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Endometriosis

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1. Introduction

Endometriosis is classically defined as the growth of endometrial glands and stroma at extra-uterine sites, most commonly implanted over visceral and peritoneal surfaces within the female pelvis (1). Though endometriosis has been described for the first time in 1690 by the German physician, Daniel Shroen, researchers remain still unsure as to the definitive cause of this disease (2). The most widely accepted theory for the pathogenesis of endometriosis (retrograde menstruation/transplantation), proposed in the 1927 by Sampson (3). Although a great deal has been learned about endometriosis since Sampson's land mark studies, there is still a lot about it that is unclear and controversial. It remains an enigmatic disorder in that the cause, the natural history, and the precise mechanisms of its presentation are not known (4).

Endometriosis is most commonly found on the pelvic peritoneum but may also be found on the ovaries, rectovaginal septum, ureter, and rarely in the bladder, pericardium, and pleura. More rarely, colon, small intestine, appendix, umbilical scar and even sites not closely contiguous to the pelvis (e.g., lung and brain tissue) may also be involved (5). It is a leading cause of disability in women of reproductive age, responsible for dysmenorrhea, pelvic pain and subfertility. The most common symptoms for women who have endometriosis are pelvic pain and infertility; both adversely affecting the quality of life. The pregnancy rate in women with endometriosis is about half of women with tubal factor infertility and is negatively correlated with the severity of disease. The cause of reproductive failure may be due to poor oocyte development, implantation or embryogenesis. In addition to infertility, a strong cause–effect relationship between endometriosis and pelvic pain is commonly observed (6, 7). Dysmenorrhoea is associated with cyclic recurrent microbleeding within various entities of ectopic endometriotic implants and consequent inflammation. Endometriosis-related adhesions and compression or infiltration of nerves in the subperitoneal pelvic space by ectopic lesions also cause painful symptoms (8, 9).

In the last few years, there is a growing interest in endometriosis, because of the large number of women it affects (about 3–10% of the female population in the reproductive age, and up to 40–80% of women complaining of pelvic pain) and the significant morbidity

associated with this disease, mainly with regard to the possible consequences on reproductive function and on the risk of developing gynecologic tumors, such as ovarian cancer (10-12). The prevalence in women without symptoms is 2-50%, depending on the diagnostic criteria used and the populations studied (9). The incidence of endometriosis is difficult to quantify, as women with the disease are often asymptomatic, and imaging modalities have low sensitivities for diagnosis. The primary method of diagnosis is laparoscopy, with or without biopsy for histologic diagnosis (13, 14). Using this standard, investigators have reported the annual incidence of surgically diagnosed endometriosis to be 1.6 cases per 1,000 women aged between 15 and 49 years. The incidence is 40-60% in women with dysmenorrhoea and 20-30% in women with subfertility. The severity of symptoms and the probability of diagnosis increase with age. The most common age of diagnosis is reported as around 40, although this figure came from a study in a cohort of women attending a family planning clinic (15).

The clinical picture of endometriosis is widely heterogeneous. A correct diagnostic work-up of these patients can sometimes be very difficult, since there are a number of gynecological, intestinal and systemic diseases mimicking endometriosis, as well as other conditions that could be associated with or area consequence of this disorder. Therefore, multidisciplinary care should been courage to ensure correct evaluation and improve the management of these patients (16).

2. Prevalence

Although endometriosis was originally felt to be a disease only seen in women who had undergone a minimum of 5 years of ovulatory menstrual cycles, it is now well-documented that endometriosis can be seen as early as the premenarchal age group, in girls who have initiated thelarche (63). Prevalence is estimated to be 6–10% in the general female population and 35–50% of the patients experience pain and/or infertility. The prevalence in women without symptoms is 2-50%, depending on the diagnostic criteria used and the populations studied (9). The true incidence of endometriosis in adolescents is difficult to quantify and estimates vary among different studies. The incidence of endometriosis is difficult to quantify, as women with the disease are often asymptomatic, and imaging modalities have low sensitivities for diagnosis. Using this standard, investigators have reported the annual incidence of surgically diagnosed endometriosis to be 1.6 cases per 1,000 women aged between 15 and 49 years (64). The incidence is 40-60% in women with dysmenorrhoea and 20-30% in women with subfertility. According to the Endometriosis Association, 66% of adult women with endometriosis report the onset of pelvic symptoms before age 20, and those who seek care for symptoms as a teen see on average 4 or more physicians before receiving a diagnosis (15).

3. Classification

The primary method of diagnosis is visualization of endometriotic lesions by laparoscopy, with or without histologic confirmation. Since the extent of endometriosis can vary widely between individuals, attempts have been made to develop a standardized classification to objectively assess the extent of endometriosis. Sampson, Acosta et al., and many other investigators developed staging systems that have all been criticized for multiple reasons,

including their inability to predict clinical outcomes, especially pregnancy rates (PRs) in infertile patients. In 1979, the American Fertility Society (AFS) (now the American Society for Reproductive Medicine, or ASRM) first proposed a classification system. This was extensively evaluated, modified in 1985, and is still used today. Despite these revisions the currently used revised AFS system has serious limitations, including not effectively predicting the outcome of treatment.

Endometriosis fertility index surgery form.

ENDOMETRIOSIS FERTILITY INDEX (EFI)
SURGERY FORM

LEAST FUNCTION (LF) SCORE AT CONCLUSION OF SURGERY

Score	Description		Left	Right
4	= Normal	Fallopian Tube		
3	= Mild Dysfunction			
2	= Moderate Dysfunction	Fimbria		
1	= Severe Dysfunction			
0	= Absent or Nonfunctional	Ovary		

To calculate the LF score, add together the lowest score for the left side and the lowest score for the right side. If an ovary is absent on one side, the LF score is obtained by doubling the lowest score on the side with the ovary.

