
ENDOMETRIOSIS: MEDICAL AND SURGICAL TREATMENT Eduardo
A. GONZALEZ-FABBRIZZI, MD.

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LEARNING OBJECTIVES:

This lecture will:

- 1) Review the recognition of endometriosis - contemporary view of the pelvic endometriosis lesions.
- 2) Discuss the effect of the: the extent of the disease and the age of the patients the previous response to treatment
- 3) The alternatives therapies
- 4) Summarize the results obtained from these procedures
- 5) Discuss the factors that influence the outcome

INTRODUCTION.

Endometriosis is a disease characterized by the presence of tissue that is histologically identical to endometrium at ectopic locations outside the uterine cavity and protean manifestations. The incidence of endometriosis is strongly influenced by the awareness of non-classical lesions and because of the long-standing interest of the group in these lesions. The prominent symptoms of the disease are chronic pelvic pain and infertility. However, some of the patients do not have clinical symptoms. Does the stage of endometriosis or its severity correlate with the pelvic pain or infertility? Patients who have minimal disease would complain of severe pain, conversely, patients who have severe lesions may not complain at all of pain. Endometriosis may not be the cause of infertility but the result of it, because many women have the disease but are not infertile..

More now than ever before, endometriosis has stimulated discussion about the best methods for recognition and treatment. The treatment of endometriosis is currently one of the most controversial issues in gynecology.

When the question of whether or not mild endometriosis should be treated was debated at the 3er. World Congress on Endometriosis held in Brussels in 1992, the audience voted inconclusively: 49,9% were in favor of treatment and 50,1% were against it (1). Current concepts is

mild endometriosis is a disease have recently been discussed in a series of articles in Human Reproduction (2).

Despite the lack of basic knowledge about the condition we have had to formulate treatment approaches which can be seen to have three main goals:

*Relief of symptoms by removing or inducing resolution of implants;
Limitation of disease progression and delay of recurrence; and
Restoration of fertility when, or if, wanted*

To meet these aims, several medical and surgical approaches have been adopted, the exact choice being dictated by recognition of endometriosis, extent of the disease, patient's age, severity of symptoms, and previous response to treatment (if any).

1) THE RECOGNITION OF ENDOMETRIOSIS - CONTEMPORARY VIEW OF ENDOMETRIOSIS

During the last decade, the attention has been focused on subtle or non-classical lesions such as white and red vesicles and polypoid lesions. Recently, the depth of infiltration of endometriotic lesions was recognized as an important aspect (3).

A) PERITONEAL ENDOMETRIOTIC LESIONS

Three basic types of the morphology of peritoneal endometriotic lesions must be distinguished:

*non-classical lesions,
pigmented classical lesions and
deeply infiltrating lesions.*

1) Non-Classical lesions: This kind of lesions were first describe by Fallon as amenorreheic endometriosis in 1950 (4), and then described by Jansen and Russell (5), Redwine (6), Martin (7) and us (8).

*Subtle or non-classical endometriotic implants:
have a limited depth of infiltration into de peritoneum (<2mm),
with a smooth or retractile surface,
could be multiple or unique,
usually small in size
and could be alone or associated a dark classical implants.*

Non-classical lesions can be pigmented, although other types of lesions can be describe:

*whitish non-pigmented lesions,
white vesicle lesions,
white protruding lesions,
hemorrhagic vesicle lesions,
peritoneal pockets lesions.*

It has been suggested that non-classical endometriotic lesions are early foci of disease originating from freshly implanted viable endometrial cells on the peritoneal surface. The laparoscopic diagnosis of the disease is seriously hindered by poor or no knowledge of non-classical endometriotic lesions. A strong association (87,5%) (8) between this kind of lesion and endometriosis was suggested. An exhaustive examination of the female pelvis during laparoscopy is recommended in search of non-classical incipient lesions. The magnification of laparoscope is useful in increasing the resolution of lesions which are detected. Laparoscopy biopsies should be systematically indicated for histological confirmation. Its inclusion in the modified 1985 American Fertility Society classification (9) should be done following the same criterium applied up to now to classical pigmented lesions.

