Review Article

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Endometriosis, a modern syndrome

Ivo Brosens & Giuseppe Benagiano*

*Leuven Institute for Fertility & Embryology, Leuven, Belgium & *Department of Gynaecology, Obstetrics & Urology, 'Sapienza' University of Rome, Italy*

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The identification of endometriosis has been a subject of intense debate over the last decade. There is, however, no doubt that Thomas Cullen was the first to describe endometriosis and adenomyosis as one disease characterized by the presence of endometrium-like tissue outside the uterine cavity. With the introduction of laparoscopy in the early 1960s three different clinical presentations of endometriosis were distinguished: peritoneal, deep adenomyotic and cystic ovarian. As soon as synthetic steroids became available, pioneer clinicians started utilizing these in an attempt to replace radical surgery by a medical treatment. While medical therapy may resort in relief, in most cases the current approach consists of a combination of medical and surgical therapy. While the pathogenesis of endometriosis is still enigmatic and complex, there is increasing evidence that endometriosis is part of a uterine reproductive dysfunction syndrome. For prevention of complications, it is very important that diagnosis is made as early as possible in a woman's life.

Key words Adenomyosis - endometriosis - pathogenesis - prevention

When was endometriosis first identified?

Over the last decade, great interest has been shown for the reconstruction of the path that led to the identification of the two conditions we call adenomyosis and endometriosis. Recently, the debate has focused on Carl Rokitansky, indicated as the "discoverer" of endometriosis[1,2]. We have argued against this attribution as, in our view, there are three conditions that must be met before credit can be given for having identified the two pathologies: (*i*) to have found the presence of epithelial structures outside the uterine cavity; (*ii*) to have identified these as endometrial glands and stroma; and (*iii*) to have clearly understood that this invasion was "benign" (and therefore, "non neoplastic") in nature[3]. Using these criteria, there is no doubt that it was the surgeon Thomas Cullen who described for the first time the full morphological and clinical picture of endometriosis and adenomyosis[4]. In 1920, he drew a scheme with the classic sites of adenomyotic lesions in the pelvis[5]. He correctly mentioned that the condition, called in these days adenomyoma, involved the presence of ectopic endometrial-like tissue in the myometrial wall, rectovaginal septum, hilus of the ovary, uterine ligaments, rectal wall and umbilicus. Cullen considered uterine adenomyoma, ovarian endometriosis and deep endometriosis as one disease characterized by the presence of adeno-myomatous tissue outside the uterine cavity and today there is increasing evidence that he may have been right.

It was John A. Sampson who created the name endometriosis[6] seven years after his fundamental paper on ovarian endometriomas[7]. Above all, he must be credited for providing the first theory on the pathogenesis of the disease. His original observation came when he operated women at the time of menstruation and found that the peritoneal lesions were bleeding, similarly to what happens in eutopic endometrium, proving to him that the tissue outside the uterus was of endometrial origin. In 1927, Sampson postulated that presence of endometrial cells outside the uterus was due to tubal regurgitation and dissemination of menstrual shedding[6].

Clearly, peritoneal endometriosis became the signature of endometriosis and the introduction of laparoscopy in the sixties provided a golden tool for the visual diagnosis and surgical therapy. As a result, endometriosis was divorced from the uterus (and adenomyosis) and research became focused on how fragments of menstrual endometrium implant on peritoneal surfaces and invade the underlying tissues. Other mechanisms have been proposed such as peritoneal metaplasia, transportation through veins or lymphatics, the presence of embryonic vestiges, and the transformation of bone marrow and endometrial stem cells, but menstrual regurgitation with the subsequent implantation of endometrial cells, under facilitating circumstances, can still explain most ectopic localizations.

Clinical presentations

Further progress, not really fully understood at the time, came when, in 1932, Hill Jr[8]. reported the presence of aberrant endometrium at microscopy in a series of 135 patients who were operated-upon for some pelvic pathology. Amongst these cases, 20 had adenomyomas of the uterus and 115 had peritoneal endometriosis. The majority of the patients were between 20 and 45 yr of age, with the youngest being 16 yr old and the oldest 61. Pelvic pain related to menstruation was the principal reason for seeking relief through surgery and this usually happened some ten-years after the onset of disease; in addition he mentioned that symptoms were progressive.

Three different types of endometriosis were subsequently distinguished.

Peritoneal endometriosis

In the 1980s it became evident that peritoneal endometriosis has multiple appearances including microscopic foci, early-active (red, glandular, or vesicular), advanced (black, puckered) and healed (white, fibrotic) forms. These lesions may represent replacement of mesothelium by an endometrial epithelium or endometrial polyp formation[9-11]. The anatomic distribution of ectopic endometrium supported the hypothesis of retrograde menstruation as the primary model of development of endometriosis[12]. The clinical importance of even very small lesions was suggested when, in a prospective study of artificial insemination in women with minimal endometriosis, Jansen[13] found reduced fecundability. Awareness of the existence of subtle peritoneal endometriosis produced an increase in the diagnosis of endometriosis, although clinical significance of early lesions remained controversial[14-16].

From all published evidence Evers *et al*[17] concluded that peritoneal endometriosis appears to be a dynamic disease, especially in the early phase, when subtle, atypical lesions may emerge and vanish again. The dynamic phase of the disease may involve a varying interval of each patient's life (*e.g.*, a period of amenorrhoea or pregnancy). Laparoscopy at the end of medical suppression of the activity of implants may lead to the erroneous conclusion that treatment has been effective. The final answer to the question whether and in which cases endometriosis is a progressive disease will have to come from long-term prospective investigations studying spontaneous evolution of peritoneal lesions without therapeutic interference.

Recto-vaginal endometriosis

As in the case of infertility, investigators found poor correlation between lesion characteristics or stage of disease and pelvic pain. A strong correlation between pelvic pain and the depth of invasion was described in the presence of implants more than 10 mm deep[18-20]. In contrast with superficial peritoneal endometriosis, these lesions have a structure closely resembling the adenomyomas described by Cullen[4]. In the late 1990s rectal endoscopic ultrasonography was proposed to diagnose the presence of deep bowel infiltration and select patients for surgery[21-22].

Ovarian endometrioma

Ovarian endometriosis can present itself as very early lesions, plaques with free-floating adhesions, deep non-cystic lesions and typical chocolate cysts with adhesions. In a detailed study of 29 ovary specimens with chocolate cysts, Hughesdon[23] found that in 90 per cent of them the ovarian endometrioma was formed

by a pseudocyst. The surface of the ovary is adherent, usually to the posterior side of the parametrium and part of the ovarian cortex is invaginated. Endometriotic tissue is found at the site of adhesion and a thin layer of superficial endometrium-like tissue extends to cover partially or fully the invaginated cortex. Hughesdon concluded that ectopic endometrium does not simply erode its way into the ovary: the ovary is actively invaginated, thus, providing a pseudocyst mimicking a uterus.