	Left	+	Right	=	LF Score
Lowest Score					

ENDOMETRIOSIS FERTILITY INDEX (EFI)

Historical Factors			Surgical Factors		
Factor	Description	Points	Factor	Description	Points
Age			LF Score		
	If age is ≤ 35 years	2		If LF Score = 7 to 8 (high score)	3
	If age is 36 to 39 years	1		If LF Score = 4 to 6 (moderate score)	2
	If age is ≥ 40 years	0		If LF Score = 1 to 3 (low score)	0
Years Infertile			AFS Endometriosis Score		
	If years infertile is ≤ 3	2		If AFS Endometriosis Lesion Score is < 16	1
	If years infertile is > 3	0		If AFS Endometriosis Lesion Score is ≥ 16	0
Prior Pregnancy			AFS Total Score		
	If there is a history of a prior pregnancy	1		If AFS total score is < 71	1
	If there is no history of prior pregnancy	0		If AFS total score is ≥ 71	0
Total Historical Factors			Total Surgical Factors		

EFI = TOTAL HISTORICAL FACTORS + TOTAL SURGICAL FACTORS:	Historical	+	Surgical	=	EFI Score

The endometriosis fertility index (EFI) is a simple, robust, and validated clinical tool that predicts PRs for patients after surgical staging of endometriosis (see figure below). The EFI score ranges from 0–10, with 0 representing the poorest prognosis and 10 the best prognosis. Half of the points come from the historical factors and half from the surgical factors. Uterine abnormality was not included in the score. The EFI is very useful in developing treatment plans in infertile patients with endometriosis. The EFI is useful only for infertility patients who have had surgical staging of their disease. It is not intended to predict any aspect of endometriosis-associated pain. It is required that the male and female gametes are sufficiently functional to enable attempts at non-IVF conception. One factor found to predict pregnancy that is not included in the EFI is uterine abnormality. Sensitivity analysis showed that even with substantial variation in the assignment of functional scores the EFI varies very little (65).

4. Anatomic sites

Endometriosis may develop anywhere within the pelvis and on other extrapelvic peritoneal surfaces. Although the condition is usually limited to the ovaries, uterosacral ligaments, and Douglas' pouch, it has been reported in almost every organ of the body. Extra-pelvic endometriosis refers to endometrial implants found elsewhere in the body, including the skin, central nervous system, gastrointestinal tract, urinary tract, lungs, and heart. Macroscopically, three forms of endometriosis are described: superficial peritoneal (or ovarian) endometriosis, endometriotic cyst of the ovary or ovarian endometrioma, and deep infiltrating endometriosis (DIE).(4)

The most commonly affected sites are the pelvic organs and peritoneum, although other parts of the body such as the lungs are occasionally affected. The extent of the disease varies from a few, small lesions on otherwise normal pelvic organs to large, ovarian endometriotic cysts endometriomas).

There can be extensive fibrosis in structures such as the uterosacral ligaments and adhesion formation causing marked distortion of pelvic anatomy. Disease severity is assessed by simply describing the findings at surgery or quantitatively, using a classification system such as the one developed by the American Society for Reproductive Medicine (ASRM) (1997). There is no correlation between such systems and the type or severity of pain symptoms (66).

Endometriosis typically appears as superficial "powder burn" or "gunshot" lesions on the ovaries,serosal surfaces and peritoneum-black, dark-brown, or bluish-puckered lesions, nodules or small cysts containing old haemorrhage surrounded by a variable extent of fibrosis. Atypical or "subtle" lesions are also common, including red implants (petechial, vesicular, polypoid, hemorrhagic, red flamelike) and serous or clear vesicles. Other appearances include white plaques or scarring and yellow-brown peritoneal discoloration of the peritoneum (66, 67).

Endometriomas usually contain thick fluid like tar; such cysts are often densely adherent to the peritoneum of the ovarian fossa and the surrounding fibrosis may involve the tubes and bowel. Deeply infiltrating endometriotic nodules extend more than 5mm beneath the peritoneum and may involve the utero-sacral ligaments, vagina, bowel, bladder or ureters. The depth of infiltration is related to the type and severity of symptoms (4).

5. Pathophysiology

5.1 Etiology

Despite extensive research, its pathogenesis still remains elusive and the disorder is considered to be 'enigmatic'. Endometriosis is a multi-factorial disease with multi-faceted features. The theories that have withstood the test of time and remain in vogue include retrograde menstruation, coelomic metaplasia, and endometrial stem cells. All the theories on its pathogenesis must be taken complementary to one another and by no way are mutually exclusive. The most widely accepted theory is the implantation of viable endometrial tissue onto peritoneal visceral structures from retrograde menstrual flow into the pelvic cavity (17). However, the origin is multifactorial, also having hormone, immune, and genetic components. The relationship of endometriosis to estrogen is well-

established. Two thirds of women with a diagnosis of endometriosis report having a family member with endometriosis. A large percentage of women with endometriosis have other co-morbidities such as fibromyalgia, chronic fatigue syndrome, hypothyroidism, allergies, asthma, and auto-immune disorders. The associated risk factors are directly related to low body mass index (BMI), and family history and are inversely related to exercise (18).

5.2 Retrograde menstruation

The earliest and most widely accepted theory relates to retrograde menstruation through the fallopian tubes with subsequent dissemination of endometrial tissue within the peritoneal cavity. Sampson's theory of endometrial implantation, offered in the 1927, proposes that retrograde menstruation through the fallopian tubes was responsible for endometriotic lesions. Three prerequisites are necessary for Sampson's theory: (1) retrograde menstruation, (2) viability of menstrual endometrial cells, and (3) implantation of endometrial cells onto the peritoneal/ovarian surfaces (3). Since the introduction of his theory, retrograde menstruation has been confirmed at laparoscopy, and it appears to occur in the vast majority of women. Keettel and Stein in the 1950s demonstrated the viability of shed menstrual endometrial cells by invitro culture of menstrual endometrium (19). The viability of retrograde menstrual endometrium has been shown by Mungyer et al by culturing endometrial glands and stroma collected from peritoneal lavage (20). In addition to these invitro studies, Ridley and Edwards injected menstrual blood into the skin of women scheduled for a laparotomy in the next 3 to 6 months. On excision of this tissue, several women had endometriotic lesions at the injection site. Further circumstantial evidence supporting Sampson's theory is the increased risk of endometriosis in women with Mullerian anomalies and other outflow tract obstructions (21).

Refluxed endometrial fragments adhere to and invade the peritoneal mesothelium and develop a blood supply, which leads to continued implant survival and growth. However, this theory fails to explain the presence of endometriosis in such remote areas outside the peritoneal cavity, as the lungs, skin, lymph nodes, and breasts. Moreover, the presence of the disease in early puberty and exceptionally also in newborns further contrasts the validity of the theory (22).

5.3 Coelomic metaplasia

The coelomic metaplasia theory claims that formation of endometriomas in the ovary or recto-vaginal endometriosis is caused by metaplasia of the coelomic epithelium, perhaps induced by environmental factors (23). Because the ovary and the progenitor of the endometrium, the müllerian ducts, are both derived from coelomic epithelium, metaplasia may explain the development of ovarian endometriosis. In addition, the theory has been extended to include the peritoneum because of the proliferative and differentiation potential of the peritoneal mesothelium.

This theory would explain why most women have some degree of retrograde menstruation but only a little percentage has endometriosis and the presence of the disease in absence of menses. However, the absence of endometriosis in other tissues derived from coelomic epithelium argues against this theory (22).

