

Endometriosis at the end of the millennium; the controversy remains

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Abstract

At the end of the 1990's, endometriosis remains an enigma. Its pathogenesis is unknown, its relationship to infertility is unclear, and controversy surrounds the epidemiology, diagnosis, management and the cause of symptoms. It is generally accepted that endometriosis develops from misplaced endometrial cells, and according to Sampson's theory, retrograde tubal transport of these cells is the pathogenetic mechanism. However, many studies have shown that this mechanism is operative in all women and that desquamated endometrial cells can be identified in the peritoneal cavity regardless of endometriosis. Our studies suggest that the ectopic survival of endometrial cells leading to endometriosis is the function of the immune system through the process of cytolysis and immune cell activated apoptosis. The effectiveness of the immune disposal of these cells is affected by both genetic and environmental factors. Environmental pollution, by immunotoxic agents such as organochlorides or ionizing radiation, may contribute to the development of endometriosis. This may explain higher and progressively increasing prevalence of endometriosis in the industrialized nations. The characteristic symptoms of endometriosis suggest abnormal prostaglandin and cytokine production, yet the reports on the concentration of these substances in different body fluids are

contradictory. Recent studies by our group and by other investigators indicate an increased synthesis of contractile prostaglandins and of several inflammatory cytokines by the monocyte/macrophage system. In the absence of non-invasive diagnostic techniques, laparoscopy has become the most commonly used procedure for both diagnosis and treatment of endometriosis. Yet the diagnostic delay, especially in teenagers, may exceed several years, and a lack of specific diagnostic criteria results in both over and under diagnosis. The association between endometriosis and infertility is controversial and the mechanisms through which endometriosis prevents pregnancy are unclear. Activation of the immune system with resulting production of abnormal autoantibodies in women with endometriosis may be associated with an early implantation failure, infertility and recurrent miscarriages. Suppression of abnormal autoantibodies and assisted reproductive techniques improve the "fertility outcome" and the management of the disease in infertile women. At this time, however, there is no cure for endometriosis, short of a definitive surgery. A variety of currently available therapeutic approaches, both medical and surgical, offer to patients a chance for a more individualized approach.

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Introduction

Endometriosis, a disease characterized by the extrauterine growth and function of the endometrial tissue, continues to baffle clinicians and scientists alike. The first reference to symptoms characteristic of endometriosis dates back to 1600 BC, and the disease has probably been present for as long as women have menstruated. Yet its cause is unknown, the mechanism of its development is unclear, the diagnosis requires invasive procedures and is frequently questionable, there is no known cure and the treatment requires repeated attempts and an almost lifelong management. The cause and effect relationship between endometriosis and infertility, although generally accepted, is controversial, and there is no agreement as to the optimal treatment when both conditions are present. Traditionally, endometriosis has been considered a disease in the domain of gynecology, yet other medical specialists often are consulted first by the patient, because symptoms and findings of the disease are not limited to the female reproductive system. For these and other reasons, endometriosis, as no other disease, has been the subject of disagreements and continuous debates, leaving practicing physicians and patients confused not only as to its nature, but also its management. This review will present the author's point of view on controversies surrounding endometriosis at the end of the 1990's.

Pathogenesis; changing concepts

Numerous theories have been proposed over the years to explain the pathogenesis of endometriosis, and the prevailing concepts have changed several times [1, 2]. Before the 1920's, endometriosis was considered a benign neoplastic disorder, and its lesions were referred to as adenomyomas, cystadenomas, cystomyomas, endometriomas, or cystic adenofibromas. In 1925, John Sampson [3] argued that "it is difficult to classify (misplaced endometrial or mullerian tissue) as true tumors", introduced the term "endometriosis", and proposed an alternative theory on its pathogenesis. Sampson postulated that endometrial cells desquamated with the menstrual flow were in some women "regurgitated" through fallopian tubes into the peritoneal cavity, where they would implant and

