue JB, Reiter RC: Interim report of a study of danazol for the treatment of endometriosis. *Fertil Steril* 1982;37:478, with permission of the American Fertility Society.

such as deepening of the voice, are irreversible. The occurrence of at least some side effects is a new universal phenomenon. One side effect is the adverse change in blood lipoproteins, with danazol causing a profound lowering of high-density lipoproteins (HDL) (Telimaa et al, 1989b). Although it appears that this effect is reversible shortly after discontinuation of the drug (Fahraeus et al, 1984), prolonged use of this medication may severely alter the risk of atherosclerotic heart disease.

Good results have generally been obtained when danazol is used to treat the anatomic manifestation of endometriosis. Dmowski and Cohen (1975) demonstrated a lessening of disease in most patients and complete resolution in nearly all women with mild endometriosis. Barbieri and colleagues (1982) noted improvement in 94%. In neither of these studies was any effect noted on adhesions.

Three additional studies have attempted to assess the quantitative effect of danazol on endometriotic implants. Döberl and colleagues (1984) reduced the additive diameter of implants by 79% to 89% with the drug. Similarly, Buttram et al (1985) noted a 61% decrease in implant volume at second-look laparoscopy. Finally, Henzl and associates (1988) found danazol to produce a 43% decrease in the revised AFS classification system score.

Dickey and colleagues (1984) correlated resolution of implant to serum estradiol levels, finding that response coincided well with depth of hypoestrogenism produced. The possibility of adjusting dosages to suit individual patients based upon serum estra-

diol levels is intriguing and one that deserves further study.

Although each of these studies assessed the effect of danazol on implants during treatment, none looked at the rate of implant recurrence following discontinuation of the medication. One placebo-controlled trial, by Telimaa and associates (1987a), examined the effect upon implants 6 months after completion of drug therapy. In the placebo group, resolution was observed in 18%, whereas the size of the implants was estimated to be increased in 23% of patients. Conversely, 60% of those treated with danazol experienced partial or complete resolution of the endometriosis. No study has assessed the long-term effects of this drug on extent of disease.

Pain relief has been evaluated in numerous uncontrolled trials, with improvement in symptoms noted in 84% to 92% (Bayer and Seibel, 1989). A randomized, controlled study showed that danazol reduced pain significantly better than placebo throughout the treatment course and up to 6 months after discontinuation of the medication (Telimaa et al, 1987a). Few data exist on the long-term recurrence of pain, although one study suggests that symptoms recur at a rate of roughly 50% per year (Barbieri et al, 1982).

Pregnancy rates following danazol treatment vary tremendously and are confined generally to retrospective, uncontrolled reports (Bayer and Seibel, 1989). However, two randomized, prospective trials have evaluated the effects of danazol on fertility. The first consisted of 12 months of follow-up in patients either untreated or treated with danazol following the diagnosis of minimal endometriosis (Bayer et al, 1988). From life table analysis, cumulative pregnancy rates were 37.2% in the danazol-treated group and 57.4% in the untreated group (Fig. 30-5). Similar results were obtained in a second randomized comparison of danazol and placebo. In this study, consisting of patients with all stages of endometriosis, the cumulative pregnancy rate at 30 months of follow-up was 33% in the danazol group and 46% in the placebo group (Telimaa, 1988). Thus there is no evidence that danazol enhances pregnancy rates in women with endometriosis-associated infertility.

PROGESTOGENS

The use of progestational agents is gaining popularity, with a large number of options ranging from the progesterone-derived medroxyprogesterone acetate (MPA) and megestrol acetate to 19-nortestosterone derivatives, such as norethindrone and norgestrel, and retroprogesterone compounds, such as dydrogesterone. The mechanism of action of these drugs is believed to be via initial decidualization of endometrial tissue with eventual atrophy. These agents may be administered according to a variety of protocols befitting the pharmaceutical diversity of the available drugs. Today, oral administration is often preferred because of the rapid reversibility of the effect of the medication.

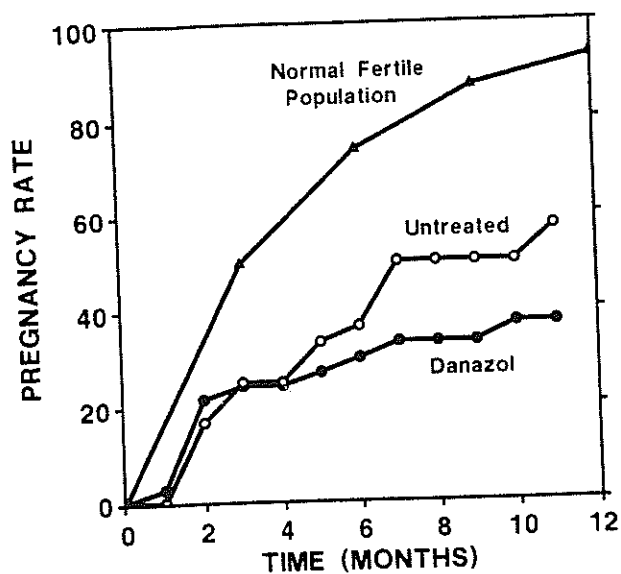


Figure 30-5
Cumulative pregnancy rates in danazol-treated and untreated patients with minimal endometriosis. The cumulative pregnancy rate in an ideal fertile population is also shown for comparison. (From Bayer SR, Seibel MM: Medical treatment: danazol. In Schenken JB [ed]: Endometriosis: Contemporary Concepts in Clinical Management. Philadelphia: JB Lippincott Company, 1989:169, with permission.) [Adapted from Cooke ID, Sulaiman RA, Lenton EA: Fertility and infertility statistics: their importance and application. Clin Obstet Gynecol 1981;8: 531.]

Side effects vary greatly, depending on the specific progestogen, the dosage, the interval of treatment, and the route of administration. A common side effect is transient breakthrough bleeding, which occurs in 38% to 47% of patients (Olive, 1989b). Other side effects include nausea, breast tenderness, and fluid retention. In contradistinction to danazol, all of these adverse effects resolve upon discontinuation of the drugs. Progestogens may adversely affect serum lipoprotein levels. High-dose MPA (100 mg/day) resulted in a 26% decline in HDL cholesterol levels, a level significantly less than for placebo but only half the reduction seen with danazol (Telimaa et al, 1989b). The significance of this effect is currently unknown.

The effect of progestogens on the extent of endometriosis has been clearly defined. In a randomized, controlled, comparative trial, high-dose MPA was administered for 6 months and followed by 6 months of observation (Telimaa et al, 1987a). At the conclusion of this time, laparoscopy revealed total resolution of implants in 50% of women and partial resolution in 13%. The corresponding figures for danazol were 40% and 20%, and for placebo 12% and 6%. Thus MPA acts as effectively as danazol and significantly better than placebo in reducing disease volume, even up to 6 months after discontinuation of therapy.

Pain relief with progestational therapy also appears to be uniformly excellent. Uncontrolled trials

suggest a relief rate of roughly 90%, regardless of the progestogen used (Timonen and Johansson, 1968; Johnston, 1976; Moghissi and Boyce, 1976; Schlaff et al, 1990). In a prospective, randomized trial, high-dose MPA relieved pain symptoms to a degree comparable to danazol and significantly better than placebo (Fig. 30-6) (Telimaa et al, 1987a).

Few publications exist regarding the attempt to enhance fertility with progestogens. However, Hull and associates (1987) reported a concurrent nonrandomized, controlled, comparative trial with oral MPA, danazol, and expectant management in women with early-stage endometriosis. Cumulative pregnancy rates were no different between the three groups at 30 months of follow-up (Fig. 30-7). Telimaa (1988) reported a randomized trial between high-dose MPA, danazol, and placebo in women at all stages of disease and being followed for up to 30 months. Results demonstrated no difference in pregnancy rates among the three groups. Thus the efficacy of progestogens in treating infertility is as yet unproven.

Gestrinone. Gestrinone (ethynorgestrienone, R2323) is an antiprogestational steroid used extensively in Europe for the treatment of endometriosis. Its effects include androgenic, antiprogestogenic, and antiestrogenic actions, although the last is not mediated by estrogen-receptor binding (Moguilewsky and Philibert, 1984). This drug is believed to enhance lysosomal degradation of the cell via a progesterone withdrawal effect Cornillie et al, 1986). This appears to be secondary to a sharp decline in estrogen and progesterone receptors as well as a substantial increase in 17 β -hydroxysteroid dehydrogenase. Additionally, there is a 50% decline in serum estradiol associated with a decrease in circulating SHBG (Robyn et al, 1984).

Gestrinone is administered orally in doses of 5 to 10 mg weekly, on a daily, twice-weekly, or three-times-weekly schedule. Side effects include androgenic and antiestrogenic sequelae (Coutinho et al, 1984). Although most side effects are mild and transient, several, such as voice changes, hirsutism, and clitoral hypertrophy, are potentially irreversible.

The effect of gestrinone on endometriotic implants has been well studied. In a randomized, placebo-controlled trial, Thomas and Cooke (1987) found improvement in the revised AFS score in 15 of 18 women (83%) taking the medication for 6 months, with 11 of 18 showing no residual disease at subsequent laparoscopic examination. Conversely, only 29% of the placebo group showed a lessening of disease. Unfortunately, no study of implant recurrence following discontinuation of treatment has been undertaken.