5.4 Induction theory

The theory of endometrial stem cells or transient amplifying progenitor cells claims that circulating stem cells originating from bone marrow or from basal layer of endometrium could differentiate into endometriotic tissue at different anatomical sites (24). In vitro studies have demonstrated the potential for ovarian surface epithelium, in response to estrogens, to undergo transformation to form endometriotic lesions. Although many putative factors have been identified, their propensity to cause endometriosis in some women but not in others demonstrates the still unidentified etiology of this disease (25).

5.5 Lymphatic or vascular spread

Evidence also supports the concept of endometriosis originating from aberrant lymphatic or vascular spread of endometrial tissue. Findings of endometriosis in unusual locations, such as the perineum or groin, bolster this theory. The lymphatic and hematogenous spread of endometrial cells can explain the presence of endometriosis in the pelvis or elsewhere. However, in the last few years, strong evidence indicates the possible role of immunologic factors and the lack of adequate immune surveillance in the pathogenesis of endometriosis (26, 27).

5.6 Hormonal effect

Endometriosis is an estrogen-dependent disorder. Aberrant production of estrogen by endometriotic stromal cells is indispensable for the development and maintenance of endometriosis especially during the period of menstruation when no ovarian estrogen is available. This notion was supported by identification in endometriotic stromal cells of the presence of all proteins/enzymes required for denovo synthesis of estrogen:steroidogenic acute regulatory protein (StAR), P450 side-chain cleavage enzyme (P450scc), 3b-hydroxy steroid dehydrogenase (3b-HSD), 17 a-hydroxylase 17,20 lyase, P450 aromatase and 17b-HSD type1. Among these enzymes, StAR and aromatase control the first and last committed steps in the biosynthesis of estrogen. StAR transports cholesterol across the mitochondrial membrane to the inner mitochondrial leaflet, where the first enzymatic reaction occurs. Aromatase catalyses the conversion of androstenedione to estrone. Estrone is further converted to 17b-estradiol (normally referred to a sestrogen) by 17b-HSD type1, whereas 17b-HSD type2 reverses this process. In disease-free uterine endometrium, no StAR or aromatase are detected but there are increased StAR and aromatase levels in extra-ovarian endometriotic implants and endometriomas. In addition, the absence of 17b-HSD type2 in pelvic endometriotic implants further favors an increase in the local concentration of estrogen (28-30).

5.7 Steroid receptor genetics

Endometriosis is an estrogen-dependent disease. The action of steroids such as estrogen, progesterone and androgen are mediated through their respective receptors (SRs). SRs are ligand (hormone)-dependent transcription factors. Upon activation with the specific hormone they can interact with hormone response elements in the promoter of target genes. Since the action of steroids such as estrogen, progesterone and androgen are mediated through their respective receptors - Estrogen Receptors (ER), Progesterone Receptors (PR)

and Androgen Receptors (AR) - these receptors must be and have shown to be intimately involved in the pathogenesis of endometriosis. ERs, PRs and AR, along with glucocorticoid receptor and mineralocorticoid receptor, form the steroid receptors (SRs) family, which is one of three members of the nuclear receptor (NR) superfamily of transcription factors. Besides the SR family, other members of the NR superfamily, such as vitamin D receptor, retinoic acid receptor, and peroxisome proliferator-activated receptor may also be involved in endometriosis (31).

5.8 Immunologic factors

There is ample evidence indicating that alterations in both cell-mediated and humoral immunity contribute to the pathogenesis of endometriosis. Increased number and activation of peritoneal macrophages, decreased T cell and natural killer (NK) cell cytotoxicities are the alterations in cellular immunity, yielding diminished removal of ectopic endometrial cells from the peritoneal cavity. In addition, increased levels of several proinflammatory cytokines and growth factors produced by immune and endometrial cells are likely to be involved in facilitating implantation and growth of ectopic endometrial cells by promoting proliferation, inflammation and angiogenesis (32).

There is evidence that TNF-α promotes the adherence of stromal cells to the mesothelium and stimulates proliferation of endometriosis stromal cells. Both of these may be important mechanisms in the pathogenesis of endometriosis, and it has been suggested that TNF-α is one of the essential factors for the pathogenesis and maintenance of endometriosis. Concentrations of TNF-α in peritoneal fluid are higher in women with endometriosis than in patients with normal pelvic anatomy and peritoneal fluid TNF-α concentrations correlate with the stage of endometriosis. Serum TNF-α levels also are significantly increased in patients with endometriosis, especially in early stages of the disease. Also, TNF stimulates the expression of prostaglandin synthase-2, which in turn increases the production of prostaglandins E2 and F2a, an indirect mechanism by which TNF may cause inflammatory pain (33-37).

Endometriotic implants contain both estrogen and progesterone receptors and respond to changes of hormonal levels with bleeding or production and release of inflammatory mediators, especially prostaglandins E2 and F. For a long time, it has been thought that prostaglandins are involved in endometriosis-related severe dysmenorrhea, and probably dyspareunia and nonmenstrual pelvic pain. Some of the data suggest that endometriotic lesions actually may produce greater amounts of prostaglandins than does eutopic endometrium. In fact, prostaglandins in endometriosis were produced mainly by Cox-2 (38-40). Matsuzaki et al. found higher levels of Cox-2 in the epithelium and the stroma of endometriosis than in normal endometrium from controls without endometriosis. They also found higher levels of Cox-2 in the stroma of eutopic endometrium of women with endometriosis than in the stroma of women without endometriosis (41). Ota et al. have published similar results, showing higher levels of Cox-2 in endometriosis than in endometrium from controls. These data support the conclusion that Cox-2 is induced by endometriosis and leads to higher levels of prostaglandins (42).

5.9 Clinical association between endometriosis and autoimmune diseases

Clinical conditions associated with endometriosis by patients, providers, and researchers alike have included headaches, arthralgias and myalgias, allergies, eczema, hypothyroidism,

fibromyalgia, chronic fatigue syndrome, and susceptibility to vaginal candidiasis. These often ill-defined entities carry an allure of mystery, paralleling many nonspecific symptoms encountered by patients with known autoimmune disease. Because of this parallelism, and with no alternative explanation for a patient's extraperitoneal symptoms, patients and health care providers may suspect an immunopathologic mechanism. The potential link between autoimmune disease and endometriosis has been studied from a number of perspectives. Some investigators have reported common clinical elements among patients with endometriosis and patients with various autoimmune processes, whereas others have reported interesting serologic parallels (43-46).

6. Risk factors

6.1 Genetic factors

Endometriosis regarded as a genetic disease due, apparently, to its reported familial aggregation. Yet even the reported familial aggregation, when examined closely, may be debatable and there has been little progress regarding the identification of genetic variants that predispose women to endometriosis. First degree relatives of patients with endometriosis have a 6.9% incidence of endometriosis in comparison with a 1% risk in controls (47).