give origin to endometriotic lesions. This "retrograde transport" according to Sampson, was the cause of endometriosis, while ectopic implantation of the endometrial cells reflected their viability after shedding. The existence of the retrograde transport and viability of desquamated mullerian cells was subsequently confirmed in many studies by Sampson and his contemporaries. Although Sampson's theory could not explain the pathogenesis of endometriosis in unusual cases of congenital absence of the mullerian system, it became generally accepted and co-existed with the older "metaplasia" and "induction" concepts. However, since the beginning of the 1980's, evidence has been accumulating that the "retrograde tubal transport" is a phenomenon common to all menstruating females and endometrial cells have been identified, especially during menses, in the peritoneal cavities, regardless of the presence of endometriosis [4-6]. Thus, the possible mechanism(s) preventing implantation of such misplaced cells and the development of endometriosis became the main focus of endometriosis research during the past two decades.

Between 1980 and 1982, four independent studies were published linking endometriosis with changes in humoral and cell mediated immunity [7-10]. In one of these, we documented a decrease in cell mediated immunity in rhesus monkeys with endometriosis, and suggested that a healthy immune system may prevent implantation of misplaced endometrial cells and the development of endometriosis [9]. In a subsequent study, we reported a similar defect in cell mediated immunity in women with endometriosis [11]. Ten years later, Oosterlynck et al [12] confirmed our studies and reported a functional defect in the natural killer (NK) cell activity in endometriosis. Subsequently, our group as well as other investigators demonstrated that in women with endometriosis functional changes are also present in other immune cells, such as monocytes/macrophages, and cytotoxic T-lymphocytes (CTL). Altogether, these data indicate that in women with endometriosis the ability of the immune cells to lyse autologous endometrial cells *in vitro* is decreased, and suggest an *in vivo* immune surveillance, recognition and destruction of misplaced endometrial cells as a mechanism preventing endometriosis.

Simultaneously with the investigation of cell mediated immunity, our group and other laboratories pursued research studies of humoral immunity in women with endometriosis. These studies demonstrated an increase in B-cell activity and a high frequency of abnormal organ- and tissue-specific autoantibodies, as well as autoantibodies to cell-derived antigens such as phospholipids, histones or DNA [7, 8, 10, 13]. It is not clear at this point whether the increased B-cell activity and abnormal autoantibodies are the result of the ectopic endometrial growth or whether their presence contributes to the development of endometriotic lesions.

An ongoing *in vitro* research at our Institute indicates a complex interaction between monocytes/macrophages and autologous endometrial cells in co-cultures. It is quite likely that this interaction, if present *in vivo*, leads to the development of endometriosis in some women and normal pelvic homeostasis in others [14-18]. In women without endometriosis, monocytes/macrophages suppress *in vitro* endometrial cell proliferation, and induce endometrial cell lysis and programmed cell death or apoptosis. In women with endometriosis, monocytes/macrophages stimulate *in vitro* endometrial cell proliferation, with a decrease in endometrial cell destruction and a decrease in apoptosis. These effects appear to be mediated through the monocyte-secreted cytokines, but predominantly through the TNF α . On the basis of these studies, we proposed that at the end of the menstrual cycle in healthy women, a signal dispatched from monocytes/macrophages to the endometrial cells, ends endometrial cell proliferation, activates apoptosis and cell destruction [16, 17]. Therefore, endometrial cells in healthy women, even if misplaced to the ectopic locations, are programmed to die, do not survive and do not implant. However, if the monocyte/macrophage signal or its transduction is abnormal, proliferation of the endometrial cells continues, while apoptosis and cell lysis are decreased. Such endometrial cells when sloughed off during menses survive, and if misplaced, implant and continue their proliferation in the ectopic sites, leading to endometriosis.