Using an endoscopic technique Brosens *et al*[24] investigated a series of endometriotic cysts *in situ* in young women with infertility and confirmed that the wall of the cyst is constituted by cortex lined by endometrial cells. They suggested that surgery should be adapted to the structure of endometrioma by adhesiolysis with opening and eversion of the cyst and followed by ablation of the superficial endometriotic tissue lining the cortex and excision of the implants at site of the adherent parametrium or ligaments. It must be stressed that surgical treatment of ovarian endometriomas is more complex than simple drainage and coagulation.

Success and failure of modern treatments

Once microscopic criteria were established in the forties and fifties, the disease became increasingly diagnosed during the subsequent decades. In the early days however, clinicians facing the issue of management of endometriosis were at a loss on what to do, to the point that in 1953, Meigs[25] recommended early and frequent childbearing as prophylaxis and even exhorted patients to subsidize their sons and daughters so that this approach may become financially feasible. He wrote: "It is the author's belief that avoidance of endometriosis through early marriage and frequent childbearing is the most important method of prophylaxis". Obviously, Meigs was not referring to peritoneal endometriosis; rather he was attempting to solve the challenges of those days: painful rectovaginal adenomyomas and cystic ovarian endometriomas in young women for whom at that time hysterectomy and castration were the only surgical cure. While for many patients Meigs' proposal was not practical, the idea led Kistner[26] to propose, in 1958, a more practical alternative: induce a state of "pseudopregnancy" to reproduce the improvement noted in endometriosis during and after pregnancy. He postulated that the positive effect of pregnancy was due to decidualization that results in necrosis and elimination of superficial endometriotic implants. This concept bears striking similarity to the approach taken by Rock *et al*[27] approximately the same time in their quest for a hormonal contraceptive[27].

Hormonal therapies

It is noteworthy that the first attempts at a hormonal management of the symptoms associated with endometriosis preceded Meigs proposal and Kistner intuition, having started almost 70 years ago. As soon as synthetic steroids became available pioneer clinicians began utilizing these in an attempt to find a medical cure for endometriosis and, interestingly enough, androgens preceded estrogens as therapeutic agents.

Androgens

The first suggestion came from Geist and Salmon[28] who, in 1941 advocated the use of androgens in gynaecological disorders. Following this lead, the first results obtained with the use of testosterone propionate began to appear. In 1944, Miller[29] wrote: "testosterone propionate can be used in diminishing the activity and decreasing the size of the lesions in endometriosis so that radical surgery can be performed with less danger". In spite of the positive results obtained, the undesirable side effects of hirsutism, acne, and deepening of the voice occurred sufficiently often to cause the clinician and the patient considerable concern. For this reason, androgen therapy never really took off and other avenues began to be explored. In 1958, commenting on the use of androgens Kistner[26] noted that "androgenic substances, while adequately documented as having produced desirable results in endometriosis, probably exert their effect through inhibition of gonadotropic substances, although direct effect of the substance upon the endometriotic area has been suggested". This great intuition prompted endocrinologists and gynaecologists to test other gonadotropin -inhibiting substances.

Oestrogens

The availability, in the late forties, of a non-steroidal, synthetic oestrogen, diethylstilbestrol (DES), prompted another line of experimental treatment for severe endometriosis.

We know today that oestrogens are intimately involved with the growth of ectopic endometrial foci and therefore, with today's wisdom, oestrogens would be – if anything – contraindicated. Indeed, although in all likelihood not an endocrine disease, endometriosis does not appear in the absence of oestrogens. Even when the disease manifests itself in post-menopausal patients, usually it does so in women treated with

oestrogens[30,31] and, in the rare occurrence in non-treated post-menopausal patients[31], it is believed that symptoms are the consequence of the progression of the oestrogen-independent fibrosis, not of the growth of new foci[32]. At the same time, there is evidence that oestrogens are not necessary for the endometrium to implant itself ectopically, whereas proliferation and growth of ectopic implants need their presence.

Finally, although endometriosis has been described in the urinary bladder of men with prostatic carcinoma[33], in the case of pure gonadal dysgenesis[34] and Turner's syndrome[35,36] streak gonads[37] and in a woman with a Rokitansky-Kuster-Hauser syndrome[38], all these patients had endogenous or exogenous oestrogens, alone or in combination with a progestin. Therefore, the concept that oestrogens are necessary in order to have active ectopic endometrial foci so far goes unchallenged.

This large body of knowledge did not exist and could not even be guessed when the first attempts were made to treat with oestrogens women with severe endometriosis. The first to do so was Karnaky[39] who, in 1945, reported apparently good results, achieving amenorrhoea with increasing daily doses of up 100 mg/day of diethylstilbestrol (DES). In his report he reached at an intriguing conclusion: "endometriosis is not stimulated to grow by large continuous doses of stilbestrol, but small doses of stilbestrol may stimulate it". In his series, five patients became pregnant after stilbestrol was discontinued. With today's knowledge, the offspring of those pregnancies should have been followed very closely, although second generation clear cell vaginal cancer has been usually attributed to use of DES in pregnancy, not before it[40].

In spite of the enthusiasm of its proponent, oestrogen treatment of endometriosis did not last, and for reasons only partially related to modern knowledge. In 1958 Kistner[26] wrote: "the unpredictability of permanent relief in endometriosis following the use of estrogenic substances alone" and the fact that "estrogen therapy also has the disadvantage of occasionally resulting in rather profuse break-through bleeding, endometrial hyperplasia and hypermenorrhea at the time of withdrawal of the hormone" make this treatment unwise.

Estrogen-progestin treatment: the "Pseudo-pregnancy" regimen

As already mentioned, knowledge gained during the forties and early fifties allowed the creation of a new concept that went under the name of "pseudo-pregnancy", the artificial creation of a hormonal situation mimicking that occurring naturally during pregnancy. Two researchers Kistner[26] and Andrews[41] share the credit for the advent of "pseudo-pregnancy" as a treatment for endometriosis. Kistner wrote: since "in many patients with this disease, conception is not always possible, either because of unknown factors producing infertility or because marriage is not contemplated" an artificial situation mimicking pregnancy can resolve the impasse[26]. His first experimental treatments involved 12 patients to whom large doses of a number of oestrogenic compounds and two progestins were administered in a "graduate scale" for periods of time up to 7 months to produce amenorrhoea, as well as a decidual reaction in the endometrium. The pseudo-pregnancy regimen resulted in an improvement of the condition, both subjectively and objectively, except for occasional side effects like uterine cramps or hypermenorrhoea.

A further step forward was introduced when – starting from the same observation of beneficial effects of pregnancy on endometriosis – the first oral contraceptive ever marketed, *Enovid* (norethinodrel plus mestranol) was administered to 23 women with endometriosis. Decidual transformation was consistently demonstrated in the eutopic endometrium and was present in the ectopic endometrium in all of the five instances in which it was obtained for study. Clinical improvement during therapy was observed in 14 of the 17 patients treated because of pain[42].