There is a prevailing view that endometriosis is a polygenic disease and, as such, genetic polymorphisms that predispose women to endometriosis can be identified through linkage or association studies. In the last decade, numerous large-scale gene expression profiling studies have demonstrated, unequivocally, that many genes such as oncogenic K-ras are deregulated in endometriosis. Yet despite many publications, seemingly little headway has been made in elucidating the specific genetic factors that have a major impact on the risk of developing endometriosis. Few, if any, positive findings from genetic association studies have been replicated, and those who tried to replicate previously reported positive findings often end up with negative results. Not surprisingly, three meta-analyses on association of endometriosis and some genetic polymorphisms coding for dioxin detoxification enzymes, sex steroid biosynthesis and their receptors found no evidence of association even though meta-analyses known to have upward biases in risk estimates, especially the 'winner's curse' of first reports (48-49).

6.2 Environmental factors and dioxin

Environmental factors, such as dioxin, might interact with multiple genetic susceptibility loci to produce the phenotype of endometriosis. Most of these environmental contaminants exhibiting estrogenic effects will lead to endocrine disruption through various environmental media such as food and water. Dietary intake of dioxin-like compounds with biological activity will increase the body burden (the total amount of these chemicals that are present in the human body at a given point in time), which might contribute to the pathogenesis of endometriosis. In addition, these chemicals can pass through the placenta to affect fetal environment. In a prospective cohort study, the rate of laparoscopically confirmed endometriosis was 80% greater among women exposed in utero to diethylstilbestrol (a synthetic estrogen originally prescribed in pregnancy to prevent miscarriage) after 10 years of follow-up. However, the relationship between endocrine

disrupting chemicals and endometriosis remains controversial because of lack of studies with sufficient statistical power (50-54).

Several excellent reviews have been published characterizing dioxins. Chemically, dioxin, an abbreviation of 2, 3, 7, 8-tetrachloro-dibenzo-p-dioxin, or TCDD, is a polycyclicaromatic agent with chloral substituent. Dioxin is a lipophilic material that could accumulate in tissues with a high fat content. There is insufficient evidence at this moment in support of the hypothesis that dioxin exposure may lead to increased risk of developing endometriosis in women. Dioxins may act similarly to estrogen in estrogen-target tissues such as endometrium (eutopic or ectopic), promoting proliferation. However, it should be noted that in the presence of Aryl hydrocarbon Receptor (AhR) agonists, the function of liganded ER is attenuated. Since the local estrogen production is increased in endometriosis due to aberrant regulation of aromatase and of type $_2$ 17 b-hydroxy steroid dehydrogenase, it is unclear what the net effect of AhR agonists such as dioxins is on ectopic endometrium (55-57).

6.3 Anatomic defects

Reproductive outflow tract obstruction can predispose to development of endometriosis, likely through exacerbation of retrograde menstruation. Accordingly, endometriosis has been identified in women with noncommunicating uterine horn, imperforate hymen, and transverse vaginal septum. Because of this association, diagnostic laparoscopy to identify and treat endometriosis is suggested at the time of corrective surgery for many of these anomalies. Repair of such anatomic defects is thought to decrease the risk of developing endometriosis (58, 59).

A number of Mullerian anomalies, most importantly those associated without flow tract obstruction, are associated with endometriosis. In a series by Schifrin et al. 15 patients (40%) younger than 20 years of age with endometriosis had a genital tract anomaly (60). This is opposed to findings by Goldstein et al who noted congenital anomalies in only 11% of 74 teenagers with endometriosis (61). The clinical course of endometriosis associated with reproductive tract anomalies is quite different from that in the adult. Sanfilippo et al described a series of patients with extensive endometriosis in association with outflow tract obstruction (62). Once correction of the outflow tract occurred, there was virtually 100% reversal of intra-abdominal endometriosis on follow-up laparoscopy. It is thought that the pathophysiology of the disease process is different in the adult as compared with adolescents with an outflow tract obstruction. Interestingly, the fact that many adolescents without flow tract obstruction show significant endometriosis at the time of laparoscopy does support the theory of retrograde menstruation as an etiology for development of endometriosis. However, given that endometriosis resolves without further treatment after correction of the outflow tract abnormality suggests that retrograde menstruation, in and of itself, is not sufficient to induce a state of progressive endometriosis. Other factors besides retrograde menstruation, such as immune system defects, may be fundamental to creating an environment for induction of progressive endometriosis (63).

7. Patient symptoms

Although women with endometriosis may be asymptomatic, symptoms are common and typically include chronic pelvic pain and infertility. As previously stated, the current ASRM

classification of endometriosis, which describes the extent of disease bulk, poorly predicts symptoms. Thus clinically, women with extensive disease (stage IV) may note few complaints, whereas those with minimal disease (stage I) may have significant pain or subfertility or both (68, 69).

The following symptoms can be caused by endometriosis based on clinical and patient experience:

- Severe dysmenorrhoea;
- Deep dyspareunia;
- Chronic pelvic pain;
- Ovulation pain;
- Cyclical or perimenstrual symptoms (e.g. bowel or bladder associated) with or without abnormal bleeding;
- Infertility;
- Chronic fatigue.

However, the predictive value of any one symptom or set of symptoms remains uncertain as each of these symptoms can have other causes. A large group of women with endometriosis is completely asymptomatic. In these women endometriosis remains undiagnosed or is diagnosed atlaparoscopy for another indication. A subset of women with more advanced disease, ovarian or deep invasive rectovaginal endometriosis, is asymptomatic as well. This makes the development of guidelines for the diagnosis and the therapy rather cumbersome. Endometriosis should be suspected in women with dysmenorrhoea, deep dyspareunia, acyclic chronic pelvic pain and/or subfertility.

8. Physical examination

Physical examination of the pelvis is useful for the diagnosis of deep infiltrating lesions or endometriotic cysts. The examination may be normal. It is more reliable when carried out during the menstrual period. Examination of the retrocervical area using the speculum, by vaginal and (possibly) rectal examination, is recommended. Examination of the vagina and cervix by speculum examination often reveals no signs of endometriosis. Occasionally, bluish or red powder-burn lesions may be seen on the cervix or the posterior fornix of the vagina. Pelvic organ palpation often reveals anatomic abnormalities suggestive of endometriosis. Uterosacral ligament nodularity and tenderness may reflect active disease or scarring along the ligament. In addition, an enlarged cystic adnexal mass may represent an ovarian endometrioma, which may be mobile or adherent to other pelvic structures (15, 63).

