TREATMENT OF MODERATE AND SEVERE ENDOMETRIOSIS

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INTRODUCTION

Wheeler and Malinak described a treatment algorithm that considers the severity of endometriosis, the patients' desires for reproduction versus symptom relief and the several acceptable forms of treatment, (revised AFS system) (1). The algorithm is shown in Table I (2).

The management of patients with pelvic pain depends largely on the patients' age and her desire for further childbearing. In the absence of absolute indications for surgery, patients who still desire childbearing can be treated with analgesics or periodic medical therapy to reduce symptoms. Laparoscopic surgery is an alternative, particularly if it can be performed at the initial diagnostic laparoscopy. If pain continues to be severe, conservative laparotomy and presacral neurectomy with or without perioperative medical therapy should be considered. When childbearing is no longer a factor and analgesics are ineffective, definitive surgery is indicated (Table II).

Medical Therapy:

Medical therapy would appear warranted primarily in women who fail to obtain relief following laparoscopy or in those who suffer from recurrence of pain but do not desire an additional laparoscopy. Medical treatment is also appropriate in those women for whom laparoscopic ablation of disease is incomplete.

The role of drug therapy in promotion of fertility, however 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. The value of medical therapy as an adjunct to surgical treatment is still open. In cases of extensive endometriosis, surgical treament is preferable to restore normal pelvic anatomical relationships and resect ovarian endometriomas (Table III).

Surgical Therapy:

Surgical therapy should be individualized because the optimum time for conception in infertile couples is the first 12 to 18 months postoperatively. The timing of surgery should optimize the complete evaluation of the couple, including an assessment of their willingness to concentrate on achieving pregnancy after surgery.

Laparoscopic Surgery:

Laparoscopic treatment is rapidly becoming the surgical method of choice in treating several forms of endometriosis which enables treatment of most cases at the time of initial diagnostic laparoscopy without increasing complications.

Additional advantages of laparoscopic surgery include shorter anesthetic time, hospital stay and shorter recovery time.

Endoscopic treatment of endometriosis consists of resection ablation or coagulation of endometriotic tissue and adhesions. Resection is achieved by surgical dissection and excision with coagulation cr suturing for hemastasis. Ablation is achieved by CO2 laser. Coagulation is achieved with unipolar or bipolar electrocautery, endothermy, or various lasers,such as, NdYAG, KTP, and Argon.

Ablation :

The physical property of CO2 laser (Table IV) makes this treatment ideal for superficial endometriotic implants. The bioeffect of the CO2 laser is a rapid increase in the temperature of intra and extracellular water. This rapid expansion of water molecules causes the tissue to vaporize. The resulting "plume" is composed of celluar debris and vapor. The CO2 laser is the only instrument that allows destruction of small lesions with minimal or no damage to surrounding tissues. This accuracy makes the CO2 laser suitable for treating lesions on the bowel and bladder and in the

vicinity of the ureter or blood vessels. Treatment of ovarian or peritoneal implants is easily accomplished with a continuous or pulse mode setting of 10-20 watts. This setting is also appropriate for vaporization adhesions.

The reduced coagulation necrosis is responsible for the decreased inflammatory reaction during healing and, theoretically, may reduce subsequent adhesion formation. Unfortunately most of the studies in the literature were uncontrolled, it is not possible to compare the results of CO2 Laser laparoscopy with other therapeutic modalities. These studies do, however, suggest that in experienced hands the results are as good as the results achieved in laparotomy. (Table V) The only study to compare postoperative adhesion formation following CO2 laser adhesiolysis with electrosurgical adhesiolysis (20) demonstrated no significant difference in adhesion formation between the two groups.

The accuracy and precision of the CO2 laser is also a disadvantage in certain situations. First, it is impossible to achieve hemostasis of large vessels, and second, destruction of several square centimeters of endometriotic implants can literally take hours. Coagulation is superior in these circumstances.

Coagulation:

The bioeffect of heat is dependent on temperature and duration of contact, whereas vaporization results from high energy delivered over short time periods. Coagulation occurs with lower temperatures over longer time periods. With temperatures between 45 C and 60 C, there is irreversible damage to cellular proteins, but no immediately visible effect. Tissues exposed to this temperature subsequently undergo coagulation necrosis. When tissues are exposed to temperatures between 60 C and 80 C 'blanching' is observed due to loss of intracellular water and coagulation of proteins.