To improve the effectiveness of the pseudo-pregnancy regimen, long-acting steroid hormones were introduced in the 1960s. Patients developed amenorrhoea, which persisted throughout the period of hormone administration, and most of them experienced considerable to complete relief of their symptoms. The oestrogen-progestin regimen has been used extensively since then for the treatment of endometriosis, although very little was published on the subject in recent years. Symptomatic relief of the disease was reported in a majority of cases and pregnancy rates in women who complained of infertility in addition to endometriosis ranged from 10 to 53 per cent[43]. It is unfortunate that, although extensively utilized, oestrogen-progestin combinations have not been properly tested. Indeed, a 2007 Cochrane systematic review aimed at assessing the effects on pain-related symptoms of oral contraceptives when compared to other treatments, found only one study that met the inclusion criteria[44].

Other hormonal regimens

During the second part of the 20th century a number of additional hormonal regimens have been proposed, the first being an antigonadotropic steroid, *danazol*. Its introduction in 1971 by Greenblatt *et al*[45] brought back the clock, since this compound has definite androgenic properties and may produce symptoms not very different from those reported in the forties.

Interesting results have been obtained with the introduction of *gestrinone*, a steroid with androgenic, antiprogestinic and antioestrogenic activities. Fedele and co-workers[46] were the first to compare the clinical effects of gestrinone and danazol, observing a significant decrease of pain-related symptoms (dysmenorrhoea, pelvic pain, deep dyspareunia) in both groups, without any significant difference. The same year Venturini and co-workers[47] showed that gestrinone significantly reduces serum concentrations of total testosterone and sex hormone binding globulin (SHBG), whereas free testosterone is slightly, but significantly, increased. Finally, oestradiol is not significantly lowered in comparison with pre-treatment follicular phase values.

Given the results obtained with a mild antiprogestin like gestrinone, it was logical to expect even better results with the first "real antiprogestin", *mifepristone*[48], widely known as the "abortion pill". Unfortunately, its use in medical abortion has created a situation where, for over 20 years, after very promising early clinical studies, no large-scale experimentation has been published. Today, however, a second antiprogestin, *ulipristal* has been marketed (as an emergency contraceptive) and work has resumed on possible applications of antiprogestins in the treatment of a number of proliferative disorders of the female reproductive tract.

Gonadotropin-releasing hormone agonist and levonorgestrel-releasing intrauterine system

Gonadotropin-releasing hormone agonists (GnRHa) have emerged as a primary medical therapy for patients with symptomatic disease, although secondary hypoestrogenic side effects may limit compliance. Add-back therapy is a means of surmounting this problem. Progestins such as norethisterone acetate may be administered with or without addition of low doses of oestrogens to safely and effectively extend GnRHa therapy while minimizing side effects. Recent studies have demonstrated that the use of add-back enhances compliance and duration of therapy[49]. The initiation of an add-back should not be deferred since there is evidence demonstrating an increase in vasomotor symptoms and bone loss if not administered concomitantly. The subset of adolescents with endometriosis who require GnRHa therapy should be administered an add-back, but – even so – they require careful monitoring of bone mineral density. Implementation of an appropriately selected add-back will significantly reduce hypoestrogenic side effects, enhance compliance, and allow for prolongation of therapy without interfering with the efficacy of GnRHa in treating symptomatic endometriosis.

A recent prospective, randomized, controlled clinical trial compared the efficacy of the levonorgestrel-releasing intrauterine system (LNG-IUS; Mirena) with a depot formulation of a GnRHa in the control of endometriosis-related chronic pelvic pain (CPP) in patients with severe endometriosis[50]. Both treatment modalities showed comparable effectiveness in the treatment of CPP-related endometriosis. Among the additional advantages of the LNG-IUS is the fact that it does not provoke hypoestrogenism and requires only one medical intervention (for its introduction) every 5 years. This device could, therefore, become the treatment of choice for CPP-associated endometriosis in women who do not wish to conceive.

Conservative surgery

Conservative surgery has obvious advantages since, in theory, aims at preserving fertility. In 1975 Kistner[51] noted that approximately 40 to 50 per cent of patients who are desirous of childbearing and who have had conservative surgical treatment will become pregnant. Such pregnancy usually occurs within the first 24 months, although in a few patients, the delay may be of 3 or even 4 years. Kistner observed that pregnancy rates were influenced by 5 factors: the extent of disease; the age; the history of additional prior surgery for endometriosis; the duration of infertility before surgery; and the length of post-surgical follow up. To improve results, he advocated short post-operative periods of pseudo-pregnancy regimen induced by hormonal treatment (see above), if all areas of endometriosis cannot be excised. A few years later, Buttram[52] reported pregnancy rates of 73, 56 and 40 per cent respectively, for patients with mild, moderate and severe endometriosis. As surgery was most beneficial in the early post-operative period he recommended that, if medical suppressive therapy is to be used in conjunction with conservative surgery to enhance fertility, it should be instituted preoperatively rather than postoperatively.

Laparoscopy

New pelvic endoscopic techniques were introduced in gynaecology in the late 1940s. Culdoscopy was a new procedure for pelvic visualization in gynaecology and it was claimed that the procedure was invaluable in the investigation of pelvic tumours, small ovarian disease, endometriosis, ectopic pregnancy and especially helpful in the detailed study of primary and secondary sterility in females. Starting in 1967, Semm[53], transformed what was called at the time "peritoneoscopy" into modern laparoscopy by improving the optical system, removing the source of light from the abdominal cavity and creating an automatic control of gas insufflations into the abdomen. Technical improvements in laparoscopy quickly produced new information on endometriosis and expanded gynaecological applications of endoscopic surgery, to the extent that in the early 1970s leading gynaecologists in Europe and US concluded that laparoscopy is the preferred tool for diagnosis and surgery of endometriosis[54].

Clearly, endoscopic surgery represented a major departure from classic gynaecological surgery, especially when, in the early 1970s, endoscopic methods for haemostasis, ligature and suture during surgical pelviscopy were introduced. Further advances occurred when Nezhat *et al*[54] introduced carbon dioxide laser for the removal of endometriotic implants, excision of endometrioma capsules, and lysis of adnexal adhesions. In a series of 102 patients, they reported a pregnancy rate of 60 per cent within 24 months after laser surgery without additional hormonal therapy. Laparoscopic vaporization with carbon dioxide laser became a popular treatment modality for endometriosis-associated infertility, yet little data existed regarding the effectiveness of such an approach. In the 1980s, laparoscopic surgery became also the preferred approach for the treatment of ovarian endometrioma and infiltrating *cul-de-sac* endometriosis[56].