Relief of pelvic pain has been encouraging. In several uncontrolled trials, improvement of symptoms was noted in more than 90% of subjects while they were taking medication (Azadian-Boulanger et al, 1984; Coutinho et al, 1984). However, within 1 year

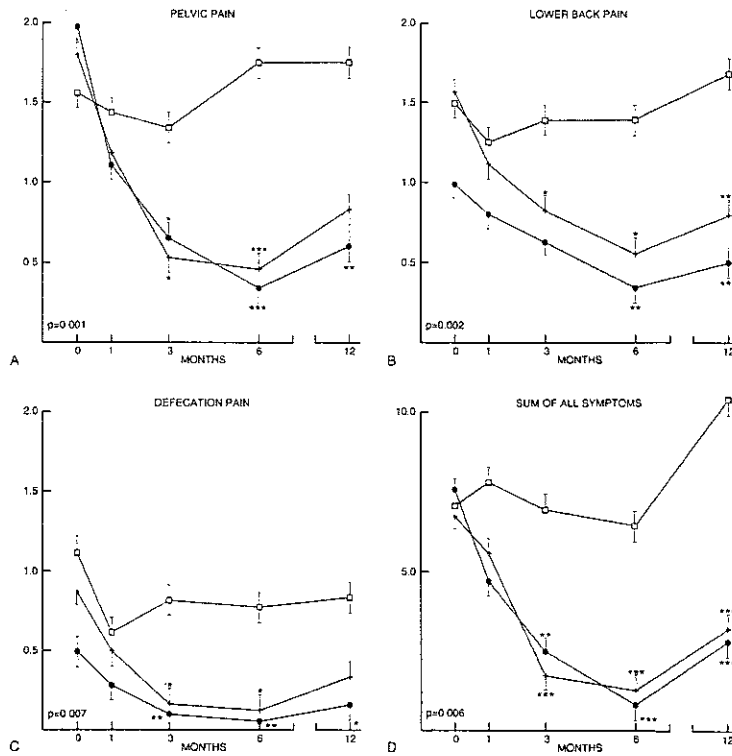


Figure 30-6

Comparison of the effects of medroxyprogesterone acetate (MPA) (+), danazol (●), and placebo (□) on (A) pelvic pain alone ($p = .001$ in analysis of variance), (B) lower back pain alone ($p = .002$), (C) defecation pain alone ($p = .007$), and (D) the six endometriosis-associated symptoms altogether (pelvic pain, lower back pain, defecation pain, dysuria, dyspareunia, diarrhea) ($p = .006$) before, during, and after the treatments. Values are given as mean \pm standard error of the scores. Asterisks indicate statistical significances of differences between MPA and placebo, and danazol and placebo at different time points (Bonferroni test): * $p < .05$; ** $p < .01$; *** $p < .001$. (From Telimaa S, Puolakka J, Rönberg L, Kauppila A: Placebo-controlled comparison of danazol and high-dose medroxyprogesterone acetate in the treatment of endometriosis. *Gynecol Endocrinol* 1987;1:13, with permission of Parthenon Publishers.)

following discontinuation of the drug, recurrence of pain was observed in 15% to 30%.

Many researchers have investigated the effect of gestrinone upon fertility. Unfortunately, nearly all studies have been small, uncontrolled, and hetero-

geneous in the cohort enrolled. An exception is a prospective trial in women with early-stage endometriosis (Thomas and Cooke, 1987). In this study, women were observed for 12 months after treatment with either gestrinone or placebo. The cumulative

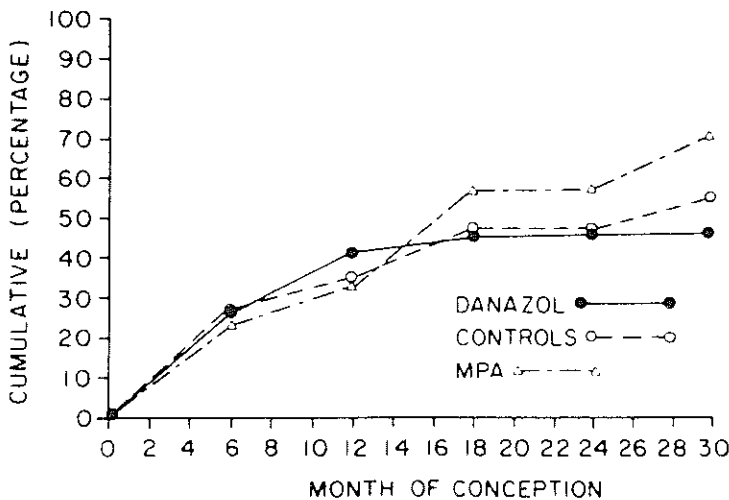


Figure 30-7

Cumulative pregnancy rates for three treatment groups with stage I and stage II endometriosis. (From Hull ME, Moghissi KS, Magyar DF, Hayes F: Comparison of different treatment modalities of endometriosis in infertile women. *Fertil Steril* 1987;47:42, with permission of the American Fertility Society.)

conception rate in the gestrinone-treated group (25%) did not differ significantly from those taking placebo (24%), and neither group showed differences from a concurrently studied cohort of patients with unexplained infertility (23%). Furthermore, when patients were divided by second-look laparoscopy into those with residual disease and those with total resolution, there was again no difference in conception rates. Thus there is no evidence that the treatment of endometriosis with gestrinone enhances fertility.

Mifepristone RU 486. Apart from its controversial role in pregnancy termination, mifepristone (RU 486) may well prove to be of value in a wide variety of gynecologic disorders, including endometriosis. The drug is an antiprogesterone and antiglucocorticoid that can inhibit ovulation and disrupt endometrial integrity. Daily doses of the medication range from 50 to 100 mg, with side effects ranging from hot flashes to fatigue, nausea, and transient elevation in liver transaminases. No effect on lipid profiles or bone mineral density has been reported.

The ability of mifepristone to produce a regression of endometriotic lesions has been variable and apparently dependent upon duration of treatment. Trials lasting 2 months in the rodent model (Tjaden et al, 1993) and 3 months in the human (Kettel et al, 1991) failed to produce regression of disease. However, 6 months of therapy resulted in less visible disease in women (Kettel et al, 1996).

Uncontrolled trials suggest possible efficacy for endometriosis-associated pain, although numbers are small. No data have yet been collected regarding fertility enhancement.

Combination Estrogen-Progestogen. The combination of estrogen and a progestogen for treatment of endometriosis, the so-called pseudopregnancy regimen, has been utilized for 40 years. This approach, like progestational therapy alone, is believed to act via initial decidualization and growth of endometrial tissue followed by atrophy. The combination can be administered orally (with combination contraceptive pills) or parenterally. Combination oral contraceptive pills such as norethynodrel and mestranol, norethindrone acetate and ethinyl estradiol, lynestrenol and mestranol, and norgestrel plus ethinyl estradiol have all been tried. Parenteral combinations have included 17-hydroxyprogesterone or depot MPA paired with stilbestrol or conjugated estrogens.

Side effects are numerous, and include androgenic, estrogenic, and progestogenic effects. Estrogens may cause nausea, thrombophlebitis, and uterine enlargement. The 19-nortestosterone-derived progestogens may cause androgenic effects such as acne, alopecia, increased muscle mass, decreased breast size, and deepening of the voice. Noble and Letchworth (1979), in a comparative trial of norethynodrel and mestranol versus danazol, found that 41% of the pseudopregnancy group failed to complete their course of therapy because of side effects of the medication. However, dosages producing sig-

nificant side effects generally involve more estrogen than found in modern contraceptive preparations. The oral contraceptives commonly prescribed today for combination therapy are most likely to produce a progestogen-dominant picture similar to that of progestogen alone.

The efficacy of pseudopregnancy has been poorly assessed. Riva and colleagues (1962), using culdoscopy, demonstrated an 80% improvement in lesions, with an 11.8% recurrence rate at 6 months. Despite the paucity of available data, oral contraceptives remain the most commonly prescribed treatment for endometriosis symptoms.

Numerous controlled trials have evaluated pain relief, generally demonstrating improvement in 75% to 89%. A randomized clinical trial compared cyclic low-dose oral contraceptives to a GnRH agonist and found no substantial difference in the degree of relief afforded these women by the two drugs, except that the GnRH agonist provided greater relief of dysmenorrhea (Vercellini et al, 1993).

Reports of pregnancy rates in women with endometriosis-associated infertility treated with oral contraceptives are sparse and uncontrolled. None provided evidence of improvement in fertility by these medications. Adamson et al (1982), using life table analysis, was able to show that treatment with oral contraceptives had a less favorable effect on the pregnancy rate than surgical treatment or no treatment for the groups analyzed (i.e., presence or absence of adnexal lesions, anatomic structures involved, and specific types of lesions).

GnRH ANALOGS

These medications are modifications of GnRH and function to down-regulate the pituitary gland. The net effect is a decline in gonadotropins and resultant "medical oophorectomy." The clinically used analogs are listed in Table 30-6. These drugs are administered subcutaneously, intranasally, or intramuscularly, with dosage schedules varying according to the specific agonist, route of administration, and degree of pituitary suppression sought. The lowering of gonadotropin levels results in decreased ovarian stimulation and serum estradiol levels in the castrate range (Meldrum et al, 1982). The time course for this decrease is roughly 3 to 6 weeks. To the degree that endometriotic tissue is dependent on estrogen for growth, such therapy affects glandular involution and stromal atrophy of implants.

Numerous side effects have been reported, and most symptoms demonstrate an increased rate with higher dosages (Olive, 1989b). Reported side effects include transient vaginal bleeding, hot flashes, vaginal dryness, decreased libido, breast tenderness, insomnia, depression, irritability and fatigue, headache, joint stiffness, and skin changes. Comparative studies carried out with GnRH analogs and danazol have shown that GnRH agonists produce less weight gain, edema, and myalgias, whereas hot flashes, de-

Table 30-6. GONADOTROPIN-RELEASING HORMONE ANALOG EVALUATED FOR THE TREATMENT OF ENDOMETRIOSIS

STRUCTURE	TRADE NAME
[D-(but)Ser ⁶ -des-Gly ¹⁰ -NEt]-GnRH	Buserelin (Hoechst)
[(Imbal)-D-His ⁶ -Pro ⁹ -NEt]-GnRH	Histrelin (Serono)
[D-Leu ⁶ -Pro ⁹ -NEt]-GnRH	Leuprolide (Abbott)
[D-(2-naph)-Ala ⁶ -GnRH	Nafarelin (Syntax)
[D-Trp ⁶ -N-Me-Leu ⁷ -des-Gly ¹⁰ -Pro ⁹ -NEt]-GnRH	Lutrelin (Wyeth)
[D-Trp ⁶ -Pro ⁹ -NEt]-GnRH	Lincol (Salk Institute)
[D-Ser(tBu) ⁶ -Aza-Gly ¹⁰]-GnRH	Zolidez (ICI Ltd)

From Olive DL: Medical treatment: alternatives to danazol. In Schenken RS (ed): Endometriosis: Contemporary concepts in Clinical Management. Philadelphia: JB Lippincott Company, 1989:200, with permission.

creased libido, and vaginal dryness were more common (Jelley and Magill, 1986; Henzl et al, 1988).