2) Pigmented classical lesions: These endometriotic implants have a large surface area and a greater depth of penetration (> 4 mm). They are easily recognized at the peritoneal surface as pigmented powder burn. Classical implants contain dilated glands, filled with a chocolate-like substances. Therefore, intermittent activity of such implants should be considered.

3) Deeply infiltrating implants: Deeply infiltrating pelvic endometriotic implants can have a small surface area but a greater depth of infiltration (>5 mm). These lesions are characterized by deep infiltration of the glands into the surrounding fibromuscular tissue. All deep lesions show a considerable degree of fibrosis. Deep lesions may not be visible at the peritoneal surface during laparoscopic investigation. They are very suspect in patients with palpable nodular findings during rectovaginal examination, and becomes more apparent during excision.

Koninckx and Martin (10) suggest that three subtypes of deep endometriosis can be distinguished:

*type I is suggested to be infiltration,
type II retraction and
type III possible adenomyosis externa.*

Donnez (11) suggest two different types of deep infiltrating endometriosis:

TYPE I : the true deep-infiltrating endometriosis is caused by the invasion of a very active peritoneal lesion deep in the retroperitoneal space. In cases of lateral peritoneal invasion, uterosacral ligaments can be involved as well as the anterior wall of the recto-sigmoid bowel

junction result in a retraction and adhesions and secondary obliteration of the cul-de-sac.

TYPE II : the pseudo deep-infiltrating endometriosis or adenomyosis of the rectovaginal septum is where the lesion originates from the rectovaginal septum tissue and consists essentially of smooth muscle with active glandular epithelium and scanty stroma.

In this study, the rectovaginal nodule was similar to an adenomyoma. Indeed it was a circumscribed nodular aggregate of smooth muscle and endometrial glands. In conclusion, Donnez suggest that the deep infiltrating endometriosis should be considered as a specific disease, different from peritoneal endometriosis and ovarian cystic endometriosis, which originates from the Mullerian rests present in the rectovaginal septum. It is not the consequence of "deep infiltrating" endometriosis. They suggest that this disease be called "rectovaginal adenomyosis" (12).

Activity of endometriotic implants: The "activity" of peritoneal endometriosis is related to the vascularity. The peritoneal red lesions were the most aggressive form of the disease, progressing to the so-called typical or black lesions (13), can invade the retro-peritoneal space by infiltration. The white lesions are a latent or quiescent form of disease. Typical (black), red and white lesions are three different stages of the peritoneal disease and their relative relation to infertility is also probably different.

Some of these small haemorrhagic and vesicular lesions are capable of producing large amounts of prostaglandin F and are often associated with much more pain than that found in those patients with extensive disease whilst patients with deposits of haemosiderin are often in the older age group and this often represents burn-out disease and is asymptomatic.

Deep endometriosis was found by pathology to be an active disease (14) and often associated with pelvic pain. It becomes more frequent with increasing age, suggesting that endometriosis is a progressive disease (15). Deep endometriosis could be related to a specific decrease in natural killer cell activity (16). The increase in plasma cancer antigen-125 (CA-125) and placental protein 14 (PP-14) concentrations were shown to be related specifically to endometriotic cyst and to deep endometriosis (17). Superficial pelvic implants secrete mainly toward the peritoneal cavity, whereas deep endometriosis secrete mainly toward the bloodstream(17). Active lesions show histologic features of proliferation, such as mitoses, secretion and accumulation of intracellular glycogen pools. In women with endometriosis, peritoneal fluid contains more and activated macrophages resulting in enhanced phagocytic activity and secretion of several substances such as a growth factor, prostaglandins and cytokines (18)

Activity of endometriotic foci is different at various depths of infiltration into the peritoneum (19)(20).

*Deep implants (>5 mm).....active in 68% of cases
Intermediate depth..... active in 25% of cases
Superficial foci..... active in 58% of cases*

B) OVARIAN ENDOMETRIOSIS

Two different types of ovarian endometriosis can be classified as:

- (1) Superficial haemorrhagic lesions*
- (2) Haemorrhagic cysts (endometriotic cyst or endometrioma)*

Superficial ovarian lesions are small vesicular lesions covering the ovarian cortex or minute red or blue spots, usually found on the lateral surface of the ovary.