In 1994 Adamson and Pasta[57] carried out a meta-analysis and concluded that either no treatment or surgery is superior to medical treatment for minimal and mild endometriosis associated with infertility; in addition, in moderate and severe disease, surgery seems to yield comparable results with both operative laparoscopy or laparotomy. They recommended that prospective, randomized trials be performed to confirm these findings, but unfortunately, in surgery prospective, double-blind randomized studies are extremely difficult to perform. One such study was published in 1994 by Sutton *et al*[58] who concluded that laser laparoscopy was a safe, simple and effective treatment in alleviating pain in women with stage I, II and III endometriosis. In 1997, Marcoux *et al*[59] published a second randomized, controlled trial and concluded that laparoscopic surgery enhanced fecundity in infertile women with minimal and mild endometriosis. In conclusion, oral contraceptives, androgenic agents, oestrogens, progestins, antigonadotropic agents, antiprogestins and GnRHa have all been used successfully, although at the present time, the latter preparations are the most popular medical therapy for endometriosis. Leuprolide acetate, goserelin acetate, and nafarelin acetate are all effective agents. Surgical therapy is appropriate, especially for advanced stages of the disease. Laparoscopy is an effective surgical approach with the goal of excising visible endometriosis in a haemostatic fashion. Since endometriosis is a chronic condition, it is not uncommon for recurrences to occur. While endometriosis remains an enigmatic disease, the introduction of new pharmacologic agents, such as GnRHa and newer endoscopic methods of surgical treatment, have facilitated and improved the overall management of this disease.

In search of the pathogenesis

As already mentioned, following Sampson's enunciation of his "retrograde menstruation" theory[7] in the late twenties, endometriosis was divorced from adenomyosis and research became focused on how fragments of menstrual endometrial tissue carried by menstruation could implant on peritoneal surfaces and invade the underlying tissues.

Peritoneal environment

While early studies concentrated on the histogenesis of endometriotic lesions, in the 1980s attention began to focus on changes in the peritoneal, ovarian and uterine microenvironments in association with endometriosis. This was made possible thanks to the increasing use of laparoscopy for tubal sterilization, or the exploration of infertility: peritoneal fluid could easily be collected for research purposes and carefully analysed. This resulted in an avalanche of publications on the pathogenesis of endometriosis.

A first major finding was an increased activation of peritoneal macrophages in infertile women with mild endometriosis[60]. Halme *et al*[61] demonstrated that retrograde menstruation through the fallopian tubes into the peritoneal cavity is a very common physiologic event in most menstruating women with patent tubes

and, therefore, additional factors must be implicated in the genesis of endometriosis.

Dmowski and collaborators[62] were the first to advocate, in 1981, a role of the immune system in the pathogenesis of endometriosis. This Group demonstrated that rhesus monkeys with spontaneous endometriosis have an altered cellular immune response to autologous antigens, suggesting that endometrial cells translocated from their normal location may implant only in women with specific alterations in cell-mediated immunity. Haney *et al*[63] in 1981 demonstrated that endometriosis is accompanied by a chronic intraperitoneal inflammatory process, as shown by the increased number of peritoneal macrophages in infertile women with endometriosis compared with normal women or women with other causes of infertility. Since peritoneal fluid is in contact with peritoneal endometrial implants, as well as with the tubal microenvironment in which fertilization occurs, subtle alterations of this fluid and/or its cellular constituents might adversely influence reproduction independent of any anatomical compromising of ovaries or oviducts.

A multitude of findings suggested that endometriosis is associated with abnormal host response, embryo toxicity, natural killer activity, macrophage recruitment and activation, up-regulation of growth factors, angiogenesis and cell adhesion molecules, all of which may play a role in the pathogenesis and development of pelvic endometriosis and infertility. Endometriosis is associated with sterile low-grade inflammation, increased concentrations of activated macrophages and many of their secretions, such as cytokines, growth factors and angiogenic factors. It has also been speculated that the type of cellular lesion, hereditary and immunological environments and local hormone concentrations in the ovary and peritoneal fluid, may determine the manifestation of the disease as cystic ovarian endometriosis, deep endometriosis or adenomyosis externa, and whether the latter is associated with adhesions.

Endometrial dysfunctions

In the late nineties, a number of reports were published suggesting that endometriosis is associated with endometrial and myometrial dysfunctions. Patients with severe endometriosis were found to have defects in endometrial receptivity including aberrant integrin expression, possibly causing decreased cycle fecundity due to defects in endometrial receptivity[64]. Both eutopic endometrial tissues and endometriotic implants from patients with endometriosis are biochemically different from normal endometrial tissues of disease-free women. Aromatase expression in eutopic endometrial tissues from patients with endometriosis may be related to the capability of implantation of these tissues on peritoneal surfaces. On the other hand, vascular endothelial cell growth factor (VEGF) may be important for both physiological and pathological angiogenesis of human endometrium, as it is an oestrogen-responsive angiogenic factor that varies throughout the menstrual cycle and is elevated in women with endometriosis[65]. VEGF content was found to be higher in the eutopic glandular epithelium of women with endometriosis during the late secretory phase, possibly suggesting a more likely tendency to implant[66]. Similarities in VEGF content were observed in the glandular epithelium of the eutopic endometrium of women with endometriosis and the so-called "red lesions", suggesting that endometriosis probably arises from the peritoneal seeding of viable endometrial cells during retrograde menstruation; these "red lesions" can be then considered as the first stage of implantation.

In a review published in 1997, Ryan and Taylor[67] concluded that three general concepts steered during the late 20th century research in endometriosis. First, there is evidence of a local peritoneal inflammatory process, including the findings of elevated cytokine and growth factor concentrations in peritoneal fluid of affected patients. Second, there is a role for angiogenic factors in the establishment of ectopic implants. Third, there is evidence for biochemical differences of eutopic and ectopic endometrium in endometriosis patients, which may contribute to both the pathogenesis and sequelae of this disorder.

Modified immunological milieu

Some twenty years ago, Dmowski and his group[68] were the first to show the existence of a deficient cellular immunity in women with endometriosis. Since then, in women with endometriosis a number of functional changes have been observed in several immunologic components of the peritoneal fluid, as well as in the serum and the hypothesis has been advanced that deficient immunity against retrograde endometrium during menstruation may be involved in the pathophysiology of the disease[69]. In addition, during endometrial cells implantation, proliferation and the formation of endometriotic lesions a wide pattern of cytokines is involved, playing a critical role in decreased immunologic surveillance, recognition and destruction of ectopic endometrial cells and possible

facilitation of the implantation of ectopic endometrial tissues.

Braun and Dmowski[70] have subsequently proposed that endometriosis may be the consequence of an immunological selection process according to which endometrial cells inherently resistant to apoptosis and immune-mediated elimination, acquire the capacity to utilize the products of an activated immune system to establish ectopic foci of the disease. In addition, cyclical inflammatory/immune cell stimulation that fails to eliminate ectopic endometrial implants results in progressive immunological derangement. Indeed, alterations in both cell-mediated and humoral immunity contribute to the pathogenesis of endometriosis through an increased number and activation of peritoneal macrophages, decreased T-cell and natural killer cell cytotoxicities. These alterations lead to an inadequate removal of ectopic endometrial cells from the peritoneal cavity[71]. It is a fact that the endometrium of women with endometriosis responds differentially to specific inflammatory cytokines by production of endometrial haptoglobulin. Upregulation of this haptoglobulin disrupts normal endometrial function and may facilitate the pathogenesis of endometriosis[72]. It seems likely that unbalanced chemokine expression contributes to the genesis of endometriosis and it is well known that chemokines regulate leukocyte migration and function and display specific roles in endometrial angiogenesis, apoptosis, proliferation, and differentiation[73].