Two major concerns are the effects of this class of drugs on the lipoprotein levels (Wheeler et al, 1993) and loss of bone mineral density (Rock et al, 1993). The latter effect is seen as early as 3 months into treatment, and may take a year or more to recover following discontinuation of therapy (Rock et al, 1993). These findings have led to alternative strategies of GnRH agonist treatment in combination with steroid hormone add-back therapy as a means of chronic administration of these drugs. Add-back is generally commenced after 3 months of unopposed agonist, and may be combination estrogen-progestogen (Friedman and Hörnstein, 1993), progestogen alone (Fahraeus et al, 1986; Surrey et al, 1990), or low-dose progestogen coupled with a bisphosphonate (Surrey et al, 1993). Results have been promising, although trials have been small and duration limited to 2 years or less.

The effect of GnRH analogs on endometriotic implants is impressive in both animals (Werlin and Hodgen, 1983) and humans. Atrophic glands and stroma are the rule among biopsied implants after treatment, but Lemay and colleagues (1984) have pointed out that, although implants appear inactive, they are capable of later growth. In comparative trials, danazol or a GnRH analog produced a similar degree of regression of implants (Henzl et al, 1988; Fedele et al, 1989a; Fedele et al, 1989b).

Pelvic pain has been extensively evaluated in a variety of uncontrolled trials, with most of these studies demonstrating a diminution of symptoms in 80% or more cases during treatment. In a randomized trial of danazol and the analog nafarelin, the two drugs produced an equivalent amount of pain relief (Henzl et al, 1988). The question of recurrence, however, remains open. In this trial, most women did not note significant pain recurrence 6 months after treatment. A second study has reported a 20% recurrence of noncyclic pain but no recurrence of dyspareunia at 6 months' follow-up (Lemay et al, 1984). In yet a third trial, however, roughly half the patients noted symptomatic recurrence by 1 year (Fedele et al, 1989a). More recent data suggest that recurrence is

stage dependent, with a 5-year recurrence risk of 36.9% for minimal disease but up to 74.4% for severe disease (Waller and Shaw, 1993).

Pregnancy rates following GnRH agonist therapy have been reported by numerous investigators. However, most studies suffer from small size, inconsistent staging, and variable length of follow-up. In comparative trials with danazol, no difference in the pregnancy rates has been detected at 1 year (Henzl et al, 1988; Fedele et al, 1989a). At this time, further data are required before any conclusions can be drawn concerning the efficacy of GnRH analogs with regard to enhancing pregnancy rates.

OTHER MEDICATIONS

A wide variety of additional medical therapies have been attempted in combating endometriosis. Some, such as estrogen and methyltestosterone, have been abandoned because of side effects (Karnaky, 1948; Katayama et al, 1976). Others, such as the antiestrogens tamoxifen and clomiphene, have been tested in only very small, uncontrolled trials (Haber and Behlak, 1987; Koninckx, 1987). Finally, several medications, such as pentoxifylline and verapamil, have appeared promising in the animal modal but have yet to undergo testing in human studies (Steinleitner et al, 1991).

A promising drug of the latter category is the GnRH antagonist. These medications differ from the GnRH agonist in that they produce an immediate inhibition of gonadotropin release. Thus their effect is faster and more direct than the long-acting GnRH agonist. The major problem with human use of this class of pharmaceuticals has been the annoying side effect of histamine release locally at the site of injection. This has been substantially reduced with the current group of third-generation antagonists.

ROLE OF MEDICAL THERAPY

Medical therapy directed at endometriosis appears to be of some value, depending upon the goal of treatment. If the objective is to diminish the anatomic extent of the disease (exclusive of pelvic adhesions)

or to reduce pelvic pain symptoms, all of the drugs thus far evaluated are efficacious. However, few data are available regarding the long-term effectiveness of such treatments, and there is some suggestion that recurrence may be substantial in some instances.

The role of medications in the promotion of fertility is less clear-cut. To date, there is no evidence that any medical therapy alone can increase the rate of conception among infertile women with endometriosis.

Surgical Treatment

CONSERVATIVE SURGERY

Surgery is the most commonly used treatment for endometriosis. Goals are to restore normal pelvic anatomy, remove visible endometriotic lesions, and eliminate conductive pathways for pelvic pain. Such surgery is generally termed "conservative" when the ability to conceive is retained, and it may be performed either laparoscopically or via laparotomy.

In regard to conservative surgery, many potential procedures can be considered. First and foremost is the removal of all active endometrial implants utilizing an atraumatic, hemostatic method. Lysis of pelvic adhesions is also accomplished, with meticulous attention to excision of the entire fibrous tissue specimen, because endometriosis is often contained within such adhesions. Uterine suspension, ovarian suspension, and partial omentectomy may be performed to reduce postoperative adhesion formation (Olive, 1989a). To reduce pelvic pain, presacral neurectomy and/or uterosacral ligament transection have been advocated.

Sutton and colleagues (1994) assessed the efficacy of laser laparoscopic surgery in the treatment of pain associated with minimal, mild, and moderate endometriosis. They found that laser laparoscopic removal of endometriosis resulted in statistically significant pain relief compared with those patients undergoing sham laparoscopy up to 6 months after surgery. In numerous uncontrolled trials, the rates of improvement were 70% to 100% immediately after surgery (Olive, 1989a; Vancaillie et al, 1989) and 82% 1 year later (Nezhat, 1987). Longer term follow-up has shown pain reduction in 66% of patients over 5 years (Redwine, 1994). Whether such relief is due to the removal of implants and adhesions or to other adjunctive procedures remains to be clarified.

A variety of surgical instruments have been used to accomplish appropriate operative procedures. Sharp dissection is quite common, as are cautery and endocoagulation. The most common location is the peritoneal surface. Lesions on this lining can be vaporized, coagulated, or excised. Excision is the preferred method for larger lesions because of the complete removal and possession of a specimen for histologic confirmation. Endometriomas may be treated by drainage, vaporization, excision and stripping, or penetration and irrigation. Most surgeons agree that simple drainage of these structures is in-

adequate, with frequent recurrence resulting, although data to support this are limited.

Laser technology has now become a mainstay of treatment for endometriosis, including carbon dioxide, neodymium:yttrium-aluminum-garnet argon, and potassium-titanyl phosphate energy (Vancaillie and Schenken, 1989). No clear advantage has been evidenced by any one of these approaches, and it is recommended that the surgeon utilize the instruments with which he or she feels most comfortable. Although laparotomy had for many been the standard for surgical therapy, laparoscopy is increasingly important in the treatment of most, if not all, cases of endometriosis. Laparoscopy offers several advantages over laparotomy. Along with the ability to treat at the time of initial diagnosis, laparoscopy is also associated with a shortened hospital stay, reduced morbidity and recovery time, and decreased rate of adhesion formation. Additionally, for minimal and mild disease, laparoscopy and laparotomy had equivalent 3-year estimated cumulative life table pregnancy rates when meta-analysis was performed (Adamson and Pasta, 1994).

Success of surgery in ablating endometriotic implants, lysing adhesions, and restoring normal anatomy is assumed to be high. The rate of success for moderate to severe disease is proportional to adequate operative exposure and thorough, meticulous surgical technique as well as complete resection of all endometriotic tissue. However, once surgery is concluded, the patient may well be subject to the conditions responsible for initially creating the disease. The risk of recurrence of implants has scarcely been evaluated. Wheeler and Malinak (1983) noted a 40% recurrence of symptomatic disease at 9 years' follow-up (Olive, 1989a). Gordts and colleagues (1984) found recurrent disease in 28% of women after 18 months or more postoperatively. Much less success has been noted with prevention of adhesion recurrence (Adhesion Study Group, 1983; Diamond et al, 1984), but as many as 50% to 60% of those patients undergoing surgery appear to demonstrate long-term restoration of normal anatomic relationships.

Conservative surgery has been used extensively in an attempt to enhance fertility. Most studies, however, are uncontrolled. In mild endometriosis, surgical treatment has resulted in pregnancy rates ranging from 40% to 75%, with MFRs reported in the 2% to 4% range with laparotomy and up to 6.5% with laparoscopy. In women with moderate disease, pregnancy rates are nearly the same; MFRs also mirror those for mild disease. Even with severe endometriosis, success rates of 20% to 50% are reported, with MFRs approximately 1.5% with laparotomy and up to 6% with laparoscopy (Olive, 1989a).

Meta-analysis encompassing studies from 1982 through 1994 carried out by Adamson and Pasta (1994) showed that either no treatment or surgery alone is superior to medical treatment for minimal and mild endometriosis associated with infertility. They found that medical treatment merely delays the

possibility of pregnancy by the duration of therapy, typically 3 to 6 months. Similarly, meta-analysis was also carried out by Hughes and associates (1993) on 25 randomized controlled trials and cohort studies. They found possible treatment benefit from laparoscopic conservative surgery, but overall they concluded that medical treatment via ovulation suppression was ineffective in the treatment of endometriosis-associated infertility. Although these medications may be considered to be an empirical intervention following the exhaustion of other treatments, the numerous side effects and the creation of the mandatory period of amenorrhea during medical treatment make the wisdom of this approach questionable.

Two retrospective, comparative trials have been reported. Guzick and Rock (1983) compared pregnancy rates in 224 women with mild or moderate endometriosis treated with either danazol or conservative surgery via laparotomy; no difference between therapies was noted in terms of subsequent success. Olive and Lee (1986) compared conservative surgery (laparotomy) to expectant management and found both modalities to be equally efficacious for mild or moderate disease. However, for severe endometriosis, surgery produced significantly better results than did no treatment. Meta-analyses have now been done (Hughes et al, 1993; Adamson and Pasta, 1994) to assess laparoscopic conservative surgery and the resultant pregnancy rates. Adamson and Pasta evaluated the pregnancy rates for surgical, medical, and no-treatment regimens, with surgical treatment involving either laparoscopy or laparotomy. Additionally, they performed meta-analysis on 25 studies previously evaluated by Hughes et al (1993). Both their results and the meta-analysis showed that either no treatment or surgery is superior to medical treatment for minimal and mild endometriosis associated with infertility. For moderate and severe disease, surgery is optimal, with laparoscopic surgery being at least as efficacious as laparotomy (Adamson and Pasta, 1994).