The most typical lesion is the endometriotic cyst or endometrioma. The cyst develops mainly towards the lateral wall of the gonad and often forms adhesions with either peritoneum of the ovarian fossa or of the posterior leaflet of the broad ligament. This may be due to cyclic fissuring of the cyst with leakage of irritating material. Microscopically, the cyst wall is composed prevalently of fibrous connective tissue and inflammatory cells, with the endometria component represented irregularly and sometimes almost absent.(21)

2) THE EXTENT OF THE DISEASE

The revised American Fertility Society (AFS) classification (9) takes into account the extent of the disease and the amount and severity of adhesions. In some women, endometriosis becomes aggressive and forms cystic ovarian endometriosis with adhesions or infiltrates deeply to form rectovaginal endometriosis. In contrast with non-classical endometriosis lesions, both of these forms of endometriosis are clearly pathological conditions, causing pelvic pain (perineural inflammatory reaction) and infertility (22).

The presence of deep infiltrating lesions frequently escape the laparoscopic diagnosis. The specific localization of deep endometriosis in the rectovaginal septum and the uterosacrals ligaments and the hormonal environment is more influenced by plasma hormone concentrations, whereas superficial endometriosis is mainly under peritoneal fluid steroid hormone control (23)(24).

3) THE AGE OF THE PATIENT

The fertility rates remain relatively stable until about the age of 30 to 32 years, beyond which they start declining. (25). In an unpublished Norwegian study, mentioned by Moen (26), of 656 patients with endometriosis, the infertile patients represented 67% of the total group, and 33% were patients with pelvic pain and/or a pelvic mass.

The majority of infertile women were between 25 and 37 years of age. It is an old observation that endometriosis is more prevalent in women with delayed pregnancies (26). Redwine (27) suggest that endometriosis is a positionally static disease, not spreading in the pelvis with advancing age. The incidence of non-classical lesions of endometriosis, which is widely accepted as an early stage, was shown to decrease with age (27). The suggestion that endometriosis may be a positionally static disease would give renewed emphasis to conservative surgery for treatment of patients desiring future fertility. However, the same author coments (6) that an evolution in appearance with age may occur, with resultant spurious effects on conclusions regarding the natural history of the disease. The incidence of endometriomas and that the depth of infiltration both increased with age, support the concept that endometriosis is a progressive disease (24). Endometriosis must be considered as a evolutive disease, increased in most women, but decreased in some.

4) PREVIOUS RESPONSE TO TREATMENT

The long-term outcome for patients treated surgically is extensively documented by Wheeler and Malinak (28)(29) and Redwine (30). They reported, on a series of 423 patients who had:

Conservative surgical therapy for endometriosis, a cumulative recurrence/persistence rate
19% at 5 years and
31,6% for the seventh postoperative year,
with a recurrence rate of 5,7% in the second postoperative year.

Waller and Shaw (31), have recently reviewed recurrence using life-table analysis in Symptomatic patients treated with GnRH-agonist at least 5 years previously.

The data indicate that at 5 years with minimal or mild disease:
the recurrence rate is 34% whereas if the initial stages were AFS 3 or 4 it is 76%.

The recurrence rates after treatment with GnRH-a are therefore similar to recurrence rates after danazol therapy.(32) (33).

The results for medical therapy would seem to be less good than the results obtained for surgical excision of disease from data available in the literature.

ALTERNATIVE THERAPY for pelvic endometriosis are:

Laparoscopic surgery therapy
Open Microsurgery therapy
Hormonal therapy

Combined (surgery + hormonal) therapy
Expectant management
In Vitro Fertilization

SURGICAL TREATMENT OF ENDOMETRIOSIS

The goal of the surgery is to remove as much lesions as possible. The more aggressive approach to removal of implants and adhesions, increase the likelihood of conception, particularly in patients with moderate and severe endometriosis with anatomical distortion (34). When the normal pelvic anatomy can be restored by adhesiolysis and mobilization of the Fallopian tubes and ovaries, pregnancy rates of 50% are observed (35). Recent avances in minimal access surgery suggest this approach is beneficial. Pregnancy rates between 40 and 81% have been reported (36).