Menstrual preconditioning and deep placentation

In a study of mothers 13 to 24 years old, Fraser *et al*[74] found that a younger age conferred an increased risk of adverse pregnancy outcomes, as manifested by lower birth weight, premature delivery and small for gestation age, that was independent of important confounding socio-demographic factors. On the other hand, the number of peritoneal areas involved in endometriosis seems to increase during the adolescence, but no longer after the early twenties[75]. The data are compatible with the menstruation preconditioning hypothesis put forward by Brosens *et al*[76] and may explain the decrease in the risk of defective deep placentation and, in the absence of pregnancy, an increase in the risk of peritoneal endometriosis.

Menstruation and pregnancy are both inflammatory events, albeit of very different magnitudes. In addition, both events are associated with variable degrees of uterine free radical production, oxidative stress, ischaemia-reperfusion injury, vascular remodelling, and angiogenesis. Therefore, it seems not only plausible but also likely that cyclic endometrial remodelling and menstruation precondition the human uterus for pregnancy. The term "preconditioning" refers to the paradoxical, yet ubiquitous, biological phenomenon that a brief exposure to a harmful stimulus at a dose below the threshold for tissue injury provides robust protection against, or tolerance to, the injurious effects of a subsequent more severe insult. In recent years, the mechanisms underpinning preconditioning have been widely studied because of its therapeutic potential in preventing cardiac or cerebral injury in different clinical settings. Notably, reactive oxygen species production, activation of redox-sensitive signalling pathways, expression of angiogenic factors such as VEGF, and resistance to cell death are major effectors in the process of preconditioning[77], all of which are highly regulated in the endometrium in response to hormonal signalling and perturbed in the presence of endometriosis.

Thus, it is tempting to speculate that endometriosis is primarily a disease of exaggerated endometrial preconditioning, which not only confers protection against hyper-inflammation and oxidative stress associated with pregnancy, but also endows endometrial cells with the mechanisms to survive in unfavourable ectopic locations. Although direct proof of cyclic menstrual preconditioning is as yet lacking, it is striking that the junctional zone myometrium is significantly thicker on T2-weighted magnetic resonance imaging in patients with endometriosis when compared with age-matched control subjects[78]. Power Doppler ultrasound studies have also shown that endometriosis is associated with increased endometrial-subendometrial blood flow during the late secretory phase of the cycle[79]. Perhaps the most compelling evidence for cyclic endometrial preconditioning comes from the observation that stromal cells purified from eutopic endometrial biopsy specimens from patients with and without endometriosis exhibit different responses to a decidualizing stimulus, even after prolonged culture[80]. Such sustained reprogramming of cellular responses likely involves epigenetic changes like DNA methylation or post-translational histone tail modifications. That this is indeed the case is substantiated by experiments in the baboon model, where induction of endometriosis and chronic inflammation resulted in a gradual decrease – over 6 to 12 months – in endometrial expression of a homeobox transcription factor involved in endometrial development named HOXA-10[81].

Endometriosis and adenomyosis

Following two decades during which adenomyosis and endometriosis were considered as totally separate entities, in 1948 Novak and de Lima[82] linked them again hypothesising a specific local hormonal reaction in ectopic endometrium. They wrote: "one cannot resist the feeling that there is some common denominator between endometrial hyperplasia and adenomyosis, and possibly also pelvic endometriosis". Their statement was based on the observation that, of a total of 134 women with adenomyosis, endometriosis was also present in 42 (31.3%).

Sixty years later, Leyendecker *et al*[83] proposed a new unified concept of the physiopathology of the two conditions, describing a physiological model leading to the local production of oestrogens at the level of both eutopic and ectopic endometria in affected women. They critically analysed uterine morphology and function in normally fertile women and in affected subjects, using modern diagnostic imaging techniques and found circumstantial evidence suggesting that endometriosis and adenomyosis are caused by trauma. In other words, chronic uterine peristaltic activity or phases of hyper-peristalsis induce, at the endometrial-myometrial interface, micro traumas with the activation of the mechanism of 'tissue injury and repair', followed by the local production of oestrogen; in due course, this results in permanent hyper-peristalsis and a self-perpetuation of the disease process.

Leyendecker and his group therefore believe that adenomyosis and endometriosis are "primarily diseases of the archimetra" (the Junctional Zone myometrium) and that there is a dislocation of the basal endometrium (with stem cell character and therefore the ability to resume embryonic growth), resulting in the ectopic formation of all "archimetrial" components such as epithelium, stroma, and paramesonephric smooth muscle cells[84].

This theory gives primary importance to the Junctional Zone myometrium, but fails to take into consideration the pivotal role of an altered endometrium in creating the conditions for the development of adenomyosis and endometriosis. Today we are proposing a new theory, namely that adenomyosis and endometriosis are phenotypes of the same disorder: the "Endometrium and Inner Myometrium Dysfunction Syndrome" (EIMDS). According to this theory, the endometrium and inner myometrium represent an important regional unit in the uterus with a key role in human reproduction. The region represents a complex structure of several polarized microenvironments controlled by sex steroid hormones, aggregates of leukocytes as local mediators to regulate sperm transport, implantation and menstruation, and in pregnancy to regulate interaction with interstitial and endovascular trophoblast invasion to achieve deep placentation. While the sequence of events is still debated there are multiple aetiologies involved in the new endometrium and inner myometrium dysfunction syndrome. Prolonged preclinical stage, involvement of different reproductive mechanisms and predisposition to a particular presentation influenced by gene-environment interaction and/or complex gene-gene interactions involving different genotypes result in clinical manifestations which are often adaptive in nature. A range of aetiologies for the EIMD syndrome has been described such as production of oestrogen at the level of endometrium and ectopic endometrial lesions, chronic uterine peristaltic activity or phases of hyperperistalsis, increased invasiveness of the basal endometrium, progesterone resistance, and defective trophoblast invasion. Interestingly enough, in addition to the dislocation of the endometrial tissue, the dysfunction results in a spectrum of pregnancy disorders involving infertility, miscarriage and major pregnancy complications such as preterm rupture of the membranes, preterm birth, small for gestation age and pre-eclampsia.

Prevention of endometriosis in adolescence

A true prevention of the consequences of endometriosis is based on increased awareness of the disease in adolescence. While the true incidence of endometriosis in young women is difficult to quantify and estimates vary among different studies**,** a majority of adult women with endometriosis report the onset of pelvic symptoms before age 20. In adolescents, however, endometriosis is predominantly represented by subtle, red and clear peritoneal lesions, which are more hormone-dependent and versatile than the typical dark pigmented scarred lesion or the deep, adenomyotic or cystic lesion of the adult[85-87] As a consequence, while pregnancy during adolescence is likely to play a role in the prevention or regression of endometriosis, adolescence is likely to offer a window of opportunity for hormonal manipulation of endometriosis[88].