Clearly, conservative surgery can be efficacious in the treatment of pelvic pain and reduction of disease. However, it is not a panacea for enhancing fertility in women with endometriosis. It appears to be of value for advanced stages of the disease, as a means of correcting distorted anatomic relationships. In the absence of such anatomic distortion, the value of surgical intervention for treating infertility remains questionable.

DEFINITIVE SURGERY

When hysterectomy with salpingo-oophorectomy is performed for endometriosis, the procedure is termed *definitive surgery*. Such surgery, in conjunction with excision of existing endometriosis, is virtually certain to eliminate complaints of pain related to the disease itself. However, resulting adhesions may produce chronic pelvic pain.

When definitive surgical therapy is applied to younger women, there is increased pressure to consider preservation of one or both ovaries. The recurrence rate of pain symptomatology has ranged from 0% to 85% in published reports (Walters, 1989). More recently, patients undergoing definitive surgery with ovarian preservation were found to have a 6.1 times greater risk of developing recurrent pain and an 8.1 times greater risk of reoperation (Namnour et al, 1995). On the basis of extensive clinical experience, Ranney (1971a) suggested four criteria by which to determine whether the ovaries should be removed:

1. Hilar areas are involved bilaterally.
2. Extensive endometriosis is present that cannot be resected.
3. A hemoperitoneum is present, necessitating emergency surgery.
4. Associated pelvic pathology is present, mandating removal.

COMBINATION MEDICAL-SURGICAL TREATMENT

Many investigators today favor combining medical and surgical approaches. Two options exist: preoperative medical treatment and postoperative hormonal intervention. Preoperative treatment has been advocated as a means of facilitating the technical aspects of surgery. Conversely, postoperative therapy has been suggested on the assumption that surgery is frequently unable to eliminate all endometriotic implants.

Unfortunately, most studies investigating these questions have serious methodologic flaws: sample sizes are small, no controlled comparisons are made, and data analysis is limited (Kaplan and Schenken, 1989). A comparison of preoperative therapy with either danazol, gestrinone, or buserelin followed by laparotomy with microsurgical excision or laparoscopy with laser excision for ovarian endometriosis was done by Nisolle and colleagues (1990a). They documented regression of endometriosis in 35% to 91% of patients depending on the preoperative medication used, but noted that hormonal treatment alone led to incomplete suppression of endometriosis. For patients with early-stage disease, Chong and associates (1990) found no differences in fertility rates after treatment with danazol, laparoscopic laser surgery, or laser surgery followed by danazol. For patients with advanced disease, a randomized study was performed comparing conservative surgery plus danazol, conservative surgery followed by MPA, and conservative surgery followed by placebo (Telimaa et al, 1987b). A confounding factor not controlled for in this study was the amount of endometriosis left behind and the ability of the surgeons to do optimal debulking. Although pregnancy rates were similar in all three groups, pain relief proved significantly better in the women undergoing combination therapy (Fig. 30-8). Thus it appears that combination therapy is the treatment of choice in order to facilitate

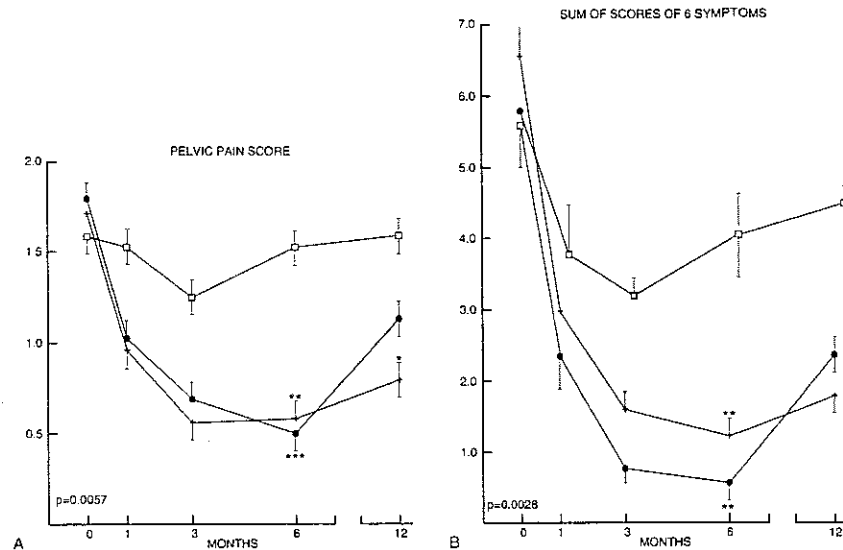


Figure 30-8

Effect of medroxyprogesterone acetate (+ — +), danazol (● — ●), and placebo (■ — ■) on pelvic pain (A) and on six endometriosis-associated symptoms (pelvic pain, lower back pain, defecation pain, dysuria, diarrhea, and dyspareunia) (B), evaluated by symptom scores before, during, and after the treatments. Results are given as mean \pm standard error of the scores. The p value indicates the statistical significance of difference between the treatment and placebo groups during the whole trial in analysis of variance. Asterisks indicate statistical significances of differences between the treatment and placebo groups at different time points in the modified Bonferroni test: * $p < .05$; ** $p < .01$; *** $p < .001$. (From Telimaa S, Rönnerberg L, Kauppila A: Placebo-controlled comparison of danazol and high-dose medroxyprogesterone acetate in the treatment of endometriosis after conservative surgery. *Gynecol Endocrinol* 1987;1:363, with permission of Parthenon Publishers.)

optimal surgical debulking, and to provide optimal pain relief in women with extensive disease that is not totally removed at the time of surgery.

Treatment of Symptoms

Although the majority of treatments for endometriosis are directed at eliminating the lesions themselves, some treatment regimens are designed to bypass the implants and attack the symptoms directly.

PAIN (Fig. 30-9)

One medical approach to pain relief is the use of *nonsteroidal anti-inflammatory drugs* (NSAIDs). NSAIDs act to reduce the amount of circulating prostaglandins produced by the endometriotic implants by inhibiting prostaglandin synthetase and/or antagonizing prostaglandin at its receptor. The success of these drugs has been variable with regard to endometriosis-associated pain. In a randomized, placebo-controlled study, neither aspirin, indomethacin, nor tolfenamic acid (a fenamate) decreased the premenstrual pain experienced by women with endometriosis (Kauppila et al, 1979). Tolfenamic acid resulted in a significant decrease in dysmenorrhea, whereas the two other medications failed to outperform placebo. In a second trial, naproxen sodium proved significantly better at providing relief of dysmenorrhea compared to placebo (Kauppila and

Rönnerberg, 1985). These data suggest that some NSAIDs may play a role in the treatment of selected aspects of endometriosis-associated pain.

Surgical procedures for pain associated with endometriosis may involve interruption of pathways of pain conduction via uterosacral nerve ablation or presacral nerve resection. Both procedures are reserved for patients with midline pelvic pain, and may be performed by either laparoscopy or laparotomy.

The goal of *laparoscopic uterosacral nerve ablation* (LUNA) is the destruction of the uterine sensory fibers and their secondary ganglia as they exit the uterus. Accordingly, no benefit will result from a LUNA if the origin of the pain is extrauterine. Therefore, the proper selection of patients for this surgery will optimize therapeutic benefit. The procedure should be offered to those patients with central pelvic pain who have failed medical therapy. It is optimal to evaluate these women at the time of pain, with recording of the subjective evaluation of pain during examination both before and after injection of the uterosacral ligaments with a long-acting local anesthetic. During the procedure itself, approximately 1.5 to 2.0 cm of uterosacral ligaments in the region adjacent to their attachment to the cervix is excised or destroyed laparoscopically using scissors, electrosurgery, or lasers.

Studies evaluating the success rates of LUNA in the treatment of endometriosis-associated dysmen-

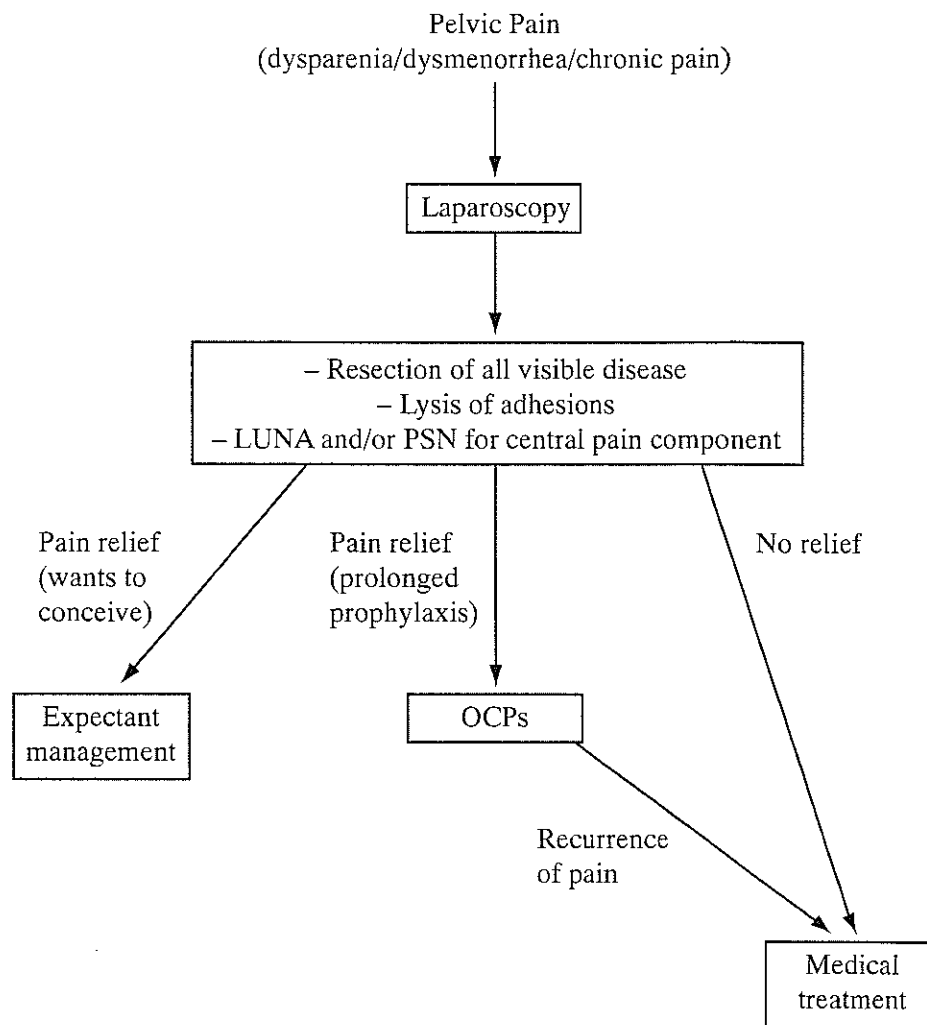


Figure 30-9

Management protocol for patients with pelvic pain caused by endometriosis. LUNA, laparoscopic uterine nerve ablation; OCPs, oral contraceptive pills; PSN, presacral neurectomy.