Incomplete as well as excessive surgery is a consequence of inadequate diagnosis and surgical inexperience.

The endoscopic access and surgical exploration constitute major progress in defining pathology more accurately before undertaking surgery.

The new access must be combined with microsurgical techniques.

Microsurgery in gynecology is not only the use of magnification but a way of performing surgery.

It is the combination of the accurate identification of the pathology and the surgical restraint not to damage healthy tissue.

LAPAROSCOPIC THERAPY SURGERY

In cases of peritoneal endometriosis diagnosed via laparoscopy, biopsy samples are taken to remove as much endometriosis as possible. Specialized instruments are introduced through multiple abdominal puncture sites: an instrument for lavage and suction is essential and fine bipolar forceps, scissors, and a atraumatic endoscopic grasping forceps are useful. Disecction is done using fine-needle diathermy, or a variety of lasers. Complete extirpation is not recommend when the result migh have been to damage vital organs such as the ureter, bladder, bowel or important blood vessels or to jeopardize fertility by causing postoperative ovarian and/or tubal adhesions, these foci can be endocoagulated. Cysts are aspirated and the cyst bed removed. Ovarioscopy (21) is proposed as a useful tool to differentiate in doubtful cases between a hemorrhagic funcional and a endometriotic cyst and to select the sites for biopsies.

The laparoscopic approach offers a number of advantages over more conventional approaches:

Precise destruction of lesions and adhesions.

minimal bleeding and

minimal damage to adjacent structures (tubes and ovaries) thus minimizing neo-adhesions formation

*non-drying of structures as occurs at laparotomy.
Can be conducted without long-term hospital stay, and less pain.*

OPEN MICROSURGERY THERAPY

Microsurgery for endometriosis consists of a series of minioperations performed under magnification using operating loupes.

Emphasis is on

limiting peritoneal damage and handling,

meticulous haemostasis and

closure of raw areas without tension using finest non-adsorbable sutures,

irrigation and lavage are essential

This may be indicated when there are ovarian cysts or significant adhesions, and the laparoscopic therapy

surgery can not be performed. Endometriomas must be treated by removing or ablating all of the cyst capsule, and thorough irrigation and

lavage are essential. Good surgical results are only obtained with regular assiduous follow-up. Check laparoscopy may be needed to

remove recurrent adhesions and to assess anatomical healing.

HORMONAL THERAPY

Endometriosis is an ovarian steroid-dependent disease. Endometriosis is a multifocal disease, some of the implants are small or deep and thus

not visible at laparoscopy. This fact limits the effectiveness of any sort of laparoscopic treatment aimed at totally eliminating endometriosis. If

all endometriotic lesions were superficial, surgery would be much easier and more effective. For this reason we consider any laparoscopic

treatment of endometriosis to be only partial and temporary, but we know that medical treatment alone is not

particularly useful as endometriosis is quickly re-established once suppression is withdrawn.

The basic goals of hormonal therapy are:

1.- to produce atrophy of endometriotic lesions and

creating a markedly hypoestrogenic environment (Gn-Rh-a)

and/or creating a high local androgen effect (danazol, gestrinone)

2.- induce a acyclic hormone environment

prevents bleeding within endometriotic implants and

prevents "reseeding" of viable fragments of endometrium undergoing retrograde transport.

The most commonly used agents are:

danazol

gestrinone and

gonadotropin-releasing hormone (Gn-Rh agonists)

Immunosuppressive effect(s) (37) and direct inhibitory effect on the growth of human endometrial cells in vitro (38) of danazol were described. The androgenic, anabolic and hepatic side effects of danazol (39) and gestrinone (41), are major drawbacks to its clinical utility. Profound hypoestrogenemia associated with hot flushes and reductions in bone mineral density are major limitations to long-term use of the Gn-Rh agonist analogues (42). To date, alternative modes of medical therapy that balance safety and efficacy without untoward side effects are not available. Recently (43), the antiprogestosterone mifepristone (RU-486) appears

to be effective in improving the symptoms and causing regression of endometriosis in the absence of significant side effects.