Current recommendations by the American College of Obstetrics and Gynecology[87] on the adolescent presenting with dysmenorrhoea include

initiation of treatment with non-steroidal anti-inflammatory medications and cyclic combined oral contraceptives (COCs). If symptoms of dysmenorrhoea continue beyond 3 months despite these interventions, adolescents should be offered a diagnostic laparoscopy. Cyclic use of COCs is recommended to avoid regression of implants at the time of laparoscopy. The use of hydroflotation is also recommended to improve the visualization of features of subtle lesions on the ovary or peritoneum such as focal micro vascularisation and free-floating adhesions[89,90]. Typical endometriosis including extensive pelvic adhesions, ovarian endometrioma and rectovaginal adenomyosis is rare in the adolescent with a normal genital tract. Adolescents found to have endometriosis should either be treated through surgical ablation, resection, or laser treatment. All adolescents who are treated at laparoscopy and histologically confirmed with endometriosis should be placed on suppressive therapy to inhibit further disease progression until they reach an age in which they desire pregnancy. The first line of recommendation for patients under the age of 16 is continuous COCs. For patients over age 16, either continuous COCs or a GnRH agonist can be considered. GnRH agonists are generally not recommended for patients under the age of 16 given concerns regarding bone mineralization.

While these recommendations can be suitable for management of severe endometriosis in the young adult, it can be questioned whether it is wise to start in the adolescent a "lesion-oriented" surgical management when lesions are subtle and versatile and likely to respond by extensive decidualization and apoptosis in response to a pseudopregnancy regimen. Experience shows that early surgery is likely to be repeated in more than 50 per cent of the cases[91]. The prevalence of "pathology-confirmed endometriosis" is indeed relatively low among multiparous women confirming the protective effect of multiple full-term pregnancies[92,93]. Therefore, rather than surgery, a "symptom-oriented" treatment based on 6-month pseudopregnancy regimen, can be a first line recommendation to start at the earliest stage that endometriosis is suspected. Criteria have been established for the presumptive diagnosis of endometriosis in the adolescent[94].

Because the Cochrane review[44] concluded that there remains a paucity of information regarding the long-term benefits of COCs in the treatment of endometriosis, prospective randomized studies using a pseudo-pregnancy scheme should be performed in adolescents with the presumptive clinical diagnosis of early endometriosis. In the absence of severe endometriosis a "problem-orientated" rather than "lesion-orientated" treatment may be indicated unless there is a specific indication for laparoscopic surgery.

References

1. Hudelist G, Keckstein J, Wright JT. The migrating adenomyoma: past views on the etiology of adenomyosis and endometriosis. *Fertil Steril* 2009; *92* : 1536-43.
2. Benagiano G, Brosens I. Who identified endometriosis? *Fertil Steril* 2011; *95* : 13-6.
3. Batt RE. Emergence of endometriosis in North America: a study in the history of ideas. *Ph.D. dissertation.* Buffalo (SA): University of Buffalo, State University of New York;, 2008. p. 109-13.
4. Cullen TS. *Adenomyoma of the Uterus*. Philadelphia: W.B. Saunders Co, 1908.
5. Cullen TS. The distribution of adenomyomatas containing uterine mucosa. *Arch Surg* 1921; *1* : 215-83.
6. Sampson JA. Peritoneal endometriosis due to the menstrual dissemination of endometrial tissue into the peritoneal cavity. *Am J Obstet Gynecol* 1927; *14* : 422-69.
7. Sampson JA. Perforating hemorrhagic (chocolate) cysts of the ovary. *Arch Surg* 1921; *3* : 245-323.
8. Hill LL Jr. Aberrant endometrium. *Am J Surg* 1932; *18* : 303-21.
9. Vasquez G, Cornillie F, Brosens IA. Peritoneal endometriosis: scanning electron microscopy and histology of minimal pelvic endometriotic lesions. *Fertil Steril* 1984; *42* : 696-703.
10. Murphy AA, Green WR, Bobbie D, dela Cruz ZC, Rock JA. Unsuspected endometriosis documented by scanning electron microscopy in visually normal peritoneum. *Fertil Steril* 1986; *46* : 522-4.
11. Wiegerinck MA, Van Dop PA, Brosens IA. The staging of peritoneal endometriosis by the type of active lesion in addition to the revised American Fertility Society classification. *Fertil Steril* 1993; *60* : 461-4.
12. Jenkins S, Olive L, Haney AF. Endometriosis: pathogenetic implications of the anatomic distribution. *Obstet Gynecol* 1986; *67* : 335-8.
13. Jansen RP. Minimal endometriosis and reduced fecundability: prospective evidence from an artificial insemination by donor program. *Fertil Steril* 1986; *46* : 141-3.
14. Jansen RPS, Russell P. Nonpigmented endometriosis: clinical, laparoscopic, and pathologic definition. *Am J Obstet Gynecol* 1986; *155* : 1154-9.
15. Stripling MC, Martin DC, Chatman DL, Vander Zwaag R, Poston WM. Subtle appearance of pelvic endometriosis. *Fertil Steril* 1988; *49* : 427-31.
16. Martin DC, Hubert GD, Van der Zwaag R, El-Zeky FA. Laparoscopic appearances of peritoneal endometriosis. *Fertil Steril* 1989; *51* : 63-7.
17. Evers JL, Land JA, Dunselman GA, van den Linden PJ, Hamiltion JC. 'The Flemish Giant', reflections on the defense

against endometriosis, inspired by Professor Emeritus Ivo A. Brosens. *Eur J Obstet Gynecol Reprod Biol* 1998; *81* : 253-8.