orrhea have shown marked improvement of dysmenorrhea ranging from 70% to 90%. When the effect of LUNA was evaluated in patients with severe incapacitating dysmenorrhea who had no pelvic pathology at laparoscopy, significant pain relief was noted in the treated group (Lichten and Bombard, 1987). Of note, though, only 44% of women had continued relief from dysmenorrhea 12 months after surgery. In another study by Sutton and colleagues (1994), women with minimal endometriosis were evaluated after either diagnostic laparoscopy followed by expectant management or LUNA with ablation of endometriosis. At 6 months after surgery, a significantly greater proportion of patients in the latter group (62%) had improvement or resolution of pain compared with the former group (23%).

Presacral neurectomy (PSN) involves interruption of the sympathetic innervation to the uterus at the level of the superior hypogastric plexus. This procedure may be performed via laparoscopy or laparotomy, but, unlike LUNA, it requires a significant degree of

surgical skill. The important anatomic landmarks are the aortic bifurcation, common iliac arteries and veins, and sacral promontory. The peritoneum over the sacral promontory is grasped and incised, and the retroperitoneal space is dissected. The retroperitoneal superior portion of the hypogastric plexus, the actual presacral nerve, is isolated below the bifurcation of the aorta, 3 or 4 cm toward the hollow of the sacrum. Once the fibers of the neural tissue have been identified, the tissue is excised for a distance of at least 2 × 2 cm over the sacral promontory. The excision is carried out medial to the ureters and common iliac vessels.

The therapeutic benefit of PSN in patients with severe endometriosis and central pelvic pain was evaluated in a prospective study by Tjaden et al (1990); they found that PSN in addition to conservative surgery was highly effective in relieving the midline component of menstrual pain. However, there was no added relief of lateral pain, back pain, or dyspareunia. Conversely, in a randomized controlled

study by Candiani et al (1992), the addition of PSN to conservative surgery for moderate or severe endometriosis did not result in a greater reduction of pelvic pain than did conservative surgery alone. Thus the role of PSN in relief of endometriosis-associated pain remains controversial.

INFERTILITY (Fig. 30-10)

Infertility associated with endometriosis has been treated empirically with advanced reproductive techniques. Controlled ovarian hyperstimulation with gonadotropins results in monthly fecundity rates of 9% to 18% in women with early-stage disease; these rates are generally higher than those in women who are not treated (expectant management). A randomized comparison of three cycles of controlled ovarian hyperstimulation with 6 months of expectant management revealed a significantly higher monthly fecundity rate among the women treated with controlled ovarian hyperstimulation (15%) than among untreated women (4.5%) (Fedele

et al, 1992). The addition of intrauterine insemination also appears beneficial. In a randomized comparison of controlled ovarian hyperstimulation with and without intrauterine insemination, the combination doubled the pregnancy rate (Dodson and Haney, 1991). Experience with in vitro fertilization (IVF) for patients with endometriosis has been evaluated by Geber et al (1995), who found no difference with stimulation between patients with male factor only, tubal factor only, or unexplained infertility versus patients with endometriosis. They found that there was no difference in mean number of ampules of human menopausal gonadotropin (hMG) administered, estradiol concentration on the day of hMG administration, number of days hMG administration, mean number of oocytes retrieved and retrieval rate, fertilization rate, number of normally fertilized embryos, number of transferred embryos per cycle, or implantation rate. More importantly, the pregnancy rates were similar, as were the miscarriage rates. Additionally, they separated the endometriosis patients based on staging, according to the revised AFS clas-

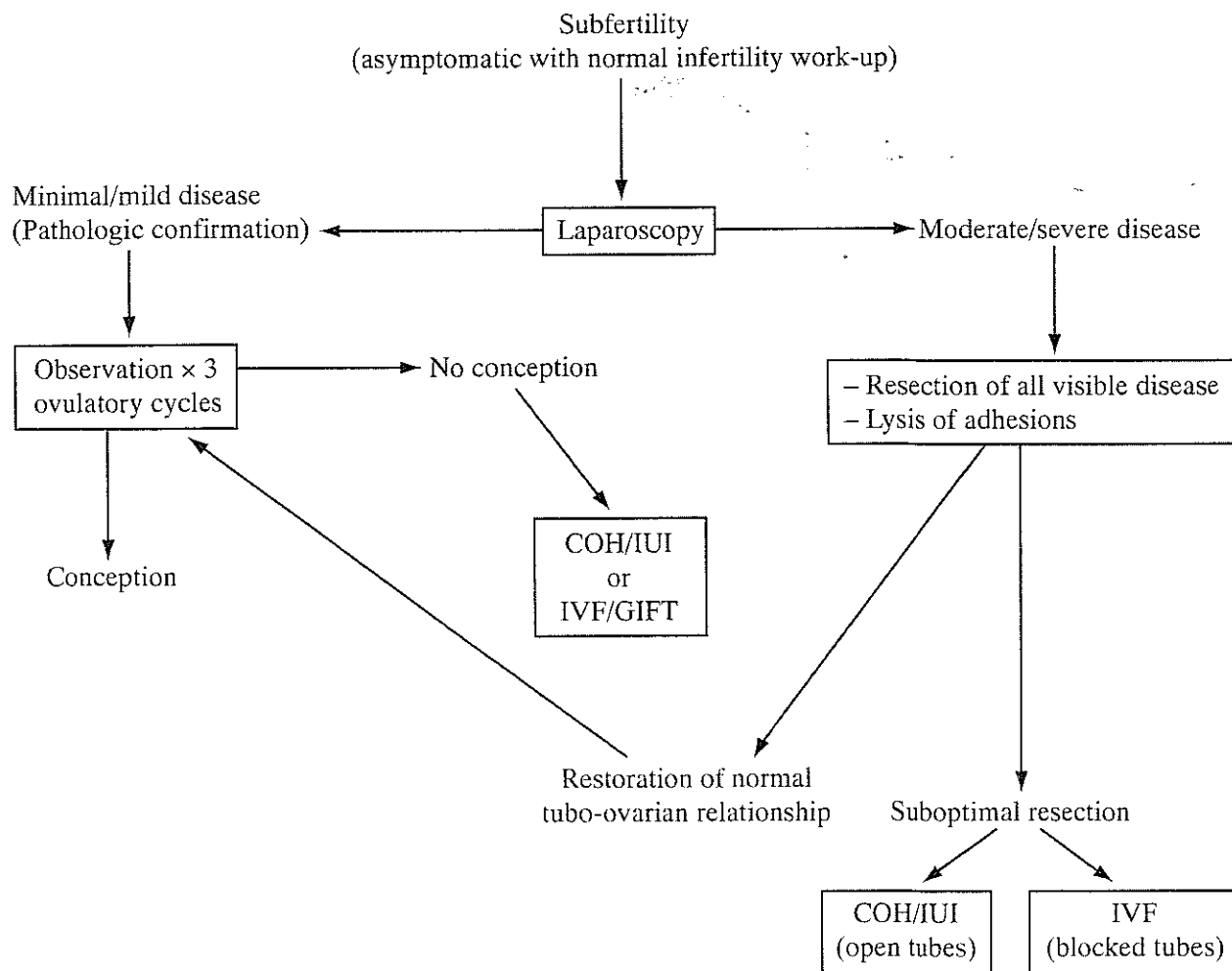


Figure 30-10

Management protocol for patients with infertility caused by endometriosis. COH/UII, controlled ovarian hyperstimulation/intrauterine implantation; IVF/GIFT, in vitro fertilization/gamete intrafallopian transfer.

sification, and found no difference in results between stage I-II and stage III-IV disease (Geber et al, 1995). Thus, the previously held belief that endometriosis adversely affected the success rates of IVF appears to be in doubt. Additionally, the original data suggesting a difference were based on laparoscopic oocyte retrieval; therefore, a lower number of oocytes were retrieved in those patients with advanced endometriosis. The advent of transvaginal oocyte retrieval has eliminated any difference with regard to stage of disease and lower pregnancy rates.

ADENOMYOSIS

Adenomyosis was first described in 1860 by Rokitansky, who noted a condition in which endometrial glands embedded in a hyperplastic muscular stroma invaded the uterine wall. He called this condition "cystosarcoma adenoids uterinum" because the nature of the growth of these areas suggested sarcomatoid tendencies. In 1896, Cullen suggested the term "adenomyosis," and he subsequently published a review of 54 cases describing what we recognize today as adenomyosis (Cullen, 1908). Still, this entity remained somewhat obscure for many years, completely escaping mention in deQuervain's 5th edition of *Clinical Surgical Diagnosis* (deQuervain, 1917). In the mid-1920s, following Sampson's papers on endometriosis, Meyer (1925) aroused new interest in adenomyosis by advocating the theory of invasive endometrial hyperplasia as its etiologic mechanism. Since that time, only a handful of investigators have consistently studied adenomyosis, and investigation into its etiology and alternative diagnostic and therapeutic modalities has been especially limited.