According to this concept, the cytotoxic effect of other immune cells such as CTL and NK cells against autologous endometrial cells observed in healthy women and discussed above, may be

a fail-safe mechanism responsible for the destruction of those endometrial cells, which by chance have survived the apoptotic signal. In women with endometriosis, this mechanism appears to be also defective, increasing the risk for the development of the disease. The development of ectopic endometrial foci in women with endometriosis may then play a critical role in the activation and differentiation of B-cells. The activated B-cells then produce autoantibodies against endometrial cells or cell-derived antigens. Such autoantibodies may on one hand limit progression and spread of endometriotic lesions, but on the other may reduce fertility by interfering with ovum capture, fertilization or implantation as well as by increasing the frequency of spontaneous abortions.

Prevalence; is it on the increase?

Epidemiologic studies of endometriosis have long been hampered by the absence of non-invasive diagnostic techniques. The disease can be diagnosed only during laparoscopy or laparotomy, which typically are not performed in asymptomatic women. Thus, the incidence of endometriosis in the general female population is unknown. Instead, prevalence data in selected groups of women undergoing laparoscopy or laparotomy for chronic pelvic pains, infertility and/or pelvic pathology have typically been quoted. These prevalence rates range widely between 1 and 53%, reflecting the selection bias of the studies [19]. The lowest rates have been reported in asymptomatic women undergoing tubal sterilization, and the highest in women with clinical suspicion of the disease.

Only one epidemiologic study has attempted to evaluate the true incidence of endometriosis, i.e., the number of new cases in a defined population diagnosed in a unit of time. Houston et al [20] reported that between 1970 and 1979 in rural Minnesota, in a geographically stable population of white females age 15 to 49, there were 108.8 to 246.9 new cases per 100 000 women per year, where 108.8 represents histologically confirmed, and 246.9 includes unconfirmed, clinically possible cases. Making allowance for cases possibly missed by the evaluation process, the maximal incidence of endometriosis as quoted by that study was 330.3 new cases per 100 000 women per year or 0.33%. Based on the 0.33% incidence, and assuming that endometriosis remains active for 20 to 30 years,

we can calculate the prevalence of the disease in that study at between 6.6% and 9.9%. This, however, may be a gross underestimate, considering that the data were from the early 1970s, before the advent of laparoscopy. If a rounded 10% prevalence figure is applied to the U.S. population of women aged 15 to 49, which according to the 1995 estimates is just above 68 million, approximately 6.8 million women may be suffering from endometriosis in the U.S. [21]. This figure is higher than the estimated 5 million of affected women, as frequently quoted by the Endometriosis Association [22].

Both prevalence and incidence rates of endometriosis appear to change with age [20]. They are the lowest for women age 15 to 19, increase with age, reaching a peak between 40 and 44, and then decline. However, the low, 0.07% incidence of endometriosis in teenagers quoted by Houston et al [20] may be erroneous, and may reflect the already mentioned under-diagnosis. In teenagers with pelvic pain, the diagnosis is not always expedient and the "diagnostic delay" that is the time interval between the onset of symptoms and the diagnostic procedure may exceed 8 years [23]. The prevalence of endometriosis in symptomatic teenagers seems to be over 50% [24].

A variety of risk factors may be associated with endometriosis. It has been demonstrated, that when first- or second-degree relatives have endometriosis, the risk is about seven-fold higher and the disease is biologically more aggressive [23, 25]. Obstructive changes in the mullerian system, congenital or acquired, may increase retrograde flow of the endometrial cells, and have been associated with the increased risk of endometriosis in teenagers [26]. Early menarche, shorter and heavier menses, and dysmenorrhea are also more common in women with endometriosis [27]. However, there is no supporting evidence for the role of socioeconomic status, race, delayed childbearing, personal hygiene, or health habits in the development of endometriosis.

