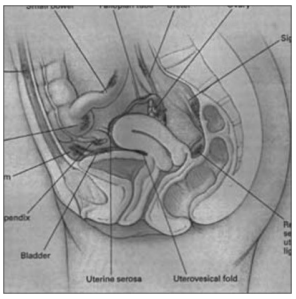
REVIEW PROF-870

ENDOMETRIOSIS



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ABSTRACT... rizk.diaa@uae.ac.ae Endometriosis is a common gynecological disorder but above all a confusing one. Despite massive volumes of literature, the cause is still unknown, none of the pathogenic mechanisms suggested convincingly explain symptomatology and indeed most lines of investigations have yielded contradictory results. Not surprisingly, therefore, there are many different approaches to treatment and attempts to provide rational therapy has not always been rewarded by permanent cure. Against this background of diagnostic and therapeutic dilemmas, endometriosis is likely to be encountered in general practice because the disease frequently affects other organ systems. Since the management of endometriosis is dependant on a basic understanding of the gynecological aspects of the disease, an attempt will be made to describe this condition here.

Keywords: Endometriosis, review.

INTRODUCTION

Endometriosis is defined as the presence of "functioning" endometrial tissue outside its normal situation, the uterine cavity[1]. This property of ectopic endometrium is responsible for the manifestations of the disease. Traditionally, endometriosis has been subdivided into two categories: adenomyosis (endometriosis interna); involving the myometrium and classical endometriosis (endometriosis externa); the term generally used to describe extra-uterine endometriosis[2]. Adenomyosis is a pure gynaecological disorder which is now considered a separate entity, both histogenetically and clinically, and will not be discussed further.

The actual prevalence of endometriosis is difficult to determine because laparoscopy or laparotomy is required to make a definitive diagnosis (vide infra). In a recent review, the estimated prevalence was at least 10% in women of childbearing age[3].

AETIOLOGY & HISTOGENESIS

The precise aetiology of endometriosis still remains unknown but there are three main hypothesis of histogenesis. The most popular, postulated by Sampson in 1922, ascribes endometriosis to the transport of viable endometrial fragments to intra-peritoneal sites by retrograde regurgitation through the fallopian tubes at the

time of menstruation[4]. In monkeys, endometriosis resulted after surgical inversion of the uterus such that menstruation occurred intra-peritoneally[5]. Endometriosis has also been described in young girls with lower genital tract atresia causing obstruction to the outflow of menstrual fluid and following accidental implantation of viable endometrial cells in abdominal incisions of caesarean section and hysterotomy or in episiotomy scars[6,7]. Retrograde menstruation however cannot explain extraperitoneal endometriosis and is said to be present in up to 90% of laparoscopies performed during the premenstrual period in normal women[3].

Alternatively, Ivanoff in 1898 and Meyer in 1903 independently suggested that because the genital canal mucosa arises from totipotent coelomic epithelium, repeated irritation of this epithelium by hormones or inflammation can induce metaplasia into endometrial tissue[8]. This could explain the development of endometriosis in nearly all ectopic sites because the coelomic epithelium may become isolated in unusual sites during development and would also explain urinary bladder endometriosis in male patients exposed to oestrogen[9]. More recently, the most likely stimulus to coelomic metaplasia was found to be the endometrial cells themselves reaching the susceptible tissue by retrograde menstruation[10].

The third mechanism, first noted by Halban in 1929, is by embolisation of endometrial fragments through myometrial lymphatic or blood vessels. Though this appears to be uncommon, vascular embolism may be responsible for extra-peritoneal endometriosis. It is often difficult to differentiate vascular involvement from tissue reaction artefact in histological specimens and therefore this mechanism is not generally accepted by pathologists[2].

Current thinking in endometriosis is directed towards possible genetic or immunological disturbances that might increase the susceptibility of some women to develop the disease. Hence, a decreased cellular immunity to the regurgitated endometriotic tissue at menstruation may increase the chances of implantation and the increased incidence of endometriosis in first degree relatives of patients, compared to control group, implicates a hereditary tendency[11,12].

