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MANAGEMENT OF ENDOMETRIOSIS

Endometriosis is the presence of islands of endometrium in extrauterine locations which exhibit the histologic and hormonal responsiveness of native endometrium. Cyclic change in these cells is associated with menstrual-like bleeding and resultant localized inflammation. Although the etiology of endometriosis is unknown, the main theories are as follows:

- Transtubal regurgitation and implantation (initially proposed by Sampson)
- Coelomic metaplasia, i.e., repeated inflammation may induce metaplasia of mesothelial cells to endometrial epithelium (as supported by Meyer)
- Lymphatic or hematogenous spread to explain extraperitoneal disease (Halban)

Incidence and Demography

Experienced clinicians estimate that 5–15% of premenopausal women have endometriosis to some degree. The disease is a common abnormal pelvic finding in women over 25 years of age. It is found in 40–50% of women who undergo surgery for the diagnosis and treatment of infertility (1).

The average age at diagnosis is 28 years; 75% of women with endometriosis are between 24 and 50 years old. With increasing awareness and improved diagnostic techniques, endometriosis is being diagnosed at earlier ages.

Initially considered a disease affecting predominantly white women, endometriosis is found in black, Oriental, and Middle Eastern women at rates similar to that of whites (1,2).

Effects of Pregnancy on Endometriosis

The behavior of endometriosis during pregnancy is extremely variable. In the first trimester, symptoms occasionally worsen, particularly when enlargement and softening of endometriomas occur. Some peritoneal lesions may regress during the later months. The benefit of pregnancy seems temporary, as the disease usually persists or recurs after delivery (3). If the disease has been treated, it appears that pregnancy delays, but does not prevent, recurrence (4).

Pathophysiology

The mechanism or mechanisms by which endometriosis causes symptoms, including infertility, are unknown. Adhesions and destruction of normal tissue which occur secondary to moderate and severe disease explain pain and infertility. Anatomic distortion does not occur in mild endometriosis, yet symptoms may be severe. Prostaglandins affect tubal motility, ovum release, and ovarian steroidogenesis and have been implicated as the cause of both somatic symptoms and infertility. The concentrations of certain prostaglandins have been found to be increased in the peritoneal fluid of some patients with endometriosis, which may explain pain and infertility caused by even minimal disease. The immunologic response and increased activity of peritoneal macrophages may be related to infertility (5). An adverse effect on ovulation has been postulated as etiologic in some infertility-related endometriosis cases.

History and Physical Examination

A thorough medical history is the best screening method. There are no pathognomonic symptoms associated with endometriosis, and there is no consistent correlation between severity of symptoms and extent of disease.

At least one of the following symptoms occurs in most patients: dysmenorrhea (28–63%), deep

dyspareunia (12–27%), and perimenstrual sacral backache (25–31%). Typically, women have progressive secondary dysmenorrhea, are nulligravid (70%), have not conceived for 3 or 4 years after a pregnancy (30%), or complain of pelvic pain (10%). Earlier studies on the natural history of the disease showed that 20–50% of women with endometriosis are infertile (6). Two-thirds of infertility patients have primary infertility; the remaining one-third have secondary infertility with an inordinately high rate of spontaneous abortion (7).

Endometriosis may cause rectal pain or bleeding, intermittent hematuria, or postcoital vaginal bleeding. It may present as an acute abdomen; mechanisms observed include torsion of an involved ovary, particularly in pregnancy; rupture of a large endometrioma; or severe involvement of the vermiform appendix. Rarely, distant foci cause pneumothorax and subarachnoid hemorrhage. In general, any complaint of pain or abnormal bleeding temporally related to menses should raise a suspicion of endometriosis.

A familial tendency is now clear; 8–10% of female first-degree relatives of those with endometriosis have the disease by a probable polygenic-multifactorial inheritance (8). Women in affected families develop endometriosis at an earlier age, are twice as likely to be severely affected, and have a greater risk for recurrence after treatment (9).