It has been suggested that the prevalence of endometriosis is on the increase and may be higher in the industrialized than in developing nations [28, 29]. Unfortunately there is a lack of good epidemiologic data and higher prevalence rates may simply indicate diagnostic advances. It is worth noting, however, that in rhesus monkeys the prevalence and severity of endometriosis are increased several years after

exposure to radiation or after treatment with organochlorides such as polychlorinated biphenyls (PCBs) or dioxin [30-32]. The organochlorides are environmental pollutants which are not metabolized as they move from animal to animal in the food chain, and their concentration is magnified as much as 25 million times. In countries with high environmental pollution, women have higher organochloride concentrations in the peripheral blood, subcutaneous fat and breast milk and also appear to have high prevalence of endometriosis [29, 33, 34]. PCBs and dioxin are known immunotoxicants and radiation destroys the immune cells. One is tempted to speculate that suppression of the immune system by systemic irradiation, PCBs or dioxin facilitates implantation of misplaced endometrial cells leading to the development of endometriosis several years after exposure.

However, it is also possible that factors other than environmental pollution contribute to the apparently high prevalence of endometriosis in the industrialized nations. D'Hooghe et al [35] reported higher frequency of endometriosis in captive as opposed to free ranging baboons and attributed this finding to either the effect of higher number of menstrual cycles uninterrupted by pregnancy or to the captivity-associated stress.

Symptoms; do they reflect abnormal prostaglandin and cytokine production?

A variety of symptoms are considered characteristic but none is pathognomonic to endometriosis. They vary in intensity, and some women may be asymptomatic. Women affected by endometriosis seek medical attention because of infertility or chronic pelvic pains. Recent studies suggest biological differences between these two groups [23]. Those with pelvic pains are more likely to be affected at an earlier age, their disease is more rapidly progressing, symptoms are more severe, and they are more likely to have a family history positive for endometriosis. Women with infertility are frequently asymptomatic, their disease is often less advanced and non-progressive.

Chronic pelvic pain symptoms, consisting of dysmenorrhea, dyspareunia, dysuria, dyschezia and/or pelvic pains unrelated to

menses are the most common symptoms of endometriosis present in about 60% to 96% of affected women. Dysmenorrhea, typically acquired and progressive, is reported by 28 to 63%, deep dyspareunia by 12 to 27%, and pelvic pain by 10 to 30%. Chronic pelvic pain symptoms have been attributed to abnormal prostaglandin metabolism in the reproductive system. The initial reports claimed changes in the concentration of several prostanoids, but predominantly in the levels of $\text{Pgf}_{2\alpha}$ and PGE_2 in the uterine endometrium, menstrual flow, peritoneal fluids, and in the contents of endometriomas. Subsequent studies, when controlled for the day of the cycle, were, however, unable to demonstrate differences in the peritoneal fluid concentrations of prostanoids between endometriosis and controls, and raised doubt regarding the relationship between endometriosis symptoms and abnormal prostaglandin metabolism. Considering, however, that most prostaglandins are unstable and rather difficult to measure in the biological specimens, and that pelvic pain symptoms respond readily to the treatment with prostaglandin synthetase inhibitors (PgSIs), the role of these substances in the pathogenesis of endometriosis symptoms needs further clarification.

About 15 to 25% of women with endometriosis have cyclic pain or bleeding or other catamenial symptoms originating outside the reproductive system and at times outside the pelvis. Such symptoms suggest extragenital or extrapelvic disease. Cyclic dyspnea, pleural effusion, pneumo and hemothorax, and cyclic hemoptysis indicate pulmonary endometriosis. Cyclic dyschezia or hematochezia suggest bowel, while cyclic dysuria and hematuria urinary system involvement. Neurologic symptoms of catamenial pattern, such as low back pain, leg or sciatic pain, sensory loss, leg weakness and foot drop suggest endometriotic lesions in the retroperitoneal space involving or compressing on the nerves, most frequently sciatic. Cyclic headaches or seizures may be caused by lesions in the brain. Cyclic pain, tenderness or swelling are commonly associated with endometriosis in surgical scars of the abdomen, perineum or vagina, or with umbilical or inguinal endometriosis. We can, therefore, conclude that regardless of location, any

symptom of catamenial pattern and any lesion that changes in relation to the menstrual cycle should raise suspicion of being endometriotic in origin. Pelvic endometriosis, in such cases, may or may not be present, and if present, may be asymptomatic.