As a general rule, dense energy such as CO2 laser causes minimal coagulation necrosis. This is beneficial for ablating endometriotic implants, but less effective for achieving hemostasis. Slow transfer of less energy, as with low power electrocoagulation and lasers other than CO2, causes only coagulation. Coagulation is achieved with monopolar or bipolar electrical energy, and laser energy (Neody: YAG, KTP and Argon).

Two electrosurgical methods are available: unipolar and bipolar. The body of the patient is incorporated into the circuit when unipolar electrocoagulation is used. Current passes from the generator to the instrument, then through the patient to the neutral pole and back to the generator. When the contact area is small, as with microtip instruments, little oscillating energy is needed to produce a cutting effect. Beyond the tip of the instument, electrical current of low denstiy is quickly dispersed through adjacent tissue, causing little damage. Because of the larger area of contact, an increased density of electrical energy is required to produce a coagulating effect and adjacent tissue may therefore be damaged. In these situations, thermal damage to peritoneum, bowel, bladder, ureter, or vessels may occur, even though the observed effect appears limited. The hazards of unipolar coagulation are well known. Since other forms of energy are available for coagulation the use of unipolar current can be limited.

When bipolar electrical sytems are used, the current passes from the generator along one jaw of the instrument, and then across the other jaw, and back to the generator. Bibolar systems are safer than unipolar, but accidents are still possible. The primary functions of bipolar instruments are to achieve hemostasis during adhesiolysis and to coagulate endometriotic cyst walls and implants. It is ill advised to use bipolar coagulation for bowel implants, because of possible coagulation necrosis and subsequent perforation.

Coagulation is also accomplished using Neodym: YAG,KTP, and Argon lasers. Several features of these lasers distinguish them from CO2 lasers and may present potential advantages for laparoscopic treatment of endometriosis.

1) Tissue is destroyed primarily by photocoagulation and not vaporization.
2) Because there is no vaporization there is little or no 'plume'.
3) Tissue penetration by the laser beam is several millimeters and because of the tissue penetration and lack of vaporization, implants can be destroyed with minimal damage to overlying peritoneum.
4) The laser energy is directed through a fiber that can be manipulated to coagulate implants in areas difficult to reach with the rigid instruments that direct the CO2 laser beam.
5) The wavelengths of the Argon laser are selectively absorbed by hemoglobin containing tissues, allowing selective absorbtion of the laser energy by hemoglobin containing endometriotic implants.

Further, the deeper penetration of tissue by coagulating laser is a potential disadvantage and requires extreme caution when treating implants overlying bowel and ureters.

Preliminary work has suggested that endoscopic treatment of endometriosis is as effective as other therapeutic modalities for endometriosis associated pelvic pain and infertility. For now, the use of endoscopic surgery seems warranted to treat endometriosis at the time of initial diagnosis. Although no studies have demonstrated that endoscopic surgery is superior to expectant management, treatment of initial diagnosis may retard further progression of disease. Additional control studies are needed to determine the benefit of endoscopic surgery.

Conservative Surgery for Endometriosis at Laparotomy (CSEL): The indications for CSEL include:

1) The persistence of symptoms, including infertility, in women with endometriosis after suitable trials of expectant, medical, or laparoscopic surgical therapy.
2) Severe endometriosis or dense adhesions precluding the technique of laparoscopic surgery.
3) The presence of concomitant impediments to fertility that are best treated at laparotomy (e.g., some uterine anomalies).
4) The request of the individual patient who, because of age, duration of infertility, or career goals, may request the most definitive treatment available, which currently continues to be CSEL.

CSEL:

How to perform conservative surgery appears to be a clear meticulous technique with pinpoint hemostasis and minimal tissue trauma is theoretically optimal. A selection of adjuvants that reduce adhesion formation and have minimal side effects is appropriate. Currently glucocorticoids or intraperitoneal dextran offer the best options. However, no data on efficacy have been generated to support these pronouncements.

Adjunctive surgical procedures often include some form of uterine suspension. Suspending the uterus has no effect on pregnancy but is a useful way to apply smooth peritoneal lined surfaces over raw areas of dissection and the uterosacral ligements can be plicated with significant posterior cul de sac disease or dissection.