Probably the only justification for treating endometriosis with hormonal therapy is

TO PREVENT IT from getting worse in some cases.

The patient should be involved in the decision to use hormonal therapy and understand the risks of replacement therapy. Hughes et.al.(44) published a quantitative overview of all the randomized trials of commonly used treatments (ovulation suppression, laparoscopic ablation and conservative laparotomy)

for endometriosis-associated infertility. The odds ratio comparing treatment with no treatment was 0.85 (0.95-1.22) thus confirming the conclusions reached from reviewing the trials individually, that:

the ovulation suppression is an ineffective treatment for endometriosis-associated infertility and well-designed trials of laparoscopic ablation deserve a high priority

COMBINED (SURGERY + HORMONAL) THERAPY

Some studies have indicated that this form of therapy in the infertile female results in a higher pregnancy rate than surgery or medical suppression alone (39)(40). A combination mode of treatment generally requires two surgical procedures (i.e. diagnostic or laparoscopic surgery followed by second-look laparoscopy or laparotomy after completion of medical suppression for 3-6 months).

Hormonal therapy is generally used on patients when:

the patient with endometriosis and pelvic pain does not desire an immediate pregnancy and

the primary treatment failed to obtain relief of pain,

or is necessary to postpone or avoid major surgery,

or in those cases in whom laparoscopic ablation of the implants is incomplete,

or to inactivate and reduce significantly the distended structure (45) (46)

Repeat laparoscopy often reveals:
persistent endometriosis (more meticulous surgery will reduce persistent disease) and
adnexal adhesions most probably a result of the disease per se or, of the previous surgery

EXPECTANT MANAGEMENT

The definition of "expectant management" include NO THERAPY (medical, surgical or the combination medical/surgical therapy). The approach to this last group must be properly interpreted. It is possible that the diagnostic laparoscopy had a beneficial effect on subsequent fertility. The mechanical lavage of the tubes with methylene blue substance might dislodge mucus plugs, straighten the tubes out, break down peritubal adhesions, or stimulate the cilia of the tubal mucosa. Furthermore, it is possible that the removal of the dye following laparoscopy simultaneously reduced peritoneal fluid volume. One might speculate that the removal of the fluid enhanced fertility by reducing the number of peritoneal fluid macrophages or the amount of peritoneal fluid prostaglandins. Studies have demonstrated a therapeutic component to hysterosalpingography (47)(48)(49).

When Seibel (50) looks at the total of all the patients with minimal endometriosis reported in the literature:

only 45% conceived following hormonal treatment.

In contrast, 58% of the patients with minimal disease conceived following no treatment at all.

Data from artificial insemination with donor (AID) cycles provide a good indicator of fecundability of normal women in whom at least the tubal factor and the male factor can be excluded. Jansen (51) using artificial insemination with frozen donor semen in patients with minimal endometriosis found that it decrease the monthly probability of pregnancy to a third or less of what it would be in the absence of endometriosis, so he suggests that minimal endometriosis, therefore, should usually be treated. However, Rodriguez-Escudero et.al.(52), using artificial insemination with fresh donor semen found that the fecundity rate of the AID-treated group was comparable to that of normal population.

That patients with minimal endometriosis should be followed expectantly for at least 6 months after their diagnostic laparoscopy

Personally, I tend to be more aggressive in operative laparoscopy.

IN VITRO FERTILIZATION

The primary medical indication for human IVF is failure of conventional therapy to provide a pregnancy for the infertile couple.(53). In patients

with severe disease, we assumed that the results would be poor and that such patients could be included in IVF programme.

CONCLUSIONS

"What exactly are we trying to diagnose ? Do all patients need treatment ?

It is still not clear which point endometriosis represents a disease, and thus when therapeutic action should be taken.