9. Differential diagnosis

The symptoms of endometriosis are nonspecific and may mimic many disease processes. Because endometriosis is a surgical diagnosis, several other diagnoses may be considered prior to surgical exploration. Since there is such an extremely variable presentation, an accurate differential diagnosis should always be performed in patients suspected of endometriosis. First of all, other gynecological disorders, such as ovarian and tubal diseases, pelvic inflammatory disease and ectopic pregnancy, should be excluded (16). Then a series of gut disorders should be considered; among these conditions, irritable bowel syndrome

(IBS) is worthy of particular attention (70). Crohn's disease should also be considered in the differential diagnosis of endometriosis, since this condition shows several similarities regarding both the locations and the anatomo-pathologic pattern (71). Although rare, familial Mediterranean fever (FMF) should be considered in the differential diagnosis of endometriosis (72). Rarely the presence of parasitic infestations has been reported in women with symptoms suggestive of endometriosis (73).

10. Laboratory testing

To exclude other causes of pelvic pain, laboratory investigations are often undertaken. Initially, a complete blood count (CBC), urinalysis and urine cultures, vaginal cultures, and cervical swabs may be obtained to exclude infections or sexually transmitted infections that may cause pelvic inflammatory disease (63).

Although concentrations of the cancer antigen CA125 are slightly raised in some women with endometriosis, the test neither excludes nor diagnoses endometriosis and is not considered useful in establishing the diagnosis. The threshold for surgery is unlikely to be influenced by the CA125 concentration and the guidelines from the Royal College of Obstetricians and Gynecologists described CA125 as having only limited value as either a screening or a diagnostic test (15).

11. Imaging and endometriosis

Endometriomas are uncommon in the adolescent population, and information regarding the adnexa can be obtained noninvasively with a pelvic ultrasound. Ultrasound as the primary imaging investigation can aid in its diagnosis. Transvaginal ultrasound (TVUS) with color flow Doppler can detect endometriomas with a high degree of accuracy. Ultrasound is limited in its ability to detect small peritoneal implants and adhesions (74).

MRI is an excellent imaging modality for the evaluation of patients with deep pelvic endometriosis, showing high accuracy in the diagnosis and prediction of disease extent. The MRI diagnosis of deep pelvic endometriosis is based on the conjoint presence of signal intensity and morphologic abnormalities in the anterior and posterior compartments of the pelvis and the presence of surrounding fibrosis. The use of endovaginal and rectal contrast is useful to better delineate the anatomy and map out the extent of disease. Atypical locations of deep pelvic and extrapelvic endometriosis have been presented and grouped under the term anterior endometriosis. An accurate diagnosis therefore resides in clinical awareness and systematic review via MRI. A key finding of malignant transformation is the presence of enhancing nodules in the endometrial cyst on T1-weighted images (74, 75).

12. Laparoscopic findings

Laparoscopy is the gold standard for the diagnosis and staging of endometriosis and allows for curative surgical resection at the same time. Patients found to have endometriosis at the time of laparoscopy should either be treated through surgical ablation, resection, or laser treatment. In addition, biopsy is recommended, as lesions of endometriosis in adolescents often take on a different appearance as compared with the typical powder-burn lesions seen in adults. Interestingly, clear or red endometriotic lesions are much more commonly seen in the adolescent population (76).

13. Histological confirmation

Histologic confirmation is essential in the diagnosis of endometriosis. The utility of peritoneal wash cytology for diagnosis of endometriosis has been reported. In most cases, only hemosiderin-laden macrophages are identified. The presence of endometrial cells is more specific but less sensitive than hemosiderin-laden macrophages for the diagnosis of endometriosis. The endometrial cells have been reported in 25%–52% of peritoneal washes done in endometriosis. However, recognition of endometrial cells as well as hemosiderin-laden macrophages is essential for diagnosis on morphological basis alone. Histologic examination of the tissue confirmed for endometriosis by the presence of both endometrioid glands and stroma (15).

14. Treatment

Treatment must be individualized, and the effect of the kind of treatment on quality of life must be considered. There is not any confidence that a uniform therapeutic way be enough and successful, however in the most of the patients there is not a curative treatment. The choice of treatment is based on various factors such as size, location and extent of the disease, type and severity of the symptomatology, wish for pregnancy, and age of the patient. (77) Planning for the treatment is based on two important symptoms: pain and infertility. All the therapeutic ways divide to two main surgical and medical treatments.

14.1 Medical treatment

1. Selective progestron receptor modulators, progestogens and anti progestins (Androgens)
2. Gn-RH agents
3. COC (Combined Oral Contraceptives)
4. Aromatase inhibitor & NSAIDs and cox2- inhibitors
5. Chinese Medications
6. Angiogenesis inhibitor
7. Gene Therapy
8. Modulation of Cytokines , inhibition of Matrix Metalloproteinase

I. Selective progestron receptor modulators, progestogens and anti progestins

a. Progestogens
   1. Medroxyprogestrone acetate / 30 mg /po /daily
   2. Megestrol acetate / 40 mg / po / daily
   3. Lynoestrenol / 10 mg / po / daily
   4. Dydrogestrone / 20-30 mg / daily

The role of the LNG IUS (Levonorgestrel intra uterin system) in management of this common and troublesome disorder has been evaluated by multiple studies.(78-80)

A pilot study examined the role of LNG IUS as a postoperative adjunct to surgical ablation for endometriosis. When compared with expectant management, the LNG IUS recipients had a reduced rate of recurrence of pelvic pain (2/20 compared with 9/20) and an increased rate of satisfaction (15/20 compared with 10/20). (81) The LNG IUS offers several

advantages for control of pelvic pain associated with endometriosis, including effective contraception, minimal systemic effects, and up to 5 years of benefit, as compared with 6 months, typical of GnRHa treatment.

Dienogest (DNG), a progestin of 19-nortestosterone derivative, has good oral bioavailability and is highly selective for progesterone receptors. Owing to its antiovulatory, antiproliferative activities in endometrial cells, and its inhibitory effects on the secretion of cytokines, DNG is expected to be an effective treatment for endometriosis. Progesterone receptor-binding affinity is higher for DNG than for progesterone.

- DNG has moderate affinity to the progesterone receptor. DNG shows low binding to the androgen receptor and almost negligible binding to the estrogen receptor, glucocorticoid receptor and mineralcorticoid receptor.
- DNG has strong oral progestational activity but antiandrogenic activity.
- An oral DNG dose of 1 mg/day is required for inhibition of ovulation in cyclic women.
- DNG has an inhibitory effect on growth and cytokine production of endometriotic cells.
- DNG is as effective as triptorelin (gonadotropin-releasing hormone agonist) for consolidation therapy after surgery for the treatment of endometriosis.
- DNG is as effective as intranasal buserelin acetate for the relief of pain symptoms associated with endometriosis.(82)

Treatment with a GnRH-a followed by long-term dienogest therapy maintains the relief of endometriosis-associated pelvic pain achieved with GnRH-a therapy for at least 12months. This regimen reduces the amount of irregular uterine bleeding that often occurs during the early phase of dienogest therapy.(83)

Complex mechanisms involving promoter regulation may be responsible for the observed aberrations in (Estradiol Receptor a, b) ERa, ERb, and PR (progesterone Receptor) expression in endometriosis. The stromal cell component of endometriotic tissue may be the primary site of these abnormalities. In endometriotic stromal cells, ERb promoter is pathologically hypomethylated and therefore hyperactive, leading to very high ERb levels. ERb suppresses ERa expression and results in strikingly high ERb-to-ERa ratios in endometriotic cells.