About 15% of women with endometriosis report generalized symptoms of a catamenial pattern, such as malaise, fatigue, aches and pains, nausea, vomiting, diarrhea, smooth muscle cramps, weight loss, low grade fever, dyspnea, etc. These symptoms typically have been considered as "somatizations" of the disease. However, at least some of these symptoms may be related to abnormal prostaglandin metabolism, since they improve during treatment with PgSIs, while others suggest abnormal systemic cytokine effects. Although the reports on peripheral concentration of prostanoids and cytokines in women with endometriosis are contradictory, recent studies indicate that production of these substances by the immune cells may be altered. We have demonstrated that in endometriosis, peripheral blood monocytes and peritoneal macrophages produce higher levels of $\text{TNF-}\alpha$, IL-6 and IL-8 , as well as other cytokines [36], while Karck et al [37] reported higher PGE_2 and $\text{PGF}_{2\alpha}$ release by the peritoneal macrophages, suggesting that the same may also apply to the peripheral monocytes.

Laparoscopic diagnosis - is it reliable?

Chronic pelvic pains and/or infertility, when associated with cul-de-sac or adnexal pathology, strongly suggest endometriosis, especially in the presence of risk factors such as a positive family history. However, a definitive diagnosis requires laparoscopy or laparotomy, and a histopathologic confirmation. During the past two decades laparoscopy has become the most common diagnostic procedure for endometriosis. It permits direct visualization of the lesions, biopsy of suspected areas, and classification (staging) of the disease. The laparoscopic appearance of typical endometriotic lesions is characteristic. Recently, however, attention has been drawn to atypical and non-pigmented lesions which may be less obvious. Laparoscopic biopsy for tissue diagnosis should probably be a routine procedure prior to the laser or electro-surgical ablation and should be required in all questionable

cases. Microscopic examination should demonstrate characteristic endometrial glands and stroma, and hemosiderin laden macrophages. At least two of the three components are necessary for the microscopic diagnosis. Atypical endometriotic lesions or lesions surrounded by fibrosis may be difficult to identify visually, without extensive surgical dissection, and tissue specimens may require multiple sections and careful microscopic examination. Furthermore, visually normal peritoneal surfaces may harbor microscopic implants, as has been demonstrated in random biopsies [38]. It is not unusual, therefore, that endometriosis is missed or misdiagnosed by the laparoscopist and/or pathologist. A recent trend among laparoscopists in the U.S. to rely exclusively on the visual diagnosis of endometriosis without biopsy and histologic confirmation is somewhat disturbing. It is not unusual that a patient with chronic pelvic pains and questionable endometriotic lesions acquires the "endometriosis" label only to discover, sometimes years and therapies later, the real cause of her symptoms. Overdiagnosing and assumption that all endometriotic lesions are symptomatic is just a part of the problem. At the other end of the scale are women with atypical endometriotic lesions which escape attention of less experienced laparoscopists and the disease remains under-diagnosed. A requirement for histologic confirmation of the visual diagnosis may not solve all problems, but may limit to some extent over- and under-diagnosing of the disease.

The imaging techniques such as ultrasonography, computed tomography (CT) or magnetic resonance imaging (MRI), currently have limited value in the diagnosis of endometriosis. In women with adnexal lesions, these techniques allow accurate assessment of the size, shape and characteristics of ovarian cysts. The definitive diagnosis of such cysts, however, still requires direct visualization and microscopic examination. Similarly, several blood tests have been proposed but at present none is diagnostic of the disease.