18. Cornillie FJ, Oosterlynck D, Lauweryns JM, Koninckx PR. Deeply infiltrating pelvic endometriosis: histology and clinical significance. *Fertil Steril* 1990; *53* : 978-83.
19. Koninckx PR, Meuleman C, Demeyere S, Lesaffre E, Cornillie FJ. Suggestive evidence that pelvic endometriosis is a progressive disease, whereas deeply infiltrating endometriosis is associated with pelvic pain. *Fertil Steril* 1991; *55* : 759-65.
20. Koninckx PR, Martin DC. Deep endometriosis: a consequence of infiltration or retraction or possibly adenomyosis externa? *Fertil Steril* 1992; *58* : 924-8.
21. Chapron C, Dumontier I, Dousset B, Fritel X, Tardif D, Roseau G, *et al.* Results and role of rectal endoscopic ultrasonography for patients with deep pelvic endometriosis. *Hum Reprod* 1998; *13* : 2266-70.
22. Fedele L, Bianchi S, Portuese A, Bomuto F, Dorta M. Transrectal ultrasonography in the assessment of rectovaginal endometriosis. *Obstet Gynecol* 1998; *91* : 444-8.
23. Hughesdon PE. The structure of endometrial cysts of the ovary. *J Obstet Gynaecol Br Emp* 1957; *64* : 481-7.
24. Brosens IA, Puttemans PJ, Deprest J. The endoscopic localization of endometrial implants in the ovarian chocolate cyst. *Fertil Steril* 1994; *61* : 1034-8.
25. Meigs JV. Endometriosis; etiologic role of marriage age and parity: conservative treatment. *Obstet Gynecol* 1953; *2* : 46-53.
26. Kistner RW. The use of newer progestins in the treatment of endometriosis. *Am J Obstet Gynecol* 1958; *75* : 264-78.
27. Garcia CR, Pincus G, Rock J. Effects of certain 19-nor steroids on the human menstrual cycle. *Science* 1956; *124* : 891-3.
28. Geist SH, Salmon UJ. Androgen therapy in gynecology. *JAMA* 1941; *117* : 2207-15.
29. Miller JR. Preoperative use of testosterone propionate as an aid to surgical treatment of endometriosis. *JAMA* 1944; *125* : 207-8.
30. Kempers RD, Dockerty MB, Hunt AB, Symmonds RE. Significant post menopausal endometriosïs. *Surg Gynecol Obstet* 1960; *111* : 348-56.
31. Legros R, Fain-Giono J. Paramenopausal and postmenopausal endometriosis. A propos of 20 cases in a series of 351 with endometriosis. *Rev Fr Gynécol Obstet* 1973; *68* : 25-33.
32. Bergqvist IA. Hormonal regulation of endometriosis and the rationales and effects of gonadotrophin-releasing hormone agonist treatment: a review. *Hum Reprod* 1995; *10* : 446-52.
33. Pinkert TC, Catlow CE, Straus R. Endometriosis of the urinary bladder in a man with prostatic carcinoma. *Cancer* 1979; *43* : 1562-7.
34. Doty DW, Gruber JS, Wolf GC, Winslow RC. 46 xy pure gonadal dysgenesis: report of 2 unusual cases. *Obstet Gynecol* 1980; *55* (Suppl 3) : 61S-65S.
35. Peress MR, Sosnowski JR, Mathur RS, Williamson HO. Pelvic endometriosis and Turner's syndrome. *Am J Obstet Gynecol* 1982; *144* : 474-6.
36. Binns BA, Banerjee R. Endometriosis with Turner's syndrome treated with cyclical oestrogen/progestogen. Case report. *Br J Obstet Gynaecol* 1983; *90* : 581-2.
37. Bösze P, Gaál M, Tóth A, Ĺászló J. Endometriosis and streak gonad syndrome. *Arch Gynecol* 1987; *240* : 253-4.
38. Rosenfeld DL, Lecher BD. Endometriosis in a patient with Rokitansky-Kuster-Hauser syndrome. *Am J Obstet Gynecol* 1981; *139* : 105.
39. Karnaky KJ. The use of' stilbestrol for endometriosis; preliminary report. *Southern Med J* 1948; *41* : 1109-11.
40. Greenwald P, Barlow JJ, Nasca PC, Burnett WS. Vaginal cancer after maternal treatment with synthetic estrogens. *N Engl J Med* 1971; *285* : 390-2.
41. Andrews MC, Andrews WC, Strauss AF. Effects of progestin-induced pseudopregnancy on endometriosis: clinical and microscopic studies. *Am J Obstet Gynecol* 1959; *78* : 776-85.
42. Thomas HH. Conservative treatment of endometriosis. Use of long-acting ovarian steroid hormones. *Obstet Gynecol* 1960; *15* : 498-503.
43. Moghissi KS. Treatment of endometriosis with estrogen-progestin combination and progestogens alone. *Clin Obstet Gynecol* 1988; *31* : 823-8.
44. Davis L, Kennedy SS, Moore J, Prentice A. Modern combined oral contraceptives for pain associated with endometriosis *Cochrane Database Syst Rev* 2007; (3) : CD001019 .
45. Greenblatt RB, Dmowski WP, Mahesh VB, Scholer HF. Clinical studies with an antigonadotropin-Danazol. *Fertil Steril* 1971; *22* : 102-12.
46. Fedele L, Bianchi S, Viezzoli T, Arcaini L, Candiani GB. Gestrinone versus danazol in the treatment of endometriosis. *Fertil Steril* 1989; *51* : 781-5.
47. Venturini PL, Bertolini S, Brunenghi MC Daga A, Fasce V, Marcenaro A, *et al.* Endocrine, metabolic and clinical effects of gestrinone in women with endometriosis. *Fertil Steril* 1989; *52* : 589-95.
48. Ulmann A, Tcutsch G, Philibert D. RU 486. *Sci Am* 1990; *262* : 42-8.
49. Surrey ES. Gonadotropin-releasing hormone agonist and add-back therapy: What do the data show? *Curr Opin Obstet Gynecol* 2010; *22* : 283-8.
50. Petta CA, Ferriani RA, Abrao MS, Hassan D, Rosa E, Silva JC, *et al.* Randomized clinical trial of a levonorgestrel-releasing intrauterine system and a depot GnRH analogue for the treatment of chronic pelvic pain in women with endometriosis. *Hum Reprod* 2005; *20* : 1993-8.
51. Kistner RW. Management of endometriosis in the infertile patient. *Fertil Steril* 1975; *26* : 1151-66.
52. Buttram VC Jr. Conservative surgery for endometriosis in the infertile female: a study of 206 patients with implications for both medical and surgical therapy. *Fertil Steril* 1979; *31* : 117-23.
53. Semm K. Laparoscopy in gynecology. *Geburtshilfe Frauenheilkd* 1967; *27* : 1029-42.

54. Cohen MR. Surgical laparoscopy in infertility. *J Reprod Med* 1975; *15* : 51-3.

55. Nezhat C, Crowgey SR, Garrison CP. Surgical treatment of endometriosis via laser laparoscopy. *Fertil Steril* 1986; *45* : 778-83.

56. Reich H, McGlynn F. Treatment of ovarian endometriomas using laparoscopic surgical techniques. *J Reprod Med* 1986; *31* : 577-84.

57. Adamson GD, Pasta DJ. Surgical treatment of endometriosis-associated infertility: meta-analysis compared with survival analysis. *Am J Obstet Gynecol* 1994; *171* : 1488-505.

58. Sutton CJ, Ewen SP, Whitelaw N, Haines P. Prospective, randomized, double-blind, controlled trial of laser laparoscopy in the treatment of pelvic pain associated with minimal, mild, and moderate endometriosis. *Fertil Steril* 1994; *62* : 696-700.

59. Marcoux S, Maheux R, Bérubé S. Laparoscopic surgery in infertile women with minimal or mild endometriosis. Canadian Collaborative Group on Endometriosis. *N Engl J Med* 1997; *337* : 217-22.

60. Halme J, Becker S, Hammond MG, Raj MH, Raj S. Increased activation of pelvic macrophages in infertile women with mild endometriosis. *Am J Obstet Gynecol* 1983; *145* : 333-7.

61. Halme J, Hammond MG, Hulka JF, Raj SG, Talbert LM. Retrograde menstruation in healthy women and in patients with endometriosis. *Obstet Gynecol* 1984; *64* : 151-4.