It is possible that this consequence of PR-B deficiency is only the tip of the iceberg with regard to pathogenesis of endometriosis, and that numerous other molecular aberrations may also contribute to the development of resistance to hormone treatments in women with endometriosis. Selective ERb ligands that target high levels of ERb in endometriotic tissue may be clinically beneficial via disrupting this mechanism.(84) PR deficiency is likely responsible for increased levels of E2 in endometriosis because progesterone fails to induce the E2-metabolizing enzyme HSD17B2 in endometriotic tissue. Some conclusion resonates with gene expression microarray studies performed on eutopic endometrium of women with endometriosis compared with that from disease-free women.(85, 86) These studies on eutopic endometrium identified distinct molecular defects that are consistent with the progesterone resistance hypothesis.

ER b agonists act as immunomodulators, enhancing the immunologic response to the explants; a second possible explanation lies an antiangiogenic effect because ER b are

present in endothelial cells of endometrial vasculature. Finally, it is possible that b receptor acts intracellularly as an ERa inhibitor, by dimerizing with the ERa molecules to form a faulty product (87).

b. Antiprogestins:
- Danazol 400-800 mg/day
- Gestrinone 1.25-2.5 Twice /week

The first medication approved for the treatment of endometriosis in the United States was the androgen danazol. The predominant mechanism of action appears to be suppression of midcycle luteinizing hormone (LH) surge, creating a chronic anovulatory state as a result, danazol creates a hypoestrogenic, hyperandrogenic state, inducing endometrial atrophy in endometriotic implants. The recommended dosage of danazol is 600 to 800 mg daily. Unfortunately, significant androgenic side effects develop at this dosage and include acne, hot flashes, hirsutism, adverse serum lipid profiles, voice deepening (possibly irreversible), elevation of liver enzymes, and mood changes. Moreover, due to possible teratogenicity, this medication should be taken in conjunction with effective contraception. Because of this adverse side-effect profile, danazol is prescribed less frequently, and when administered, its duration should be limited. Gestrinone (ethylnorgestrienone; R2323) is an antiprogestational agent prescribed in Europe for the treatment of endometriosis. Gestrinone equals the effectiveness of danazol and of GnRH agonists for relief of endometriosis-related pain. Mifepristone is a PA (Progestron Antagunist) currently approved only for use in medication abortion and, in some countries, as an emergency contraceptive, but 3 small trials have demonstrated a reduction in endometriosis symptoms with Mifepristone therapy.(88 ,89)

II. Gn-RH agents

- Lueprolide 500mg/DAY SC or 3.75 mg /month IM
- Gosereline 3.6 mg /month SC
- Buserelin IN 300 /day
- Nafarelin IN 200/day
- Triptorelin 3.75 mg /month IM

Treatment with GnRHa for 3 months is as effective as the 6-months treatment as far as pain is concerned, and when combined with estro-progestational agents ('add-back therapy') up to a maximum of 2 years, is effective for pain and safe in terms of protecting bone density.(77)

Like GnRH agonists, the GnRH antagonists share some homology with the native GnRH molecule. These drugs act by blocking the GnRH receptor directly and preventing it from activating. This result in a downregulation of the pituitary gland, a reduction of gonadotropin secretion, and a suppression of ovarian steroid production Unlike GnRH agonists, however, these drugs do not cause an initial stimulation of gonadotropin and ovarian hormone secretion. At the molecular level, GnRH antagonists interrupt the basic activation process of the GnRH receptor, blocking the receptor dimerization synthesis and secretion of luteinizing hormone (LH) and follicle stimulating hormone (FSH). Given the high binding affinity, relative abundance and long half-life of the antagonist, these molecules monopolize the GnRH receptors. As a result of the above characteristics, the

GnRH antagonists offer the theoretical advantage of working faster and more effectively than GnRH agonists, with better patient compliance because of earlier amelioration of symptoms (90).

III. COC (Combined Oral Contraceptives)

Hormone therapy obtains a good initial response, is well tolerated by patients, and can be discontinued if there are adverse effects. Combined hormone therapy with estrogens and progesterone [91] has been used for small lesions, with total or partial remission of the symptoms in a high percentage of cases. Medical treatment alone does not lead to the definitive cure of deep, severe endometriosis but only induces temporary disappearance of active lesions [92]

These drugs can be used conventionally in a cyclic regimen or may be used continuously, without a break for withdrawal menses. The continuous regimen may be preferable for its decreased frequency of menses for women who fail to achieve pain relief with cyclic COC therapy. To maintain relief from pelvic pain while minimizing hypoestrogenic side effects, several regimens are proposed. Oral contraceptives plus dienogest, a novel progestogen, or a gonadotropin-releasing hormone agonist with estrogen supplementation (add-back therapy) can be used in long-term administration. The relief from pelvic pain achieved with a gonadotropin-releasing hormone agonist can be sustained by long-term administration of a tapered dose of danazol or medium-to-low doses of oral contraceptives. Local treatment with the levonorgestrel-releasing intrauterine system is an option for long-term suppression of pelvic pain.(93) For patients with recurrent ovarian endometriosis after conservative surgery or conservative surgery plus medical therapy, LNG-IUS and COC (combined oral contraceptives) may be used to control and reduce endometriotic cysts, relieve pain and reduce the level of CA125. LNG-IUS has the advantages of a greater convenience and minor systemic side effects (94). Long-term OCP therapy can be a reliable adjuvant post-operative measure to prevent or reduce frequency/severity of recurrent dysmenorrhoea and anatomical relapse of endometriosis. Since both continuous and cyclic OCP administration regimens seem to have comparable effects, the choice of regimen can be modulated according to patient preferences. The protective effect seems to be related to the duration of treatment.(95)

IV. Aromatase inhibitor & NSAIDs and cox2- inhibitors

Large quantities of estrogen can be produced locally within ectopically located endometrium via an intracrine mechanism, via the expression of the enzyme aromatase. This enzyme, not expressed in normal endometrium, is stimulated by prostaglandin E2 (PGE2); the resulting estrogen production then stimulates PGE2, further enhancing estrogen. An obvious therapeutic target would thus be this aromatase enzyme and aromatase inhibitors were tested in the rodent endometriosis model, with good success [96].