In order to facilitate comparative studies and data analysis, and to better assess the response to treatment and the prognosis regarding recurrence or fertility, classification or staging of endometriosis has been attempted on several occasions. However, all attempts have relied on clinical opinions rather than statistical studies, and on arbitrarily assigned points and stages

without consideration given to the natural course of the disease, biological changes, or symptoms. Thus, none of the proposed classifications has fulfilled stated objectives and all have been extensively criticized. For a lack of a better system, revised AFS classification of endometriosis published in 1985 is still in use [39].

Endometriosis and infertility

In infertile women the prevalence of endometriosis ranges between 15 and 25%, but when all other infertility factors are ruled out it may be as high as 70 to 80%. In women with endometriosis, the prevalence of infertility has been estimated at 30 to 40%, although formal studies are lacking. The estimated risk of infertility is 20 times greater in women with endometriosis than in those without [40]. Treatment of endometriosis improves fertility and post-treatment pregnancy rates are frequently used as indicators of the effectiveness of therapy. Thus, an association seems to exist between endometriosis and fertility. However, infertility in women with endometriosis is relative and spontaneous conceptions are known to occur. The probability of conception appears to be inversely related to the severity of the disease.

The exact mechanism(s) of infertility in endometriosis is unknown. In the severe disease, periovarian and peritubal adhesions, and/or ovarian endometriomas interfere mechanically with conception. The effect of mild endometriosis on fertility is controversial. Monthly fecundability rates in women with untreated, mild endometriosis undergoing artificial insemination with the donor sperm were lower by comparison to healthy controls according to some studies [41, 42], but were not different according to others [43, 44]. In minimal or mild endometriosis several mechanisms of infertility have been suggested, and a variety of substances capable of interfering with ovulation, endocrine function, gamete/embryo transport, fertilization and implantation have been identified [45]. Tummon et al [46] recently reported that the fertility rate per cycle in women with mild endometriosis is only 2%, and that it can be increased with controlled ovarian hyperstimulation combined with AIH (COH/AIH) to only 11%, far below the 20-25% fertility rate expected in healthy women of the same age.

It is quite likely that the difference between expected and observed fertility rates with COH/AIH in mild endometriosis is secondary to the defective ovum capture and/or defective gamete/embryo transport by the fallopian tubes. *In vitro* fertilization/embryo transfer (IVF/ET) can overcome such a defect and should be considered the next step in the management, after failed COH/AIH cycles. However, with the increase in the IVF success rates to about 50% reported recently by the leading Centers, IVF/ET may become a viable alternative to COH/AIH and may be considered as the initial approach. At the present time in women under 35 with stage I/II endometriosis, we recommend COH/AIH for three to four cycles with or without corticosteroids, depending on the presence of autoantibodies. If there is no conception we proceed at that time to IVF/ET. It should be kept in mind, however, that ovarian stimulation cycles, by raising estradiol levels, most likely also accelerate the recurrence and progression of endometriosis. Therefore, the advantages (increased pregnancy rate) and disadvantages (accelerated progression of the disease) of ovarian stimulation during COH and IVF cycles need to be carefully evaluated for each patient.

Introduction of IVF-ET procedures two decades ago has allowed better evaluation and treatment of infertility associated with endometriosis. It is generally agreed that the disease, with the exception of its advanced stages, has no adverse effects on ovarian response to stimulation or number of eggs retrieved. Fertilization rates also appear to be comparable, notwithstanding an occasional contradictory report. There is controversy, however, regarding the IVF pregnancy rates. The majority of investigators report comparable results in women with and without endometriosis. The contradictory studies claim lower implantation rates as the cause of lower pregnancy rates in endometriosis. Arici et al [47] reported implantation rates in stage I and II endometriosis of only 2.8% and 5.5% in stage III and IV, as compared to 5.1% in women with tubal disease. Simon et al [48] also observed lower implantation and pregnancy rates and attributed those to poor embryo quality. It is unclear whether, and if so, to what extent endometriosis affects embryo quality and implantation rates. The results of contradictory