Definition

Adenomyosis is defined as the presence of endometrial glands and stroma within the myometrium, accompanied by compensatory hypertrophy of the myometrium. Although all agree on this basic definition, the exact depth of invasion required to elicit a diagnosis of adenomyosis remains the subject of some controversy. Proposals have ranged from 1 high-powered field (1.8 mm using a 100× objective) below the endometrial surface to one third of the thickness of the uterine wall. The majority of articles written today refer to a depth of approximately 3 mm, or 1 low-powered field, below the basal layer of endometrium.

Pathogenesis

In the mid-19th century, Rokitansky (1860) described a condition in which elongated endometrial glands were found embedded in a hyperplastic endometrial

stroma. He noted two variants of this condition: one in which the glands grew into the uterine musculature, and another in which they grew downward into the endometrial cavity, forming a polyp. Schatz (1883) later interpreted Rokitansky's findings to be a variant of uterine leiomyomata. He called this condition "fibroadenoma cysticus et polyposum."

Chiari (1887) subsequently described an abnormal growth of endometrial glands into the uterine musculature in the areas of the uterine cornu and proximal fallopian tube. This was the first mention of salpingitis isthmica nodosum, which he believed to be a variety of adenomyosis.

Several investigators in the 1880s and 1890s thought that adenomyosis either represented an embryonic error in müllerian cell distribution or was due to invasion of the myometrium by hyperplastic basal endometrium (Diesterweg, 1883; Ruge, 1889; Schroeder, 1892). In 1893, Hauser proposed idiopathic stromal hyperplasia as the etiology for adenomyosis. Subsequently, Von Recklinghausen (1896) proposed that adenomyosis was the result of displacement of mesonephric (wolffian) elements. He noted that these ectopic glandular elements were most commonly found on the posterior uterine wall and in the area of the uterine cornu, and he believed that these regions were more likely sites for wolffian than müllerian vestiges.

In the late 1890s and early 1900s, Meyer (1900, 1909) proposed chronic endometritis as the etiologic event that initiated invasive endometrial hyperplasia. He therefore referred to this condition as "adenomyometritis." Combining two earlier proposals, Cullen (1908) claimed that basal endometrial invasion was responsible for the majority of cases of adenomyosis, but he held out the possibility that müllerian rests could account for the encapsulated form of adenomyosis (adenomyomas). Taussig (1938) later described lymphatic transmission of endometrial components. Although this theory was used to describe pelvic endometriosis (endometriosis externa), it also offered another possible explanation for adenomyosis. Subsequently, Marcus (1961) proposed that some müllerian totipotential cells existed within the myometrium that could differentiate into endometrial cells, offering another explanation for the development of adenomyosis.

Today, we have come full circle, with most investigators believing that adenomyosis results from basal endometrial hyperplasia invading a hyperplastic myometrial stroma. Of note is the interesting observation that all organs in the human body that contain cavities also possess a submucosal region, with the exception of the uterus. It is thought that one of the main functions of this submucosa is to prevent the inward growth of glands that line these cavities.

If basal endometrial and stromal hyperplasia are, in fact, the cause of this disorder, then what etiologic event initiates this process? To date, four primary theories have been espoused: (1) heredity, (2) trauma, (3) hyperestrogenemia, and (4) viral transmission.

Heredity. Meyer (1897) initially described the finding of adenomyosis in a fetus delivered at term. Subsequently, various authors described cases of adenomyosis in young females age 4 to 14 (Emge, 1962). Because none of these young women had yet undergone menarche, hereditary transmission was suggested as the etiologic mechanism. This theory has not been evaluated further.

Trauma. Trauma has been recognized as a possible etiologic mechanism since Zaleski's elegant rabbit experiment in 1936. In that study, vigorous curettage of one pregnant rabbit uterine horn was performed while pregnancies were allowed to continue in the opposite horn. Adenomyosis was subsequently identified only in the horn that had undergone curettage. Several investigators have anecdotally described finding adenomyosis during repeat cesarean sections, and it is well known that endometrial tissue can implant after hysterotomy (Scott et al, 1954). A retrospective study of 485 cases of adenomyosis, however, failed to demonstrate any association between previous cesarean sections and the subsequent development of adenomyosis (Harris et al, 1985).

Hyperestrogenemia. In the mid-1930s, several investigators suggested that hyperestrogenemia could initiate the development of adenomyosis. Pierson (1938) treated two castrated rabbits with 0.1 mg folliculin twice a week and noted the subsequent development of adenomyosis. More recently, Huseby and Thurlow (1982) treated hybrid mice with low-dose diethylstilbestrol. These mice exhibited elevated levels of prolactin, as determined by mammary gland morphology, and they developed protrusions of endometrium into the myometrium—a phenomenon analogous to adenomyosis in humans. It was unknown in this study whether these changes were due to hyperestrogenemia or hyperprolactinemia, but Huseby and Thurlow favored hyperprolactinemia, because they could duplicate these findings by transplanting pituitary grafts into day-old mice. It should be noted that neither of these investigations definitively ruled out pre-existing adenomyosis before estrogen administration was initiated.

In a well-designed study demonstrating synergism between estrogen and prolactin, Mori et al (1984) reported an increased incidence of adenomyosis in mice that had anterior pituitary grafts. Adenomyosis did not develop initially but did so after continuous supplementation with estrogen and progesterone. Conversely, in mice that did not receive pituitary grafts but did receive continuous steroid supplementation, adenomyosis failed to develop. Therefore, it appears that in this model estrogen and/or progesterone plus prolactin maybe required for adenomyosis to develop. In addition, it appears, in similar experiments, as though bromocriptine may be able to prevent the development of adenomyosis (Mori et al, 1991).

A more recent study has suggested that estrogen is synthesized in both eutopic and ectopic endometrial tissue in women with adenomyosis, and that this estrogen may affect the growth of adenomyosis (Yamamoto et al, 1993). In this study, myometrial aromatase and estrone sulfatase activity was significantly greater in women with adenomyosis than in controls. This appears to confirm earlier work demonstrating that aromatase activity was higher in adenomyotic tissue than in normal myometrium or endometrium (Urabe et al, 1989).

Viral Transmission. Although investigators occasionally mention viral transmission as a possible etiologic mechanism, no scientific studies have evaluated this proposed process.

Histopathology

At the time of hysterectomy, the adenomyotic uterus has usually been described as globular or boggy. It is grossly enlarged in at least 60% of cases, but rarely exceeds 12 weeks' gestation in size; most weigh between 80 and 200 g (Molitor, 1971; Bird et al, 1972). In his classical article in which he found parity to be the primary determinant of uterine weight, Langlois (1970) defined the upper limits of normal uterine weight as 130 g for nulliparous women, 210 g for parity of one to three, and 250 g for parity of four or more. With these criteria, if cases with associated leiomyomata are excluded, uterine weight is not appreciably elevated by adenomyosis.

Grossly, these uteri are usually hyperemic with thickened walls (Fig. 30-11). Although most investigators have reported that the posterior wall is more frequently involved than the anterior wall, Bird et al (1972) found adenomyotic foci to be equally distrib-

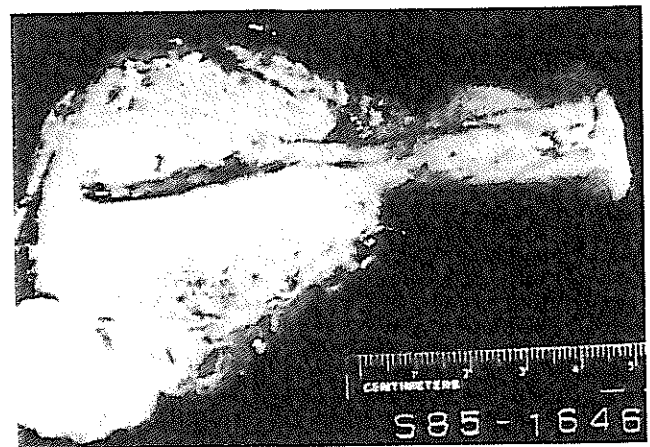


Figure 30-11

Adenomyotic uterus demonstrating asymmetric thickening of the myometrium. A leiomyoma, which frequently coexists with adenomyosis, is present at the posterior fundal aspect of the uterus. (Courtesy of Philip T. Vaiente, MD, Department of Pathology, University of Texas Health Science Center at San Antonio.)

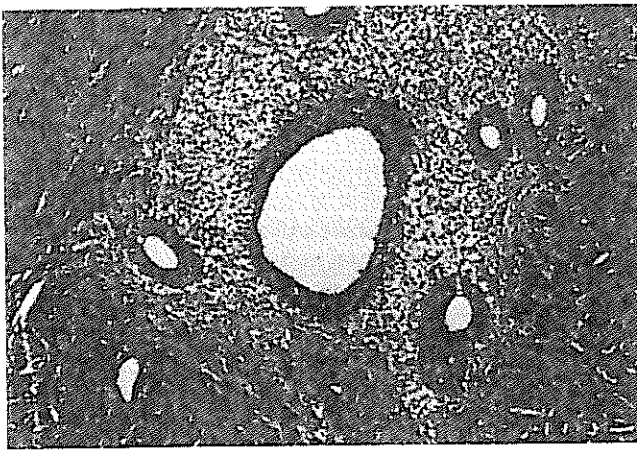


Figure 30-12

Photomicrograph depicting adenomyotic foci surrounded by hypertrophic smooth muscle cells. (Courtesy of Philip T. Valente, MD, Department of Pathology, University of Texas Health Science Center at San Antonio.)

uted when they took an additional six sections for histopathologic examination. The foci are frequently scattered diffusely throughout the myometrium but occasionally can be large and localized, forming structures called adenomyomas.