The expression of COX-2 was recently demonstrated in ectopic endometrial cells, showing higher concentration with respect to the eutopic endometrium [97]. COX-2 selective inhibitor given at the minimal dosage is effective against the pelvic pain symptoms (dysmenorrhoea, dispareunia, and chronic pelvic pain) associated to endometriosis [98].

Aromatase inhibitors have similar hypoestrogenic side-effect profiles as GnRH agonists, but hold promise in severe, refractory cases of endometriosis.

Treatment of rats with induced endometriosis using the nonsteroidal aromatase inhibitor fadrozole hydrochloride or YMsl l resulted in a dose-dependent volume reduction of endometriosis transplants.(99, 100)

In a pilot study, preliminary data were generated suggesting a potential future use of this drug, but randomized controlled trials are needed to confirm these data.(101) The effect of medical treatment in terms of pain relief in women with rectovaginal endometriosis appear substantial.(102)

V. Chinese Medications (CM)

In recent years, the Chinese medicine treatment of EM has won favorable therapeutic effects with few adverse reactions. The CM treatment of EM puts stress on therapy according to syndrome differentiation, varying the treatment for different individuals and emphasizing different sides in different stages of a menstrual cycle. It is non-traumatic with less adverse effect and good long-term effectiveness. It is favorable in combination with various approaches like acupuncture and moxibustion, retention enema and Western medical treatment, and could be extensively applied in clinical practice to function effectively in improving clinical symptoms and physical signs of patients and raising their quality of life.(103) Dong, et al treated EM with Guizhi Fuling capsule combined with intervention paracentesis implemented under ultrasonographic guidance to achieve good efficacy. The patients' cystic fluid was drawn out through puncturing and then the cystic cavity was washed repeatedly with 0.5% Lidocaine, then absolute alcohol was injected into the cavity The outcome shows that the therapeutic efficacy in the two groups was the same, but adverse reaction of Guizhi Fuling Capsule was significantly less than that of Gestrinone.(104)

Xue treated 41 patients with Mifepristone (25 mg/d, starting from the 1st day of the menstruation) combined with Chinese decoction, consisting of chuanxiong, dragon's blood, peach kernel, achyranthes root, yanhusuo rhizome, typha, trogopterus dung, red peony root, Chinese angelica root, cyperus tuber, red sage root, etc., one dose a day for 6 successive months, and the total effective rate obtained was 92.7%, which was better than that of Mifepristone or Chinese herbal medicine alone.(105)

Yu used Xiaoyi Zhitong Decoction combined with Mifepristone to treat 76 patients for 3 months, which resulted in a total effective rate of 92% and a recurrent rate of 5.3%.(106)

VI. Angiogenesis inhibitors

The most prominently studied among angiogenic factors is the vascular endothelial growth factor (VEGF), which is responsible for inducing early vascular growth. In any event, one logical therapeutic step would be to attempt inhibition of these new vascular structures as a way of deterring the development of endometriosis. The only human study thus far conducted with an angiogenesis inhibitor was the treatment of endometriosis associated pain with thalidomide; pain relief was noted in these patients [107].

VII. Gene Therapy

HOX genes, encoding homeodomain transcription factors, are dynamically expressed in endometrium, where they are necessary for endometrial growth, differentiation, and

implantation. In human endometrium, the expression of HOXA10 and HOXA11 is driven by sex steroids, with peak expression occurring at time of implantation in response to rising progesterone levels. However, the maximal HOXA10 and HOXA11 expression fails to occur in women with endometriosis resistance to progesterone which can explain inhospitable implantation environment and medical treatment failures in endometriosis. Alterations in progesterone receptor expression and decreased HOX gene expression secondary to hypermethylation of its promoter region are the possible mechanisms of the progesterone resistance. A gene therapy approach involving the manipulation of HOXA10 expression or by using DNA demethylation agents to restore methylation aberrations can potentially have a role in the future treatment of endometriosis.(108-110)

A new study compared women suffering chronic pelvic pain (CPP) secondary to endometriosis with women experiencing CPP due to either myofascial abdominal/pelvic pain or pelvic adhesions to determine if there are specific psychological variables uniquely associated with endometriosis .No differences were obtained across the three groups for any of the outcome measures. Effect size computation supported the absence of clinical differences across the groups for these measures. These findings fail to support the presence of a unique psychological profile or disproportionate psychological disturbance for women with CPP due to endometriosis. These data illustrate the importance of considering control groups that include chronic pain when exploring psychological contributions to specific chronic pain conditions.(111)

VIII. Modulation of Cytokines, lnhibition of Matrix Metalloproteinase

In rats with experimental endometriosis, recombinant human TNF-α-binding protein can reduce 64% of the size of endometriosis-like peritoneal lesions (112).

In nude mice, suppression of MMPs by progesterone or by a natural inhibitor slows the establishment of ectopic lesions by human endometrium. (113)

14.2 Surgical treatments

The goal of surgery is to excise all visible endometriotic lesions and associated adhesions-peritoneal lesions, ovarian cysts, deep rectovaginal endometriosis-and to restore normal anatomy.

Laparoscopy is the gold standard for diagnosis and the primary means of treatment at this time. Laparoscopy is used with different goals such as diagnosis, ablation, excision and lysis of adhesions.

Excisional removal of ovarian endometriomas seems superior to drainage and ablation for both improved spontaneous pregnancy rates and improved pain symptoms. Laparoscopic treatment of endometriosis carries a long-term substantial relief of symptoms for a significant percentage of women. (114) Laser ablation does not appear to be more effective than conventional electrosurgical ablation of endometriosis.

Radical procedures such as oophorectomy or total hysterectomy are indicated only in severe situations and can be performed either laparoscopically or by laparotomy. Laparotomy should be reserved for patients with advanced-stage disease who cannot undergo a laparoscopic procedure and for those in whom fertility conservation is not necessary.

In patients with severe endometriosis it has been recommended that surgical treatment be preceded by a 3-month course of medical treatment to reduce vascularization and nodular size (115).

Postoperative medical treatment is rarely indicated because it does not work based on randomized trials, because it prevents pregnancy, and the highest pregnancy rates occur during the first 6 to 12 months after conservative surgery (116, 117).

Presacral Neurectomy (PSN):

For some women, transection of presacral nerves lying within the interiliac triangle may provide relief of chronic pelvic pain. PSN is used in a limited manner and not recommended routinely for management of endometriosis related pain.