reports need to be interpreted with caution, taking into account the design of each study and patient selection. When donor oocyte recipients were evaluated, there was no apparent difference in the implantation rates according to the presence (n = 55, implantation rate = 12%) or absence (n = 184, implantation rate = 13%) of endometriosis [49]. We recently analyzed IVF cycle parameters including pregnancy rates in women with endometriosis who were autoantibody positive or negative [50]. A significant difference in the pregnancy rates: 22.9% in autoantibody-positive and 45.7% in autoantibody-negative patients was observed. It is possible that abnormal autoantibodies in the peripheral circulation or follicular fluids adversely affect *in vitro* fertilization and early embryo development, and subsequently interfere with embryo implantation. This concept is supported by reports indicating that anti-phospholipid antibodies bind to mouse pre-embryos and human trophoblasts [51]. If so, the practice of repeated oocyte washing and cumulus-corona cell removal during egg collection as advocated by some laboratories for women with endometriosis, may explain similar fertilization rates, embryo development and implantation rates in endometriosis and in tubal disease as reported by these centers [52].

Controversies in the management

Endometriosis in most women is a progressive disease [23] and as such requires repeated medical and/or surgical interventions. However, in some women minimal disease may be non-progressive as demonstrated by repeated laparoscopies and if asymptomatic may not require treatment [53]. In baboons with minimal endometriosis repeated laparoscopies demonstrated that without treatment some implants undergo spontaneous resolution while new ones appear in other locations [54].

The unknown etiology precludes cause-directed and curative treatment of endometriosis, and all treatment methods short of definitive surgery are typically followed by the recurrence. A variety and number of currently available therapies may present a challenge to some physicians, but offer to patients a chance for a more individualized approach. Thus, physicians who advocate only one method of treatment, regardless how effective, probably provide a disservice

to some of their patients. We prefer to individualize the management depending on the intensity of symptoms and extent of the disease, and considering factors such as age, fertility status, desire for its preservation, and previous treatment history. Prior to the selection of treatment, alternative therapeutic approaches, medical, surgical, and combined, their advantages and disadvantages, indications and contraindications, side effects and risks are discussed with the patient.

Surgical resection of endometriotic lesions is a traditional approach. It is conservative when combined with reconstruction of the reproductive system to preserve and enhance fertility, or definitive when hysterectomy and oophorectomy are performed. Unfortunately, laparotomy frequently leads to post-operative adhesions which further interfere with fertility and/or contribute to pelvic pains. Laparoscopic surgery leaves fewer adhesions, and with recently developed sophisticated laparoscopic instruments, even extensive endometriosis is amenable to laparoscopic resection. Unfortunately surgical resection is limited to visible and accessible lesions. Microscopic, deep subperitoneal, or lesions on vital organs are frequently left behind. These, as well as uncorrected pathophysiological mechanisms, give rise to subsequent recurrence. How frequently a patient can undergo repeated resections or ablations, even if the surgery is minimally invasive, is an unanswered question, but concerns have been raised regarding the effect of such treatments on subsequent ovarian function and the response to ovarian stimulation.

Medical treatment, therefore, at least in some women, may be preferable and superior to surgery. It is simple, does not require special skills or sophisticated equipment, and is cost effective. There is no destruction of ovarian tissue and no postoperative adhesions. The disadvantages include the length of treatment and its side effects. Contrary to the common misconception, there is no drug available to "eradicate" endometriosis. Current hormonal regimens modulate the endocrine milieu and induce hypoestrogenic or hyperprogestational state in which uterine and ectopic endometrium undergo atrophy or decidual changes. During the drug-induced amenorrhea, endometriotic lesions become gradually resorbed. It may take several months to achieve complete regression.

In advanced endometriosis, resolution of endometriomas may be incomplete and there is no effect on adhesions. Currently available treatment options include: gonadotropin releasing hormone agonists (GnRH-a), danazol and progestogens with or without estrogens.