62. Dmowski WP, Steele RW, Baker GF. Deficient cellular immunity in endometriosis. *Am J Obstet Gynecol* 1981; *141* : 377-83.

63. Haney AF, Muscato JJ, Weinberg JB. Peritoneal fluid cell populations in infertility patients. *Fertil Steril* 1981; *35* : 696-8.

64. Lessey BA, Castelbaum AJ, Sawin SW, Buck BA, Schinnan R, Bilker W, *et al.* Aberrant integrin expression in the endometrium of women with endometriosis. *J Clin Endocrinol Metab* 1994; *79* : 643-9.

65. Shifren JL, Tseng JF, Zaloudek CJ, Ryan IP, Meng YG, Ferrara N, *et al.* Ovarian steroid regulation of vascular endothelial growth factor in the human endometrium: implications for angiogenesis during the menstrual cycle and in the pathogenesis of endometriosis. *J Clin Endocrinol Metab* 1996; *81* : 3112-8.

66. Donnez J, Smoes P, Gillerot S, Casanas-Roux F, Nisolle M. Vascular endothelial growth factor (VEGF) in endometriosis. *Hum Reprod* 1998; *13* : 1686-90.

67. Ryan IP, Taylor RN. Endometriosis and infertility: new concepts. *Obstet Gynecol Surv* 1997; *52* : 365-71.

68. Dmowski WP, Steele RW, Baker GF. Deficient cellular immunity in endometriosis. *Am J Obstet Gynecol* 1981; *141* : 377-83.

69. Barcz E, Kamiński P, Marianowski L. Role of cytokines in pathogenesis of endometriosis. *Med Sci Monit* 2000; *6* : 1042-6.

70. Braun DP, Dmowski WP. Endometriosis: abnormal endometrium and dysfunctional immune response. *Curr Opin Obstet Gynecol* 1998; *10* : 365-9.

71. Ulukus M, Arici A. Immunology of endometriosis. *Minerva Ginecol* 2005; *57* : 237-48.

72. Sharpe-Timms KL, Nabli H, Zimmer RL, Birt JA, Davis JW. Inflammatory cytokines differentially up-regulate human endometrial haptoglobin production in women with endometriosis. *Hum Reprod* 2010; *25* : 1241-50.

73. Guo SW. Nuclear factor-κB (NF-κB): an unsuspected major culprit in the pathogenesis of endometriosis that is still at large? *Gynecol Obstet Invest* 2007; *63* : 71-97.

74. Fraser AM, Brockert JE, Ward RH. Association of young maternal age with adverse reproductive outcomes. *N Engl J Med* 1995; *332* ; 1113-7.

75. Redwine DB. Age-related evolution in color appearance of endometriosis. *Fertil Steril* 1987; *48* : 1062-3.

76. Brosens JJ, Parker MG, McIndoe A, Pijnenborg R, Brosens IA. A role for menstruation in preconditioning the uterus for successful pregnancy. *Am J Obstet Gynecol* 2009; *200* : 615. e1-6.

77. Otani H. Ischemic preconditioning: from molecular mechanisms to therapeutic opportunities. *Antioxid Redox Signal* 2008; *10* : 207-47.

78. Brosens JJ, Barker FG, De Souza NM. Myometrial zonal differentiation and uterine junctional zone hyperplasia in the non-pregnant uterus. *Hum Reprod Update* 1998; *4* : 496-502.

79. Xavier P, Beires J, Barros H, Martinez-de-Oliveira J. Subendometrial and intraendometrial blood flow during the menstrual cycle in patients with endometriosis *Fertil Steril* 2005; *84* : 52-9.

80. Klemmt PA, Carver JG, Kennedy SH, Koninchx PR, Mardon HJ, *et al.* Stromal cells from endometriotic lesions and endometrium from women with endometriosis have reduced decidualization capacity. *Fertil Steril* 2006; *85* : 564-72.

81. Kim JJ, Taylor HS, Lu Z, Ladhani O, Hastings JM, Jackson KS, *et al.* Altered expression of HOXA10 in endometriosis: Potential role in decidualization. *Mol Hum Reprod* 2007; *13* : 323-32.

82. Novak E, de Lima OA. A correlative study of adenomyosis and pelvic endometriosis, with special reference to the hormonal reaction of ectopic endometrium. *Am J Obstet Gynecol* 1948; *56* : 634-44.

83. Leyendecker G, Wildt L, Mall G. The pathophysiology of endometriosis and adenomyosis: tissue injury and repair. *Arch Gynecol Obstet 2009; 280* : 529-38.

84. Leyendecker G, Mall G, Noe M, *et al.* Dislocation of basal endometrium: A unifying concept of the development of endometriosis and adenomyosis. *Reproduktionsmedizin* 2003; *19* : 181-8.

85. Laufer MR, Goitein L, Bush M, Cramer DW, Emans SJ. Prevalence of endometriosis in adolescent girls with chronic pelvic pain not responding to conventional therapy. *J Pediatr Adolesc Gynecol* 1997; *10* : 199-202.

86. Kalu E, McAuley W, Richardson R. Teenagers, adolescents, endometriosis and recurrence: a retrospective analysis of recurrence following primary operative laparoscopy. *Gynecol Surg* 2008; *5* : 209-12.

87. Dovey S, Sanfilippo J. Endometriosis and the adolescent. *Clin Obstet Gynecol* 2010; *53* : 420-8.

88. Bandera CA, Brown LR, Laufer MR. Adolescents and endometriosis. *Clin Consult Obstet Gynecol* 1995; *7* : 200-8.

89. Laufer MR. Identification of clear vesicular lesions of atypical endometriosis: a new technique. *Fertil Steril* 1997; *68* : 739-40.

90. Brosens I, Gordts S, Campo R. Transvaginal hydrolaparoscopy but not standard laparoscopy reveals subtle endometriotic adhesions of the ovary. *Fertil Steril* 2001;: *75* : 1009-12.

91. Laufer MR. Current approaches to optimizing the treatment of endometriosis in adolescents. *Gynecol Obstet Invest* 2008; *66* (Suppl 1) : 19-27.

92. Cheong Y, Tay P, Luk F, Gan HC, Li TC, Cooke I. Laparoscopic surgery for endometriosis: How often do we need to re-operate? *J Obstet Gynaecol* 2008; *28* : 82-5.

93. Sangi-Haghpeykar H, Poindexter AN 3rd. Epidemiology of endometriosis among parous women. *Obstet Gynecol* 1995; *85* : 983-92.

94. Missmer SA, Hankinson SE, Spiegelman D, Barbieri RL, Malspeis S, Willett WG, *et al*. Reproductive history and endometriosis among premenopausal women. *Obstet Gynecol* 2004; *104* : 965-74.

Reprint requests: Dr Giuseppe Benagiano, Department of Gynaecology, Obstetrics & Urology, 'Sapienza' University of Rome, Italy
e-mail: Giuseppe.Benagiano@uniroma1.it