Laparoscopic presacral neurectomy can be offered to treat midline pelvic pain.(114, 118)

Deep Rectovaginal and Rectosigmoidal Endometriosis:

Surgical treatment of DIE (Deeply Infiltrating Endometriosis) requires a professional who is able to perform surgery in the gynaecological, urological, gastrointestinal and nervous structures of the pelvis, as the disease 'knows no boundaries'. There is no scientific validation either that a multispecialty team approach is superior for the treatment of bowel endometriosis, which could also make the multisurgeon model 'experimental' and therefore unethical. (119)

Preoperative laxatives, starch-free diet, and full bowel preparation are needed to allow perioperative bowel suturing, if needed. Ureter stents may be required before excision of peritoneal endometriosis surrounding the ureter. A multidisciplinary approach involving gynecologic and gastroenterologic surgeons and urologists is desirable.

Bladder endometriosis is rare .The common clinical manifestations of bladder endometriosis include menouria and urethral and pelvic pain syndrome occurring cyclically. Cystoscopy is the most useful diagnostic test with confirmation by histologic study. Treatment must be individualized according to the patient's age, desire for future pregnancies, the severity of the symptoms, the site affected, and whether other organs are involved. transurethral resection-endometrioma biopsy to confirm the diagnosis and hormone blockade with LH–RH analogues is the initial treatment most commonly used in recent years, despite an estimated recurrence of 25–35% .(120)

Analogues have been the medical treatment of choice because their introduction, and the estrogens, androgens, progestogens, and danazol used in previous years have fallen into disuse because they lead to more adverse effects. Analogues induce a postmenopause like anovulatory state, a hypogonadotropic hypogonadism with serum estrogen concentrations dropping to sterilization levels, which causes the endometrial tissue to regress. (121, 122)

Ureter endometriosis was related with reproductive tract endometriosis. It has insidious process resulting in difficulty for early diagnosis. It's important to treat pelvic deep infiltrating endometriosis and ovarian endometrioma to prevent ureter from further involvement. Post-operative treatment of pelvic endometriosis is the key point of preventing

relapse of ureter endometriosis.(123) The laparoscopic approach for ureteral endometriosis is very well tolerated and has a reasonable incidence of complications, as well as a low rate of recurrence.

Considering the difficulty of achieving a strictly scientific approach to low disease prevalence, the surgeon dealing with ureteral endometriosis must adapt surgery to achieve a balance between conservative purposes and the risk of recurrence on the one hand, and a radical approach and risk of morbidity on the other. Ureterolysis could be used as the initial surgical step for patients with ureteral endometriosis, and may be the only treatment if the extension of ureteral involvement is limited in length and there is no residual ureteral damage or dilatation.

For patients displaying extended severe ureteral involvement, stenosis, or moderate or severe hydronephrosis with a high risk of having intrinsic ureteral disease, ureterolysis is probably insufficient and ureteroneocystostomy likely represents a wiser surgical strategy (124).

Long-term probability of pain recurrence after repeat conservative surgery for recurrent endometriosis varies between 20 and 40%. The association of presacral neurectomy to the treatment of endometriosis might be effective in reducing midline pain; however, no studies have evaluated this procedure among patients with recurrent disease. The medium-term outcome of hysterectomy for endometriosis-associated pain is quite satisfactory; nevertheless, probability of pain persistence after hysterectomy is 15% and risk of pain worsening 3–5%, with a six times higher risk of further surgery in patients with ovarian preservation as compared to ovarian removal. The conception rate among women undergoing repetitive surgery for recurrent endometriosis associated with infertility is 26%, whereas the overall crude pregnancy rate after a primary procedure is 41%.

Repeat conservative surgery for pelvic pain associated with recurrent endometriosis has the same limitations as primary surgery, with long-term cumulative recurrence rates ranging from 20 to 40%. Conversely, only one woman out of four will conceive after repeat conservative surgery for infertility, almost half the pregnancy rate after primary surgery and with no substantial advantages over IVF. (102)

Assisted Reproduction and Endometriosis:

The treatment of endometriosis-related infertility is dependent on the age of the woman, the duration of infertility, the stage of endometriosis, the involvement of ovaries, tubes, or both in the endometriosis process, previous therapy, associated pain symptoms, and the priorities of the patient, taking into account her attitude toward the disease, the cost of treatment, her financial means, and the expected results.

The success of surgery in relieving infertility is probably related to the severity of endometriosis. A recent retrospective multicenter analysis (125) reported cumulative pregnancy rates of 39%, 31%, 30%, and 25% in patients with endometriosis stages I , II, III, and IV, respectively ,l2 months after surgical treatment.

Endometriosis-associated infertility can be successfully treated with intrauterine insemination, but only if it is done in combination with ovarian stimulation (126).

However, there is clear evidence that the pregnancy rate in an insemination program is lower in women with endometriosis than in women with unexplained infertility. (127, 128) More recent studies that reported a normal fertilization rate but a reduced implantation rate per embryo transferred in women obtaining oocytes from donors with endometriosis (129, 130). This reduced implantation rate could be related to increased interleukin-6 levels in follicular fluid of women with endometriosis when compared with controls (131).

15. Recurrence

Endometriosis tends to recur unless definitive surgery is performed. The recurrence rate is about 5% to 20% per year, reaching a cumulative rate of 40% after 5 years. Liu and coworkers found an approximately 15-percent rate of recurrence at 2 years following initial surgery. Pain recurs within 5 years in about one in five patients with pelvic pain treated by complete laparoscopic excision of visible endometriotic lesions (132).

16. References

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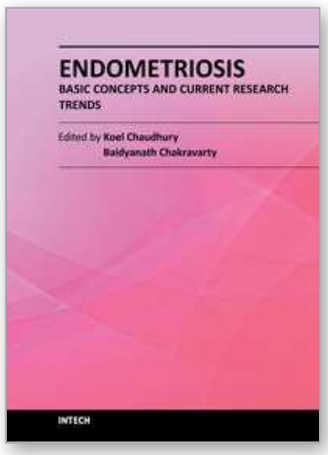

Endometriosis - Basic Concepts and Current Research Trends

Edited by Prof. Koel Chaudhury

ISBN 978-953-51-0524-4
Hard cover, 490 pages
Publisher InTech
Published online 09, May, 2012
Published in print edition May, 2012

This book provides an insight into the emerging trends in pathogenesis, diagnosis and management of endometriosis. Key features of the book include overviews of endometriosis; endometrial angiogenesis, stem cells involvement, immunological and hormonal aspects related to the disease pathogenesis; recent research reports on infertility, endometrial receptivity, ovarian cancer and altered gene expression associated with endometriosis; various predictive markers, and imaging modalities including MRI and ultrasound for efficient diagnosis; as well as current non-hormonal and hormonal treatment strategies This book is expected to be a valuable resource for clinicians, scientists and students who would like to have an improved understanding of endometriosis and also appreciate recent research trends associated with this disease.

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