Presacral neurectomy appears not to increase pregancy rates but offers a significant chance for improving severe dysmenorrhea or dyspareunia.

Wheeler and Malinak demonstrated a cumulative recurrence rate of endometriosis in 13% of patients at 3 years and 40% at 5 years (21).

There are few data evaluating the results of conservative surgery upon amelioration of pelvic pain. Studies to date are retrospectively assessed, statistically inadequate and interpreted in a cavalier manner.

Fertility enhancement:

In moderate endometriosis a 50% pregnancy rate has been reported, but cycle fecundity rates are only 2% - 3.6% per month (Table VI). No significant differences have been demonstrated between conservative surgery and danazol therapy or expectant management.

Conservative surgery for severe diseases would be a logical choice. Nevertheless, a 39% pregnancy rate in severe endometriosis which translates to a cycle fecundity rate of 1.2% - 1.5% is reported (Table VII).

To date no randomized clinical trials have been performed to demonstrate that conservative surgery enhances fertility in women with severe endometriosis. It seems rational to perform surgical intervention only when other factors such as coexisting pathology and significant alteration of normal anatomic relationships, are present.

Definitive Surgery:

13% of the women with endometriosis will have to have definitive surgery.

The treatment of choice for most women who have involvement of other organ systems, such as, the bowel or urinary tract, who have intractable pain and who have completed their families is total abdominal hysterectomy, bilateral salpingo-oophorectomy, and resection of all residual implants.

Although endometriotic lesions can regress during medical therapy, bowel resection should be considered if more than 50% of the bowel lumen is compromised.

Approximately 3 - 5% of patients with endometriosis will have the disease in the appendix. The appendix should

be removed in all patients undergoing definitive surgery and examined if undergoing conservative surgery.

Bladder lesions may be superficial or penetrate into the bladder wall but seldom cause obstruction. Ureteral involvement often lead to obstruction, ureteral obstruction may require diversion, reimplantation or reanastamosis.

In view of the risk of osteoporosis and other effects of estrogen depletion, hormone replacement therapy is advocated in patients undergoing oophorectomy for endometriosis.

If significant endometriosis is present after total abdominal hysterectomy and bilateral salpingo-oophorectomy three to six months waiting prior to initiating hormone replacement therapy will prevent reactivation in most of the cases.

Combination Therapy:

Because of the microscopic widespread nature of this disease, a combination of surgical therapy to excise the visible implants and medical therapy to induce a regression of the microscopic implants makes sense. It has been said that the advantage of preoperative administration of hormonal therapy is that implants may be excised more easily at the time of surgery, this may also decrease the risk of postoperative adhesion formation. Unfortunately this treatment protocol would necessitate two surgical procedures. The advantage of postoperative medical therapy is that lesions left behind after surgery are treated and one surgical procedure is necessary. Most conceptions following surgical therapy occur within the first 12 months after surgery, therefore, by treating surgical patients with danazol for a prolonged period postoperatively, the time interval within the highest potential fertility may be passed over.

Wheeler and Malinak reported 19 patients with severe endometriosis treated with conservative laparotomy followed by danazol, 400 to 800 mg daily until they were amenorrheic for three months. 79% of the patients conceived. This was compared to a control group that consisted of patients treated with surgery alone, in whom only 36 (30%) of 119 patients conceived (32).

Buttram and coworkers in a nonrandomized prospective study, compared danazol in conjunction with conservative surgery, danazol alone, and conservative surgery alone (12). A trend toward higher pregnancy rates was noted with preoperative danazol compared to surgery alone. The authors concluded that preoperative danazol affords a higher pregnancy rate than postoperative danazol although the differences were not significant. Several other studies report the use of preoperative medical treatment with conservative surgery.

Only one study found a striking advantage to the use of postoperative medical therapy. Other studies using danazol comparing both preoperative and postoperative therapy have found either no difference or an advantage to preoperative danazol in success in achieving pregnancy (Table VIII).

A decision to use preoperative or postoperative hormonal therapy with conservative laparotomy or laparoscopy should be based on therapeutic results. Unfortunately, none of the studies on combination therapy prospectively compared results to surgery alone, medical therapy alone, and expectant management. Thus, the value of combination therapy remains speculative.