Physical examination should include inspection of all abdominal and perineal scars. Cervical and vaginal examination may reveal lower tract involvement. Adnexal masses due to endometriosis may vary in size, shape, and consistency and are usually asymmetric, fixed, cystic, or indurated. The uterus is retroverted in approximately 50% of women with endometriosis diagnosed surgically; it may be displaced or fixed, mimicking pelvic malignancy. Rectovaginal examination reveals involvement of the posterior cul-de-sac, uterosacral ligaments, or rectum, as suggested by the presence of nodularity or induration associated with exquisite tenderness.

Diagnosis

Laparoscopy is the most valuable diagnostic tool, particularly in an infertile woman without somatic complaints or findings (10). The earliest macroscopic findings are 2- to 10-mm superficial brownish or blue-black raised lesions on peritoneal surfaces. Older lesions are puckered as a result of fibrosis. Endometriosis may also invade adjacent structures. Ovarian endometriomas appear as smooth, cystic masses that adhere to contiguous viscera. Concomitant pelvic adhesions range from delicate to obliterative. Ultrasound, barium enema, and intravenous pyelography are occasionally useful in preoperative evaluation.

The posterior cul-de-sac and ovaries are the most common sites of involvement, followed by the serosa of the uterus, rectosigmoid, and bladder. The cervix, vagina, and vulva are the most frequent sites of extraperitoneal endometriosis.

The diagnosis is suggested microscopically by the presence of hemosiderin-laden macrophages or mesothelial reaction and is confirmed histologically by the presence of endometrial glands and stroma. Biopsy of several lesions should aid diagnosis.

Classification

Numerous classification systems have been proposed, based on histologic grading, sites and extent of involvement, and extent of adhesions. Comparative studies have failed to demonstrate the superiority of any classification, however (11). Detailed description of operative findings in individual cases is essential.

One mechanism for doing so is the American Fertility Society classification (Fig. 1). Although it does not dictate therapy and may not correlate with clinical symptoms, this classification is useful in a descriptive way to document the extent of disease.

Therapy

Expectant Therapy

In young infertile women with mild endometriosis, the expectant approach dictates the completion of an infertility evaluation and treatment of factors contributing to infertility. Thus, expectant therapy is not synonymous with "no treatment" (7). This approach has improved pregnancy rates without specific therapy for endometriosis (12); correction of anovulation coexistent with mild disease has also resulted in pregnancy. Medical or surgical treatment alternatives are indicated if pregnancy does not occur within 6–12 months of expectant therapy or if pain is progressive (7).

Medical Therapy

Androgens and estrogens, notably diethylstilbestrol (13), were first used in the treatment of endometriosis during the 1930s. Because of low preg

THE AMERICAN FERTILITY SOCIETY REVISED CLASSIFICATION OF ENDOMETRIOSIS

Patient's Name _____ Date _____

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

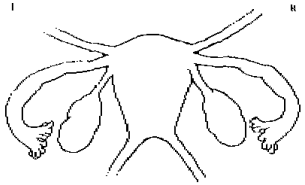
Laparoscopy _____ Laparotomy _____ Hysterography _____
Recommended Treatment _____
Prognosis _____

PERITONEUM	ENDOMETRIOSIS	<1cm	1-5cm	>5cm
	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	16	36
	L Filmy	1	2	4
	Dense	4	16	36
TUBE	R Filmy	1	2	4
	Dense	4*	16*	36
	L Filmy	1	2	4
	Dense	4*	16*	36

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

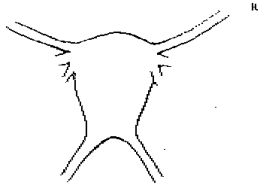
Additional Endometriosis

To Be Used with Normal Tubes and Ovaries



Associated Pathology _____

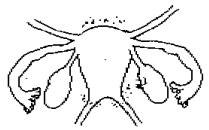
To Be Used with Abnormal Tubes and/or Ovaries



For additional supply write to: The American Fertility Society, 2131 Magnolia Avenue, Suite 201, Birmingham, Alabama 35256

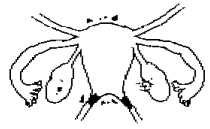
EXAMPLES & GUIDELINES

STAGE I (MINIMAL)