We must think not only in the disease, we must think in the patient too.

Recognition of lesions may be more important than the technique used.

The degree of therapy depends on:

the patient's age,

history,

time of infertility,

psychologic status,

physical findings,

goals of surgery and

other factors of infertility.

The endoscopic access must be: the first therapeutic approach and combined with microsurgical principles.

Probably the only justification for treating endometriosis with hormonal therapy is

TO PREVENT IT to getting worse in some cases

The patients with minimal endometriosis should be followed expectantly for at least 6 months after their diagnostic laparoscopy, but I suggest to be operative in it.

Until it is proven that endometriosis without anatomic distortion causes infertility it is possible that medical or surgical treatment is unnecessary or even harmful (54)

The results of these studies will certainly contribute to the design of new medical treatment protocols that satisfy patients' needs on individual bases.

REFERENCES:

- 1) BROSENS IA: New principles in the management of endometriosis. Acta Obstet Gynecol Scand 1994; Suppl.159:18-21
- 2) HUMAN REPRODUCTION: Debate. Is mild endometriosis a disease ? Hum Reprod 1994; 9:2202-2211
- 3) MARTIN DC, HUBERT G, LEVY B:Depth of infiltration of endometriosis. J Gynecol Surg 1989; 5:55-59
- 4) FALLON J, BROSNAN JT, MANNING JJ et.al.:Endometriosis: a report of 400 cases. Rhode Island Med J. 1950; 33:15-23
- 5) JANSEN RPS, RUSSELL P: Nonpigmented endometriosis: clinical, laparoscopic, and pathologic definition. Am J Obstet Gynecol 1986, 155:1154-1159
- 6) REDWINE DB: Age-related evolution in color appearance of endometriosis Fertil Steril 1987; 48:1062-1063
- 7) MARTIN DC, HUBERT GD, VANDER ZWAAG R, EL-ZEKY FA: Laparoscopic appearances of peritoneal endometriosis. Fertil Steril 1989; 51:63-67
- 8) GONZALEZ-FABBRIZZI EA, NICHOLSON RF: Imagen pelviana endometriosa minima no clasica. Publicacion de la Sociedad Argentina de Esterilidad y Fertilidad. Reproducción 1988; 3:79-85
- 9) The AMERICAN FERTILITY SOCIETY: Revised American Fertility Society classification of endometriosis: 1985, Fertil Steril 43:351
- 10) KONINCKX PR, MARTIN D: Deep endometriosis: a consequence of infiltration or retraction or possible adenomyosis externa ? Fertil Steril 1992; 58:924-928
- 11) DONNEZ J, NISOLLE M, CASANAS-ROUX F, BASSIL S, ANAF V: Rectovaginal septum, endometriosis or adenomyosis: laparoscopic management in a series of 231 patients. Hum Reprod 1995; 10:630-635
- 12) DONNEZ J, NISOLLE M. CASANAS-ROUX F, BRION P, DA COSTA FERREIRA N: Stereometric evaluation of peritoneal endometriosis and endometriotic nodules of the rectovaginal septum. Hum Reprod 1995; 11:224-228
- 13) NISOLLE M, CASANAS-ROUX F, ANAF V, MINE JM, DONNEZ J: Morphometric study of the stromal vascularization in peritoneal endometriosis. Fertil Steril 1993; 59:681-684