In Vitro Fertilization and Embryo Transfer (IVF/ET):

Approximately 40% of women with advanced endometriosis and infertility will be unable to conceive even after surgical and medical therapy. For these women IVF/ET is a viable treatment option.

In two studies, high abortion rates were observed in the first 8 weeks following successful implantation. Chillik and coworkers reported that all patients with moderate and severe endometriosis who became pregnant aborted within the first 8 weeks, in contrast to a 17% abortion rate in women with mild and minimal endometriosis (33).

In a recent study from Norfolk, Oehninger, et al compared the IVF/ET results in three groups:group one, previous history of endometriosis but normal pelvis at the time of retrieval (23 patients, 54 cycles); group two, patients with stage 1-2 endometriosis (91 patients, 191 cyles); group three, stage 3-4 endometriosis. (22 patients, 35 cycles). Group three had significantly fewer preovulatory oocytes and immature oocytes retrieved and fewer embryos transferred per transfer. The fertilization rate and the per-cycle and per-transfer pregnancy rates were similar in three groups. However, the miscarriage rate was higher in group 3(71.4%) than in groups 1 and 2(22.2% and 36.9%, respectively) and the ongoing pregnancy rate per cycle was lower (5.7% versus 12.9% and 15.1% in groups 1 and 2) (34).

These data reflect the compromised reproductive potential in patients with moderate and severe endometriosis probably as a result of a reduced oocyte recovery rate and poor embryo quality.

In summary advanced stages of endometriosis appear to adversely affect pregnancy rates, primarily due to the impaired folliculogenesis and technical problems in recovering oocytes. The quality of the embryo and endometrium may also contribute to the impaired reproductive success after IVF/ET in women with endometriosis.

TABLE I: ENDOMETRIOSIS TREATMENT ALGORITHM

	DESIRES CHILDBEARING		CHILDBREARING COMPLETE
CHIEF COMPLAINT	INFERTILITY	PELVIC PAIN	PELVIC PAIN
Stage III	1. Laparoscopic Rx 1. CSEL ± PSN 2. Medical Rx 3. IVF/ET	1. Laparoscopic Rx 2. CSEL + PSN 3. Medical Rx	1. Laparoscopic Rx 2. Medical Rx 3. TAH ± BSO 3. CSEL + PSN
Stage IV	1. CSEL + perioperative medical Rx 2. CSEL alone 3. Laparoscopic Rx + postoperative medical Rx 4. IVF/ET	1. CSEL + PSN + perioperative medical Rx 2. Medical Rx 3. Laparoscopic Rx + medical Rx	1. TAH + BSO 1. CSEL + PSN + medical Rx 2. Laparoscopic Rx + medical Rx

Rx = treatment; CSEL= conservative surgery for endometriosis at laparotomy; PSN = presacral neurectomy; TAH = total abdominal hysterectomy; BSO = bilateral salpingo-oophorectomy; IVF/ET = in vitro fertilization/embryo transfer; ± = indicates adjunctive treatment option based on individual patient findings.

TABLE II. TREATMENT FOR ENDOMETRIOSIS AND ASSOCIATED PELVIC PAIN

Desires Childbearing
- Analgesics
- Medical therapy
- Laparoscopic surgery
- Conservative laparotomy, presacral neurectomy plus perioperative medical therapy

Childbearing Complete
- Analgesics
- Medical therapy
- Total abdominal hysterectomy
- Total abdominal hysterectomy and bilateral oophorectomy ± perioperative medical therapy

TABLE III: EFFECT OF DANAZOL ON INFERTILIY

	Number Pregnant/Number Treated (%)	
Author, Year	Moderate	Severe
Dmowski, Cohen, 1978 (3)	16/35 (46%)	3/11(27%)
Audebert et al, 1979 (4)	-	8/13(62%)
Ronnberg et al, 1979 (5)	-	3/20(15%)
Van Zyl et al, 1980 (6)	2/3(66%)	3/3(100%)
Moore et al, 1981 (7)	2/7(28%)	--
Barbieri et al, 1982 (8)	6/16(38%)	9/18(50%)
Buttram et al, 1982 (9)	1/6(17%)	0/4(0%)
Guzick, Rock, 1983 (10)	15/38(40%)	--
Puleo, Hammond, 1983 (11)	3/13(23%)	2/6(33%)
Buttram et al, 1985 (12)	3/6(50%)	3/3(100%)
TOTALS	48/124(39%)	31/78(40%)

TABLE IV: COMPARİSON OF CURRENTLY USED LASERS IN INFERTILITY SURGERY.