On microscopic examination, the hallmark of adenomyosis is invasion of endometrial glands and stroma into the myometrium. As noted above, the exact depth of invasion required to confirm the diagnosis remains a source of some controversy. The cells lining the adenomyotic glands resemble those of the basal endometrium. They can, however, occasionally undergo metaplasia and resemble tubal or cervical epithelium. Surrounding these glands are hypertrophic smooth muscle cells (Fig. 30-12).

Although the majority of adenomyotic glands demonstrate proliferative features, they can frequently respond to circulating hormones and can be in phase with the endometrial glands. After excluding those samples with proliferative or atrophic surface endometrium, Molitor (1971) found functional ectopic endometrium in 33% of his specimens. In addition, in his review of adenomyosis in pregnancy,

Azziz (1986) reported a 57% incidence of decidualization of adenomyotic foci.

Although it is known that adenomyotic tissue contains receptors for estrogen, progesterone, and androgens, the relative levels of these receptors are not well defined. Initially, Tamaya and associates (1979) reported finding decreased levels of estrogen and androgen receptors in 10 minced adenomyotic uteri. Progesterone receptors were absent in four of these cases and diminished in the others. These investigators also found delayed histologic dating in the adenomyotic foci and attributed this to the lower progesterone receptor levels. Subsequently, in an analysis of 319 uteri, 21 of which contained adenomyosis, estrogen receptor levels were found to be somewhat lower and progesterone receptor levels slightly higher in those uteri from patients with adenomyosis than in those from patients with no demonstrated pathology (Van der Walt et al, 1986). Obviously, more study is needed in this area.

Epidemiology

The reported incidence of adenomyosis has varied widely over the years, ranging from a low of 5.7% in 1283 uteri removed for leiomyomata to a high of 69.6% from unselected hysterectomy specimens (Table 30-7) (Cullen, 1908; Counsellor, 1938). Although some of this disparity can be explained by the use of different histologic definitions for adenomyosis, most of the variation is likely due to the degree of fervor with which pathologists pursue the diagnosis. As a result of the focal nature of this condition, the diagnosis of adenomyosis can be very difficult to make. In an excellent prospective study by Bird et al (1972), 200 consecutive hysterectomy specimens were examined histologically. When three routine sections of myometrium were examined, adenomyosis was found in 62 women. Six additional tissue blocks were then examined, three each from the anterior and posterior uterine walls, and an additional 61 cases were discovered, raising the incidence from 31% to 61.5%.

Table 30-7. INCIDENCE OF ADENOMYOSIS

STUDY	INCIDENCE (%)	COMMENTS
Cullen (1908)	5.7	1283 uteri removed for fibroids
Emge (1954)	15	1412 hysterectomy specimens
Benson and Sneed (1958)	21.4	701 premenopausal hysterectomies
Emge (1959)	29.3	280 postmenopausal hysterectomies
Molitor (1971)	3.8	3207 hysterectomy specimens
Bird et al (1972)	31	200 consecutive hysterectomy specimens
	61.5	Same 200 cases, 6 additional histologic sections examined
Owolabi and Strickler (1977)	10	1619 hysterectomy specimens
Discepoli et al (1979)	20.6	1500 hysterectomy specimens
Thompson and Davron (1986)	15.9	702 hysterectomy specimens

Table 30-8. INCIDENCE OF ADENOMYOSIS IN HYSTERECTOMY SPECIMENS BY AGE

STUDY	NO. OF ADENOMYOTIC UTERI	PATIENT AGE					
		20-29	30-39	40-49	50-59	60-69	70-79
		No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Emge (1962)	210	6 (2.8)	48 (22.9)	99 (47.1)	48 (22.9)	8 (3.8)	1 (0.5)
Molitor (1971)	281	4 (1.4)	66 (23.5)	148 (52.7)	55 (19.6)	4 (1.4)	4 (1.4)
Bird et al (1972)	123	3 (2.4)	25 (20.4)	62 (50.4)	28 (22.7)	4 (3.3)	1 (0.8)
Thompson and Davion (1986)	112	19 (17.0)	54 (48.2)	33 (29.4)	5 (4.5)	1 (0.9)	—

A major source of difficulty in establishing the true incidence of adenomyosis lies in the fact that, although published reports may cite the number of cases of adenomyosis found in relation to patient age (Table 30-8), they uniformly fail to report the total number of hysterectomies performed in each age group. Thus the relative incidence of adenomyosis as a function of age has never been defined.

Another source of difficulty in establishing the true incidence of adenomyosis is the fact that most studies evaluate only women undergoing hysterectomies, thereby creating a selection bias. Two necropsy studies have been performed, reporting an incidence of adenomyosis in 50% and 53.7% of specimens (Lewinski, 1931; Kistner, 1964). Although these studies involve a different type of selection bias (i.e., women with hysterectomy have been excluded), they do illustrate the fact that the true incidence of adenomyosis is probably nearer the upper end of the published range.

On the surface, parity appears to correlate with adenomyosis, because up to 93% of treated patients are parous (Owolabi and Strickler, 1977; Vercillini et al, 1995). However, these figures tend to mimic those of the general population, hence their significance is called into question. If true, this would confirm an interesting paradox, because parity may be protective against endometriosis yet a risk factor for the development of adenomyosis. There does not appear to be any significant correlation between adenomyosis and race or obesity (Benson and Sneed, 1958; Rao and Persaud, 1982). Likewise, there does not appear to be any significant predilection for adenomyosis to coexist with other specific gynecologic pathology. In a retrospective study of 134 patients undergoing hysterectomy, Vercillini et al (1995)

found an essentially equal coexistence of adenomyosis with fibroids (23%), genital prolapse (26%), cervical cancer (19%), endometrial cancer (28%), ovarian cancer (28%), and ovarian cysts (21%).

Clinical Presentation

The most frequently cited profile of adenomyosis symptomatology includes the triad of abnormal uterine bleeding, secondary dysmenorrhea, and an enlarged, tender uterus. Other symptoms, such as dyspareunia and chronic pelvic pain, present less commonly (Table 30-9). Unfortunately, however, none of these symptoms (or even the triad itself) are pathognomonic for adenomyosis. Kilkku et al (1984) preoperatively assessed the symptomatology of 212 women scheduled for hysterectomy with complaints suggestive of adenomyosis or endometriosis. Because adenomyosis frequently is accompanied by other pelvic pathology, it is often difficult to attribute symptoms solely to this condition (Table 30-10). In addition, up to 35% of affected patients may be asymptomatic (Benson and Sneed, 1958).

Abnormal uterine bleeding encompasses menorrhagia, which has been reported to affect as many as two thirds of adenomyosis patients, as well as metrorrhagia, which occurs somewhat less frequently (Emge, 1962; Molitor, 1971; Bird et al, 1972). The increased blood loss reported at the time of menstruation by these patients has been confirmed in one study (Fraser et al, 1986). Although the exact mechanisms remains unclear, the increased bleeding may result from the greater endometrial surface area found in enlarged uteri. Other postulated mecha-

Table 30-9. ADENOMYOSIS SYMPTOMATOLOGY

SYMPTOM	REPORTED INCIDENCE (%)
Menorrhagia	51-68
Metrorrhagia	11-39
Dysmenorrhea	20-46
Dyspareunia	7
Asymptomatic	3-35

Table 30-10. ASSOCIATION OF ENDOMETRIOSIS WITH OTHER GYNECOLOGIC PATHOLOGY

CONDITION	REPORTED ASSOCIATION (%)
Uterine leiomyomata	19-57
Endometrial hyperplasia	7-33
Endometriosis	0-28
Salpingitis isthmica nodosa	1-20

nisms offer a role for prostaglandins (mefenamic acid administration has been shown to reduce menstrual blood loss) or the hyperestrogenemia often noted in these patients (Fraser et al, 1986).

Dysmenorrhea is probably also related to prostaglandins, but the mechanism of dyspareunia in the absence of associated endometriosis is unknown. As with many other conditions, it appears that the severity of symptoms is associated with the extent of disease (Benson and Sneed, 1958).

Because these symptoms are so nonspecific, it is not surprising that adenomyosis is seldom correctly diagnosed preoperatively. Most investigators have reported a correct preoperative diagnosis in fewer than 10% of cases (Israel and Woutersz, 1959; Marcus, 1961; Owolabi and Stricker, 1977; Thompson and Darion, 1986). However, owing to selection bias, incomplete pathologic examination of surgical specimens, and a limited number of well-designed studies, our true ability to diagnose adenomyosis prospectively is impossible to ascertain.

Adjunctive Diagnostic Testing

Radiologic

Hysterosalpingography. Numerous investigators have explored the use of various radiologic modalities to aid in the prospective diagnosis of adenomyosis. In the largest study of hysterosalpingography (HSG) to date, Marshak and Eliasoph (1955) were able to diagnose adenomyosis correctly in only 38 of 150 patients with "proven" adenomyosis. They did not note either the total number of patients examined or the incidence of false-positive diagnosis. The most commonly described findings on HSG include endometrial diverticuli and honeycomb defects protruding into the myometrium (Siegler, 1974; Wolf and Spataro, 1988). This test is fraught with inaccuracy, however, because the myometrial spiculations frequently ascribed to adenomyosis resemble those of lymphatic or vascular dye intravasation.

Ultrasonography. Unfortunately, abdominal ultrasonography has failed to demonstrate utility as a diagnostic tool. In the late 1970s, one group proposed 5- to 7-mm irregular myometrial sonolucencies as an ultrasonographic finding characteristic of generalized adenomyosis (Walsh et al, 1979). This was subsequently disputed by Siedler et al (1987), who noted generalized uterine enlargement, normal myometrial echogenicity, and preservation of uterine contour in the majority of their patients with documented adenomyosis. Several more recent studies have failed to clarify this issue.

Transvaginal ultrasonography has only been evaluated as a diagnostic modality since the early 1990s. Fedele (1992) evaluated 43 women undergoing hysterectomy for menorrhagia with preoperative transvaginal ultrasound. He described numerous small myometrial anechoic areas with irregular hyperech-

ogenic outlines in 22 women. The sensitivity of this technique was reported to be 80% with a specificity of 74%. Other investigators have reported lower sensitivities of 48% (Ascher et al, 1994) and 53% (Wood et al, 1993). Further studies are certainly needed in this area as transvaginal ultrasonography assumes an even greater role in algorithms for gynecologic therapies.