- 14) CORNILLIE FJ, LAUWERYNS JM, SEPPALA M, RITTINEN L, KONINCKX PR: Expression of endometrial protein PP14 in pelvic and ovarian endometriotic implants. *Hum Reprod* 1991; 6:1411-1415
- 15) OOSTERLYNCK DJ, CORNILLIE FJ, WAER M, VANDEPUTTE M, KONINCKX PR: Women with endometriosis show a defect in natural killer activity resulting in a decreased cytotoxicity to autologous endometrium. *Fertil Steril* 1991; 56:45-51
- 16) OOSTERLYNCK DJ, MEULEMAN C, WAER M, VANDEPUTTE M, KONINCKX PR: The natural killer activity of peritoneal fluid lymphocytes is decreased in women with endometriosis. *Fertil Steril* 1992; 58:290-295
- 17) KONINCKX PR, RIITTINEN L, SEPPALA M, CORNILLIE FJ: CA-125 and placental protein 14 concentrations in plasma and peritoneal fluid of women with deeply infiltrating pelvic endometriosis. *Fertil Steril* 1992; 57:523-530
- 18) HALME J, BECKER S, HAMMOND MG, RAJ MHG and RAJ S: Increased activation of pelvic macrophages in infertile women with mild endometriosis. *Am J Obstet Gynecol* 1983; 145:333-337
- 19) MARTIN DC : Atlas of endometriosis, Gower Medical Publishing , 1993
- 20) OOSTERLYNCK DJ, MEULEMAN C, WAER M, VANDEPUTTE M, KONINCKX PR: Angiogenic activity of peritoneal fluid from women with endometriosis. *Fertil Steril*, 1992; 58:290-295
- 21) BROSENS IA, PUTTERMANS PJ, DEPREST J: The endoscopic localization of endometrial implants in the ovarian chocolate cyst. *Fertil Steril* 1994; 61:1034-1038
- 22) KONINCKX PR: Is mild endometriosis a disease ? *Hum Reprod* 1994; 9:2202-2204
- 23) CORNILLIE FJ, OOSTERLYNCK D, LAUWERYNS JM, KONINCKX PR: Deeply infiltrating pelvic endometriosis: histology and clinical significance. *Fertil Steril* 1990; 53:978-983
- 24) KONINCKX PR, MEULEMAN C, DEMEYERE S, LESAFFRE E, CORNILLIE FJ: Suggestive evidence that pelvic endometriosis is a progressive disease, whereas deeply infiltrating endometriosis is associated with pelvic pain. *Fertil Steril*; 1991: 55:759-765
- 25) MAROULIS GB: Effect of aging on fertility and pregnancy. *Semin Reprod Endocrinol*; 1991; Vol.9 No.3, pag.165-175

- 26) MOEN MH: Why do women develop endometriosis and why is it diagnosed? *Hum Reprod* 1995; 10:8-11
- 27) REDWINE DB: The distribution of endometriosis in the pelvis by age groups and fertility. *Fertil Steril* 1987; 47:173-175
- 28) WHEELER JM, MALINAK LR: Recurrent endometriosis: incidence, management, and prognosis. *Am J Obstet Gynecol* 1983; 146:247-250
- 29) WHEELER JM, MALINAK LR: Recurrent endometriosis. *Contrib Gynecol Obstet* 1987; 16:13-21
- 30) REDWINE DB: Conservative laparoscopic excision of endometriosis by sharp dissection: life table analysis of reoperation and persistent or recurrent disease. *Fertil Steril* 1991; 56:629-634
- 31) WALLER KG, SHAW RW: Gonadotropin-releasing hormone analogues for the treatment of endometriosis: long-term follow-up. *Fertil Steril* 1993; 59:511-515
- 32) BARBIERI RL: Danazol: molecular, endocrine and clinical pharmacology. In Chadha D, Buttram VC, eds. *Current concepts in endometriosis*. New York: Alan R Liss, 1990: 241-252
- 33) WHEELER JM, KNITLE JD, MILLER JD: Depot leuprolide versus danazol in treatment of women with symptomatic endometriosis. *Am J Obstet Gynecol* 1992; 167:1367-1371
- 34) CANDIANI GB, FEDELE L, VERCELLINI P: Laparotomy versus laparoscopy in the surgical treatment of endometriosis: the end of an era? *Acta Eur. Fertil*; 1989, 20:163-166
- 35) ROCK JA, GUZIAK DS, SENGOS C, SCHWEDITSCH M, SAPP KC, JONES HW. The conservative surgical treatment of endometriosis: evaluation of pregnancy success with respect to the extent of disease as categorized using contemporary classification systems. *Fertil Steril* 1981, 35:131-137
- 36) SUTTON CJG. Minimally invasive surgical approach to endometriosis and adhesiolysis. In Studd J and Jardine Brown C. (eds). *The Yearbook of the Royal College of Obstetricians and Gynaecologists*. RCOG Press, London 1993, pp 117-125.
- 37) HILL JA, BARBIERI RL, ANDERSON DJ: Immunosuppressive effects of Danazol in vitro. *Fertil Steril* 1987; 48:414-418
- 38) ROSE GL, DOWSETT M, MUDGE JE, WHITE JO, JEFFCOATE SL. The inhibitory effects of danazol, danazol metabolites, gestrinone, and testosterone on the growth of human endometrial cells in vitro. *Fertil Steril* 1988, 49:224-228
- 39) BUTTRAM VC Jr., REITER RC, WARD S. Treatment of endometriosis with danazol: report of a 6-year prospective study. *Fertil Steril* 1985; 43:353-360
- 40) BUTTRAM VC Jr.: Use of danazol in conservative surgery. *J. Reprod Med (Suppl.)* 1990; 35:82-86