CHARACTERISTICS	CO2	ARGON	ND:YAG
Wave length	10.6 mm	0,5 mm	1.06 mm
Tissue effect	Vaporization	Coagulation	Coagulation
Depth of tissue effect	0,1 mm	0,5 mm	4mm
Tissue effect dependent on color	No	Yes	Yes
Absorbance by water	Strong	None	Slight
Beam scatter	None	Slight	Moderate
Requires fiber	No	Yes	Yes

TABLE V. PREGNANCY RATES AFTER ENDOSCOPIC VAPORIZATION OF ENDOMETRIOSIS

	No. Pregnant/no. Treated (%)		
Author, Year	Moderate	Severe	Cumulative Follow-up
Kelly, Roberts, 1983 (13)	3/7(43%)	-	6/10 (60%) 6 months
Chong, 1985 (14)	--	--	21/32 (66%) 12 months
Feste, 1985 (15)	4/6 (66%)	2/5 (40%)	30/58 (52%) 12 months
Martin, 1985 (16)	3/19 (19%)	1/4 (25%)	11/50 (22%) 9 months
Davis, 1986 (17)	15/26 (58%)	2/7 (30%)	37/65 (57%) 12 months
Nezhat et all 1986 (18)	32/51 (63%)	12/27 (44%)	62/102 (61%) 18 months
Olive, Martin 1987 (19)	22/48 (46%)	10/20 (50%)	55/117 (47%)
TOTAL	79/157 (50%)	27/63 (43%)	222/434 (51%)

TABLE VI: CONSERVATIVE SURGERY FOR MODERATE ENDOMETRIOSIS

Author, Year	No. Pregnant/ No. Treated	%	Cycle Fecundity Rate
Acosta et al, 1973 (22)	30/60	50%	
Hammond et al 1976 (23)	3/5	60%	
Garcia, David, 1977 (24)	7/19	37%	
Sadigh et al 1977 (25)	17/23	74%	
Schenken, Malinak, 1978 (26)	12/36	33%	
Buttram, 1979 (27)	28/50	56%	
Rock et al, 1983 (28)	48/88	55%	0.020
Rantala et al, 1983 (29)	22/39	56%	
Gordts et al 1984 (30)	42/99	42%	
Olive, Lee 1986 (31)	22/43	51%	0.036
TOTALS	231/462	50%	

TABLE VII: CONSERVATIVE SURGERY FOR SEVERE ENDOMETRIOSIS

Author, Year	No. Pregnant No. Treated	%	Cycle Fecundity Rate
Acosta et al, 1973 (22)	13/39	33%	
Hammond et al, 1976 (23)	0/2	0%	
Garcia, David, 1977 (24)	14/49	29%	
Sadigh et al, 1977 (25)	20/42	48%	
Schenken, Malinak, 1978 (26)	6/21	29%	
Buttram, 1979 (27)	32/68	47%	
Rock et al, 1981 (28)	39/81	48%	0.015
Rantala et al, 1983 (29)	18/46	39%	
Gordts et al, 1984 (30)	20/57	35%	
Olive, Lee, 1986 (31)	10/34	29 %	0.014
TOTALS	127/439	39%	

TABLE VIII: PREGNANCY RATES WITH POSTOPERATIVE THERAPY

Author, Year	Regimen	No. Pregnant/No. Treated (%) Moderate	Severe	Cumulative
CONSERVATIVE LAPAROTOMY AND DANAZOL				
Audebert et al, 1979 (4)	Danazol	-	-	4/13 (30%)
Wheeler, Malinak, 1981 (31)	Danazol	-	15/19 (79%)	15/19 (79%)
Chong, Baggish, 1984 (14)	Danazol	11/13 (85%)	3/10 (30%)	14/23 (61%)
Rönnberg Jarvinen, 1984 (5)	Danazol	-	-	14/44 (32%)
Buttram et al, 1985 (12)	Danazol	0/1	7/22 (32%)	8/24 (33%)
Stage of endometriosis				

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