PERITONEUM
Superficial Endo – 1-5cm 2
R. OVARY
Superficial Endo – <1cm 1
Filmy Adhesions – <1/3 1
TOTAL POINTS 4

STAGE II (MILD)

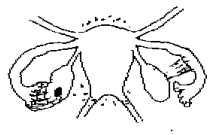


PERITONEUM
Deep Endo – >5cm 6
R. OVARY
Superficial Endo – <1cm 1
Filmy Adhesions – <1/3 2
L. OVARY
Superficial Endo – <1cm 1
TOTAL POINTS 9

STAGE III (MODERATE)

PERITONEUM
Deep Endo – >5cm 6
CULDESAC
Partial Obliteration 4
L. OVARY
Deep Endo – 1-5cm 16
TOTAL POINTS 26

STAGE III (MODERATE)



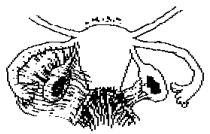
PERITONEUM
Superficial Endo – >5cm 3
R. TUBE
Filmy Adhesions – <1/3 1
R. OVARY
Filmy Adhesions – <1/3 1
L. TUBE
Dense Adhesions – <1/3 16*
L. OVARY
Deep Endo – <1cm 4
Dense Adhesions – <1/3 4
TOTAL POINTS 29

STAGE IV (SEVERE)

PERITONEUM
Superficial Endo – >5cm 3
L. OVARY
Deep Endo – 1-5cm 32**
Dense Adhesions – <1/3 8**
L. TUBE
Dense Adhesions – <1/3 8**
TOTAL POINTS 51

*Point assignment changed to 16
**Point assignment doubled

STAGE IV (SEVERE)



PERITONEUM
Deep Endo – >5cm 6
CULDESAC
Complete Obliteration 40
R. OVARY
Deep Endo – 1-5cm 16
Dense Adhesions – <1/3 4
L. TUBE
Dense Adhesions – >2/3 16
L. OVARY
Deep Endo – 1-5cm 16
Dense Adhesions – >2/3 16
TOTAL POINTS 114

Determination of the stage or degree of endometrial involvement is based on a weighted point system. Distribution of points has been arbitrarily determined and may require further revision or refinement as knowledge of the disease increases.

To ensure complete evaluation, inspection of the pelvis in a clockwise or counterclockwise fashion is encouraged. Number, size and location of endometrial implants, plaques, endometriomas and/or adhesions are noted. For example, five separate 0.5cm superficial implants on the peritoneum (2.5 cm total) would be assigned 2 points. (The surface of the uterus should be considered peritoneum.) The severity of the endometriosis or adhesions should be assigned the highest score only for peritoneum, ovary, tube or culdesac. For example, a 4cm superficial and a 2cm deep implant of the peritoneum should be given a score of 6 (not 7). A 4cm deep endometrioma of the ovary associated with more than 4cm of superficial disease should be scored 20 (not 24).

In those patients with only one adnexa, points applied to disease of the remaining tube and ovary should be multiplied by two. (**Points assigned may be circled and totaled. Aggregation of points indicates stage of disease [minimal, mild, moderate, or severe].)

The presence of endometriosis of the bowel, urinary tract, fallopian tube, vagina, cervix, skin etc., should be documented under "additional endometriosis." Other pathology such as tubal occlusion, hemoperitoneum, uterine anomaly, etc., should be documented under "associated pathology." All pathology should be depicted as specifically as possible on the sketch of pelvic organs, and results of observation (laparoscopy or laparotomy) should be noted.

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FIG. 1. American Fertility Society Endometriosis Classification System (from American Fertility Society: Revised Classification of Endometriosis: 1985. Fertil Steril 43:351, 1985. Reproduced with permission of the publisher, The American Fertility Society, Birmingham, Alabama)

nancy rates, the frequent occurrence of severe side effects, and the availability of newer regimens, these agents are now rarely used (7).