- 41) COUTINHO EM. Treatment of endometriosis with gestrinone (R-2323), a synthetic anti-estrogen, anti-progesterone. *Am.J.Obst.Gynecol.* 1982, 144:89
- 42) DLUGI AM, MILLER JD, KNITTLE J., Lupron Study Group. Lupron Depot (leuprolide acetate for depot suspension) in the treatment of endometriosis: a randomized, placebo-controlled double-blind study. *Fertil Steril* 1990; 54:419-427
- 43) KETTEL KL, MURPHY AA, MORALES AJ, ULMANN A, BAULIEU EE, YEN SSC. Treatment of endometriosis with the antiprogestosterone mifepristone (RU-486). *Fertil Steril* 1996; 65:23-28
- 44) HUGHES EG, FEDORKOW DM, COLLINS JA. A quantitative overview of controlled trials in endometriosis-associated infertility. *Fertil Steril* 1993; 59:963-970
- 45) DONNEZ J, NISOLLE M, KARAMAN Y, et.al. CO2 laser laparoscopy in peritoneal endometriosis and in ovarian endometrial cyst. *J Gynecol Surg* 1989; 5:361-365
- 46) DONNEZ J, NISOLLE M, GILLET N, SMETS M, BASSIL S, CASANAS-ROUX,F: Large ovarian endometriomas. *Hum Reprod* 1996; 11:641-646
- 47) DECHERNEY AH, KORT H, BARNEY JB, DE VORE GR: Increased pregnancy rate with oil-soluble hysterosalpingography dye. *Fertil Steril* 1980; 33:407
- 48) MACKAY RA, GLASS RH, OLSON LE, VALDYA R: Pregnancy following hysterosalpingography with oil and water soluble dye. *Fertil Steril* 1981;35:696
- 49) GOODMAN SB, REIN MS, HILL JA; Hysterosalpingography contrast media and chromotubacion dye inhibit peritoneal lymphocyte and macrophage function in vitro: a potential mechanism for fertility enhancement. *Fertil Steril* 1993; 59:1022-1027
- 50) SEIBEL MM, BERGER MF, WEINSTEIN FG, TAYMOR ML: The effectiveness of danazol on subsequent fertility in minimal endometriosis. *Fertil Steril* 1982; 38:534-537
- 51) JANSEN RPS: Minimal endometriosis and reduced fecundability: prospective evidence from an artificial insemination by donor program. *Fertil Steril* 1986; 46:141-143
- 52) RODRIGUEZ-ESCUADERO FJ, NEYRO JL, CORCOSTEGUI B, BENITO JA: Does minimal endometriosis reduce fecundity ? *Fertil Steril* 1988; 50:522-524
- 53) AMERICAN FERTILITY SOCIETY: Ethical considerations of assisted reproductive technologies. *Ethics Committee*, 1994; 62: Supplement 1:35S

54) WINKEL CA: Endometriosis: making conservative (Fertility-sparing) therapy more viable. Endometriosis 2000, Lister Hill Auditorium, National Institute of Health, Bethesda, Maryland, May15-17,1995