Magnetic Resonance Imaging. MRI has been applied to pelvic pathology, and preliminary results in adenomyosis patients are encouraging (Lee et al, 1985; Mark et al, 1987). Mark et al correctly predicted adenomyosis in 8 of 20 patients studied using T₂-weighted images. Ten of the remaining 12 patients were correctly predicted not to have adenomyosis; in the other 2, radiologic diagnosis was uncertain. The investigators described a unique-appearing, wide low-signal-intensity band surrounding the normal high-signal-intensity endometrium in patients with diffuse adenomyosis. Microscopic adenomyotic foci, however, were not demonstrated. T₂-weighted imaging appears to offer significant advantages over either unenhanced or contrast-enhanced T₁-weighted imaging. MRI has also been evaluated as a technique for differentiating adenomyosis from leiomyomata (Togashi et al, 1989). Ninety-three patients were evaluated preoperatively, and the results were correlated with surgical pathology. All 16 cases of adenomyosis were correctly diagnosed preoperatively. More widespread application of this new technology, however, must await further study. In addition, cost may prohibit development of MRI as a widespread screening test.

Serum Markers

CA-125 is an antigen produced by ovarian epithelial cells. It is secreted into the blood, and its use has been advocated in a variety of gynecologic conditions. Although some have used it to predict recurrences of nonmucinous ovarian carcinomas, others have attempted to assess nonoperatively the status of recurrent endometriosis by determining serial CA-125 levels. In 1985, Takahashi et al reported elevated preoperative serum levels of CA-125 in six of seven study patients. Although elevated, these levels were significantly lower than those commonly found in patients with ovarian carcinomas. One month following hysterectomy, all patients had normal levels of CA-125. Using immunohistochemistry, these same investigators localized the CA-125 antigen to glandular epithelium present in the adenomyotic foci of eight hysterectomy specimens (Kijima et al, 1987). Another study, however, failed to reproduce these findings (Halila et al, 1987). In their report of 22 women, 11 of whom had adenomyosis, Halila and associates noted normal preoperative CA-125 levels in all adenomyosis patients. These levels did not significantly change when tests were repeated 1 and 5 weeks postoperatively. The reason for the discrepancy in these studies is not readily apparent, but it

is hoped that further work will be conducted in this area.

Serum cystine aminopeptidase and leucine aminopeptidase levels have also been used as potential markers for adenomyosis. Levels of these enzymes have been reported to be elevated in several benign and malignant conditions involving the uterus and ovary (Blum and Sirote, 1977). No controlled trials have been performed to evaluate the clinical utility of these measurements.

Histopathology

As with endometriosis, histopathologic confirmation remains the gold standard in the diagnosis of adenomyosis. To this end, and in the hope of avoiding hysterectomy, two alternative tissue sampling techniques have been proposed. Popp et al (1993) described Tru-cut myometrial biopsies in 40 women performed under either laparoscopic or ultrasonographic guidance. There were no false-positive diagnosis or complications, and the sensitivity of the technique ranged from 40% to 70%, depending on the number of specimens obtained. Brosens and Barker (1995) performed myometrial needle biopsies on 40 hysterectomy specimens from 27 women with adenomyosis and 13 women without adenomyosis. They compared the histologic findings from 8 biopsies per uterus with myometrial block specimens from the same uteri, and were able to confirm adenomyosis in 12 of 27 positive specimens (sensitivity, 44%). The accuracy of the technique was dependent on the depth of glandular invasion into the myometrium, and the authors concluded that at least four biopsy specimens would have to be obtained in order to reliably diagnose adenomyosis that had invaded at least one third of the way into the myometrium. Regardless of the number of biopsy specimens obtained (up to eight), the sensitivity of diagnosing superficial adenomyosis never exceeded 9% (Brosens and Barker, 1995). Based on these findings, they concluded that this procedure should only be contemplated in a select population of prescreened patients.

McCausland (1992) described a hysteroscopic sampling technique involving removal of a 5-mm deep strip of myometrium from the posterior fundus using 70W cutting current delivered through a loop electrode. He evaluated 90 patients complaining of menorrhagia, 50 of whom had hysteroscopically normal endometrial cavities. Of those 50, 33 had significant adenomyosis, believed to be the likely etiology of their abnormal bleeding. Using a subjective scale to assess menorrhagia, McCausland concluded that the depth of invasion of the adenomyosis correlated significantly with the degree of menorrhagia.

Adenomyosis in Pregnancy

On the basis of the only large study of adenomyosis in pregnancy, an analysis of 151 uteri obtained at

cesarean hysterectomy, it appears that the incidence of this condition is 17.2% (Sandberg and Cohn, 1962). Although 50 years ago it was suggested that adenomyosis in pregnancy markedly increased the risk of obstetric complications—specifically, postpartum hemorrhage, uterine atony, and uterine rupture—that has not proved to be the case (Haydon, 1942). In his excellent review of this subject, Azziz (1986) noted only 29 cases of complications in more than 80 years' worth of literature, a surprisingly low figure in light of the incidence of this entity.

Associated Gynecologic Pathology

Adenomyosis rarely occurs as an isolated finding (Table 30–10). Up to 80% of adenomyotic uteri are associated with such conditions as leiomyomata, endometrial hyperplasia, peritoneal endometriosis, and uterine cancer. The fact that all of these entities, except endometriosis, are associated with prolonged estrogen exposure has been frequently cited as evidence that adenomyosis results from hyperestrogenemia. Adenomyosis occurs most frequently in association with leiomyomata (up to 57% of the time), and the similarity of symptomatology in these two conditions serves to make accurate preoperative diagnosis very difficult (Benson and Sneed, 1958). Despite their obvious similarities, adenomyosis and pelvic endometriosis coexist in only 28% of women or less (Israel and Woutersz, 1959; Emge, 1962; Mathur et al, 1962; Molitor, 1971; Bird et al, 1972).

Salpingitis isthmica nodosum, an inflammatory process of uncertain etiology affecting the proximal fallopian tube, also occurs in association with adenomyosis. Its observed coexistent frequency was 1.4% in one study and 19.8% in another (Benson and Sneed, 1958; Molitor, 1971). Abnormalities of the endometrial lining ranging from hyperplasia to adenocarcinoma are frequently associated with adenomyosis. The reported incidence of coexistent hyperplasia also demonstrated hyperplasia in the adenomyotic foci (Molitor, 1971). The vast majority of these cases have demonstrated simple endometrial hyperplasia (Fig. 30–13); however, atypical hyperplasia can occur. Molitor (1971) reported an incidence of 3.5% for atypical hyperplasia in an analysis of 281 adenomyotic uteri.

Adenomyosis frequently occurs in association with endometrial adenocarcinoma. In one study, 60% of 100 patients with adenocarcinoma also had adenomyosis (Marcus, 1961). Other reported incidences are much lower, at 10% to 33% (Hernandez and Woodruff, 1980). In addition to arising within the same uterus as adenomyosis, adenocarcinoma may arise from within adenomyotic foci. It appears as though the coexistence of adenomyosis does not have an impact upon the prognosis for patients with endometrial adenocarcinoma (Hall et al, 1984). Isolated reports have described other types of uterine cancer that have been reported in association with

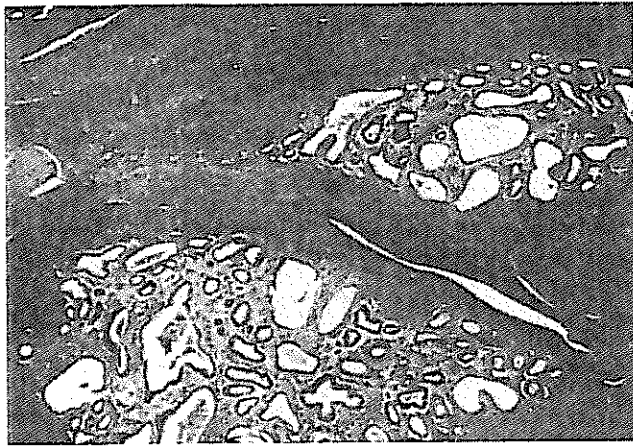


Figure 30-13

Photomicrograph of adenomyotic foci demonstrating cystic hyperplasia. (Courtesy of Philip T. Valente, MD, Department of Pathology, University of Texas Health Science Center at San Antonio.)

adenomyosis. Specifically, müllerian adenosarcoma, endometrial stromal sarcoma, and leiomyosarcoma, all of which were believed to have developed within adenomyotic foci, have been reported (Gisser and Toker, 1978; Oda et al, 1984). Although no one has specifically reported on the incidence of adenocarcinoma within adenomyotic uteri, it is thought to be relatively rare.

Treatment

The mainstay of both the diagnosis and treatment of adenomyosis remains hysterectomy. Until a safe and consistently effective method exists for directed myometrial biopsy, one will be able to diagnose adenomyosis accurately only by surgical removal of the uterus, thus effectively treating this condition simultaneously.

Concerning medical management, in the mouse model, bromocriptine has a suppressive effect upon adenomyosis (Nagasawa and Mori, 1982). Conversely, prolactin, progesterone, and possibly even growth hormone appear to accelerate the development of the disease (Nagasawa et al, 1985, 1987). RU 486, an antiprogestational agent that inhibits the effects of progesterone at uterine receptor sites, has been shown to suppress the development of adenomyosis markedly when given for up to 30 days. This finding may have some implication for future human studies (Nagasawa et al, 1989).

Anecdotal evidence exists that progesterone may exacerbate the development of adenomyosis in humans as in mice (Falk and Mullin, 1989). Danazol, an antigonadotropic derivative of 17 α -ethinyl testosterone used effectively in the treatment of endometriosis, has not been extensively studied in this condition. Several small studies, however, have failed to demonstrate any benefit of treatment for 6 months

with a daily dose of either 400 or 800 mg (Lauersen et al, 1975; Ingerslev, 1977). GnRH analogs may have a potential application in treatment, but, to date, only isolated case reports have been published to evaluate this possibility.

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