In current medical therapy, medroxyprogesterone acetate (Curretab; Depo-Provera; Provera; Provera Dosepak) is the most common progestin used. The major disadvantages are low pregnancy rates, breakthrough bleeding (with oral medication), and persistent anovulation following parenteral administration (7). This therapy is occasionally recommended when childbearing is not a concern and surgery is not indicated.

Kistner was the first to report success in the use of high-dose estrogen-progestin combination therapy (pseudopregnancy) that simulates the hormonal milieu of pregnancy (14). Symptoms are resolved partially or completely in 53% of women with endometriosis, and pregnancy rates are 40–50%. In addition, increased danazol use (Chronogyn; Danocrine) has further diminished the use of pseudopregnancy. Recent studies, however, demonstrate higher pregnancy rates and more prolonged pain relief with conservative surgical therapy than with pseudopregnancy. Low-dose combination oral contraceptives commonly relieve pain in young women with mild endometriosis who are not attempting pregnancy (15).

Danazol, first used clinically in 1971, is usually the medication of choice when medical therapy is indicated. The drug affects multiple sites, including the hypothalamus, pituitary gland, ovary, endometrium, and sex hormone-binding globulin; its effects result in atrophy of islands of endometrium. Anovulation is consistently observed during therapy, but ovulatory function returns within one or two cycles after treatment. The drug is begun on the fifth day of menses. Optimum dosage is controversial, with reported daily doses ranging from 200 to 1000 mg. The current recommendation on the package insert is 800 mg daily. Danazol may be started at 400 mg twice daily, but clinical observations suggest that half this dose may be as effective. Average duration of therapy is 6 months, with a reported range of 12–78 weeks. Barrier contraception is recommended during therapy and for the first menstrual cycle after treatment. The effects on the fetus conceived in the first post-treatment cycle are at present unclear (16). Danazol therapy during early pregnancy has been associated with masculinization of the external genitalia of a female fetus (17).

Side effects are dose dependent; they occur often but rarely prompt discontinuation of the drug. The most common are weight gain, edema, irregular bleeding, and depression. Less common are decrease in breast size, skin rash, acne, hirsutism, and deepening of the voice (16).

Danazol therapy alone is most beneficial for women with mild or moderate disease. Pain is relieved in 72–100% of these women, and improvement of disease has been observed by laparoscopy in 85–95%. Pregnancy rates following danazol therapy vary from 28–60% (18). It is less effective in relieving symptoms of severe endometriosis, particularly with extensive ovarian involvement and significant adhesions (16).

Laparoscopic Therapy

Fulguration of endometriosis and lysis of adhesions is acceptable for women with mild or moderate disease but is insufficient for severe or extensive disease. Cautery must be applied judiciously to avoid bowel, bladder, or ureteral injury. Destruction of implants by carbon dioxide or argon laser directed through the laparoscope may lessen operative risks because the depth of tissue necrosis can be minimized. There are insufficient data to conclude that laser fulguration is superior to conventional techniques (19).

In some patients, a second-look laparoscopy after conservative surgery or danazol may be useful to evaluate therapeutic success, separate filmy adhesions, or coagulate small foci of recurrent endometriosis (19).

Conservative Surgical Therapy

The indications for conservative surgical therapy of endometriosis include the following (1):

- Adnexal masses
- Symptoms, including infertility, that are refractory to expectant or medical therapy
- Severe endometriosis in a woman who has a desire for future fertility
- Concomitant conditions that affect fertility and are best treated surgically, e.g., leiomyomas, müllerian fusion defects, or pelvic adhesions
- The patient's desires, as influenced by age, duration of infertility, obstetric history, and life goals

After laparoscopic diagnosis, conservative surgical therapy may be performed while the patient is under the same anesthetic, or it may be delayed. Ninety percent of patients choose immediate surgery, and there seems to be no greater risk of complications or diminished pregnancy rates.

A low transverse incision usually provides adequate exposure, although a vertical incision may

be better in an obese woman with a narrow pelvis. Gentle handling of tissue throughout the procedure is imperative. Grasping instruments and "sponge sticks" are avoided; gentle retraction with the surgeon's fingers or Teflon-coated malleable retractors is preferable. All pelvic organs are intermittently irrigated with an isotonic solution.