GnRH-a are synthetic polypeptides analogous to the native GnRH. Administered continuously, they downregulate GnRH receptors in the pituitary and suppress FSH and LH and ovarian function. The degree of ovarian suppression depends on the type, route of administration and the dose of the agonist. Treatment is typically continued for six months and results in amenorrhea, endometrial atrophy, resolution of endometriosis and symptomatic improvement. There is probably no direct effect of GnRH-a on the ovary or endometrium. Available in the United States for clinical use are intranasal Nafarelin, intramuscular depot Leuprolide and subcutaneous implants of Zoladex (Goserelin). Buserelin and decapeptyl are additionally available in Europe. Side effects of GnRH-a are the result of hypoestrogenism and manifest as menopausal symptoms of varying intensity. With estradiol levels below 20 pg/mL, there is increased calcium mobilization from the bones and the risk of osteoporosis. GnRH-a may aggravate clinical depression and migraine headaches. Combined with low dose estrogen and/or progestogen, as an add-back therapy, GnRH-a have been recommended as a maintenance therapy to prevent or delay recurrence of endometriosis.

However, GnRH-a stimulate ovarian function (flare effect) for the first two weeks of treatment before the state of suppression develops. In some women, especially those with the polycystic ovarian disease, GnRH-a in the recommended doses may have a continuous stimulating rather than suppressive effect. It is important therefore to monitor peripheral estradiol levels, and if necessary, adjust the dose upwards. Recently introduced to clinical trials, GnRH antagonists do not exhibit the flare effect, seem to be better tolerated than GnRH-a, and have better effectiveness [55]. They are, however, not available as yet for the clinical use.

Danazol is a steroid derivative, chemically related to the synthetic androgen, 17 α -ethinyl testosterone (ethisterone). Administered orally in four divided doses, 10-15 mg/kg/day (about

800 mg/day in most women), danazol effectively inhibits ovarian function. Lower doses or less frequent administration schedules are usually less effective. Ovarian suppression is both direct (through ovarian enzymes) and indirect (through gonadotropins) and estradiol levels during treatment range between 20 and 60 pg/mL. Danazol may also have a direct suppressive effect on the endometrium through endometrial androgen and progesterone receptors. The most interesting, however, is danazol's effect on the immune system. In women with endometriosis and infertility and/or recurrent miscarriages caused by abnormal autoantibodies, danazol suppresses autoantibodies and improves reproductive performance [56]. Side effects of danazol are primarily androgenic/anabolic, and include skin oiliness, acne, hirsutism, weight gain, and deepening of the voice. The androgenic effects, however, are mild and usually well tolerated.

Danazol should be avoided in patients with a history of liver disease, elevated liver enzymes, atherosclerosis or abnormal lipid metabolism. There is no contraindication to repeated courses of danazol, but if the drug was not optimally effective or had disturbing side effects, other hormonal preparations should be considered.

Estrogen/progestogens are constituents of oral contraceptives. They are considered less effective in the management of endometriosis than other regimens. Centrally they suppress FSH and LH, but in the endometrium bind to estradiol and progesterone receptors, inducing decidual rather than atrophic changes. Administered continuously in the individually adjusted doses, they induce hyperhormonal amenorrhea. Most effective are combination type birth control pills with strongly progestational properties. In some women, especially at the beginning of treatment, the symptoms of endometriosis may increase and endometriotic lesions may enlarge. Side effects are the same as of birth control pills.

Oral or parenteral progestogens have inconsistent suppressive effect on the ovarian function. Acting synergistically with endogenous estrogens, they induce decidual changes in the endometrium, similar to those observed with estrogen/progestogens. Clinically, they seem to be less effective than regimens inducing endometrial atrophy. Side effects of progestogens alone are fewer and they are better tolerated than estrogen/progestogen preparations.

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