Presacral neurectomy may be performed to relieve central pelvic pain. There is no evidence that this procedure directly improves conception rate. Rare complications include intraoperative bleeding.

Endometriotic islands are fulgurated or excised, depending on the degree of invasiveness. Near the bladder, bowel, or ureter, excision of retracted or invasive lesions is preferable. Raw surfaces are reperitonealized with a primary closure or, rarely, with a free peritoneal graft.

Ovarian involvement varies from pinpoint lesions to invasive nodules or endometriomas that invade or displace tissue and compromise ovarian vasculature. The former may be safely fulgurated, but the latter must be resected and the ovary must be repaired to ensure good blood supply. This is indicated in bilateral disease. When unilateral ovarian involvement is extensive, excision of a severely diseased adnexa is indicated, provided the opposite ovary is intact. This improves pregnancy rates and appears to decrease the likelihood of recurrence.

The uterosacral ligaments are resected only if significantly involved with disease. Uterine suspension by plication of the uterosacral ligaments and shortening of the round ligaments lifts the adnexa from the cul-de-sac, preventing contact of the tube and ovary with dissected and fulgurated areas, thereby minimizing adhesions. This may help alleviate deep dyspareunia.

Appendectomy should be performed if the appendix appears diseased. Gastrointestinal and urinary tract endometriosis is usually superficial and rarely penetrates to mucosa. Excision of these lesions with primary closure is adequate. If there is large bowel obstruction or mucosal involvement, primary resection is indicated after preoperative bowel preparation.

Intraperitoneal solutions during surgery or parenteral administration of steroids, antibiotics, and antihistamines postoperatively or both may reduce the frequency and extent of adhesions after surgery. Although commonly employed, their clinical efficacy remains unproved (1,7).

Conservative surgical treatment of endometriosis is associated with few complications. Approximately 75% of women with mild endometriosis, 60% with moderate disease, and 40% with severe disease conceive after surgery. The majority (80%) conceive within the first 18 months postoperatively.

Annual rates of recurrence following conservative surgery range from 0.9% in the first postoperative year to 13% in the eighth year. Cumulative rates of recurrence are 14% at 3 years and 40% at 5 years. Recurrence is independent of the severity of disease. Postoperative pregnancy appears to delay but not prevent recurrent endometriosis (4).

Combined Medical-Surgical Therapy

Early studies failed to demonstrate that conservative surgery with pseudopregnancy has any advantage over surgery alone. The postoperative administration of danazol initiated prior to hospital discharge may improve pregnancy rates in selected patients; a preliminary study demonstrated a 79% pregnancy rate in women with severe disease after 3–6 months of postoperative danazol therapy. This additional therapy is indicated when there are known residual lesions or when there is a likelihood of microscopic foci. The length of time between surgery and pregnancy is not significantly altered by postoperative danazol therapy (20). The effect of such therapy on recurrent disease is undetermined.

Preoperative use of danazol may facilitate surgical removal of endometriosis and diminish postoperative adhesion formation. Recurrence and pregnancy rates after preoperative danazol use are unknown.

Definitive Therapy

Abdominal hysterectomy is indicated in women with severe disease when future childbearing is not a consideration or when the disease has been refractory to medical or conservative surgical therapy. Ovarian tissue can be preserved if the blood supply is not impaired and the ovaries are free of disease. Significant residual endometriosis, especially involving the bowel, bladder, or ureters, may preclude the preservation of ovarian tissue. Exogenous estrogen therapy is initiated in the immediate postoperative period for women whose ovaries are removed. When significant residual disease is present, withholding estrogen therapy for 6 months may allow atrophy of lesions. Medroxyprogesterone acetate or continuous oral contraceptives may be effective during this period as medical therapy for active residual disease and suppression of

hot flushes. The risk of stimulation of residual endometriosis with estrogen replacement therapy is the same as the risk without such therapy—1–3% (1).

It is important to emphasize that the management of endometriosis should be strictly individualized. This concept is of the greatest importance in the treatment of the infertile couple.

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