In summary, there seems to be more than one mode of origin for endometriosis and a single theory cannot explain all cases. Retrograde endometrial implantation is a plausible explanation for intra-peritoneal endometriosis either on its own or by inducing coelomic metaplasia whereas vascular or lymphatic embolism might account for extra-peritoneal disease. Immunological or genetic factors can probably explain why some women develop endometriosis while others do not.

PATHOGENESIS

A key concept in the understanding and treatment of endometriosis is that female sex hormones are of central importance in maintenance of the disease[13]. This fact is highlighted by several clinical observations (Table-I). The development of endometriosis is extremely unlikely in the absence of endogenous ovarian function such as prior to the menarche, after the menopause or in patients with dysgenic gonads. However, it is possible in conditions following exogenous administration of female sex hormones[8]. The presence of endometrium or of menstruation is not essential provided that the ovaries are normal because endometriosis was reported in a woman with primary amenorrhoea associated with uterine agenesis, the disease most probably resulting from hormonally-induced coelomic metaplasia[14].

Endometriotic implants contain oestrogen and progesterone receptors but do not always respond to progesterone stimulation as the normally situated endometrium[13]. Nevertheless, either oestrogen or progesterone, alone or in combination, can support the growth of endometriotic tissue and a hypo-oestrogenic or a hypo-progestogenic environment results in endometrial atrophy. It must be remembered that only cyclic hormonal stimulation will have this effect since pregnancy or chronic non-cyclic administration of either oestrogen or progesterone, results in inhibition of ovulation and withdrawal of endogenous hormonal support which in turn causes atrophy of ectopic endometrium[1].

Table-I. Clinical evidence of the importance of female sex hormones in maintenance of endometriosis
1- Endometriosis is uncommon prior to the menarche
2- Endometriosis occurs infrequently after the menopause.
3- Endometriosis is common in women with uninterrupted cyclic menstruation for more than 5 years.
4- Ovarian ablation usually results in complete and prompt regression of ectopic endometrium.
5- Endometriosis is rarely observed in amenorrheic women and improves or stabilies during episodes of induced amenorrhea such in pregnancy.
6-Frequent pregnancies, if initiated early in reproductive life, appear to prevent the development of endometriosis.
7- Prolonged use of combined oral contraceptives decrease the risk of endometriosis.

In summary, endometriosis is a hormone-dependant disease seen during reproductive years and occasionally after the menopause as a result of hormone replacement therapy. Ectopic endometrium is inactivated by continuous exposure to female sex hormones.

PATHOLOGY

Endometriosis can affect almost any organ of the body but seldom affects extra-genital organs without genital involvement[8].Indeed, the spread of endometriotic process is unique and a "cancer-like" behavior is most descriptive[4]. The basic defect is repeated "ectopic" menstruation in closed spaces which is frequently terminated by fibrosis and scarring. Table II gives the most likely sites of endometriosis, including the most frequently affected extra-genital organs, and the relative distribution of endometriosis within these sites according to two of the largest surveys in the literature[5,8]. Endometriosis has been also described in the lung, pericardium, pleura and limbs[8].

In any site, endometriosis presents either diffusely or as isolated nodules of variable size; generally not surpassing a few millimeters in diameter; and appearance according to the phase of the menstrual cycle [2]. The Colour of these nodules vary from bluish to red or brown "powder burns" in the late stage of the disease with puckering of adjacent tissues[5]. The commonest site of endometriosis is the ovary and in up to 50 % of patients, both ovaries are involved (Table II). Ovarian endometriosis may be nodular on the surface or characteristically is cystic within the cortex. The cysts are usually multiple in the early stage but subsequently coalesce into a single large cyst. As a result of surface bleeding, the cyst becomes densely adherent to surrounding structures particularly the serosa of the sigmoid colon, the ileum or lateral pelvic peritoneum. The contents of the cyst are usually thick resembling a chocolate syrup and hence often termed a "chocolate cyst"[4].

Extra-genital endometriosis affects the serosal surface, penetrating endometrial tissue only rarely reaches mucosa, but hormonal influences culminate in intramural trapping of epithelial debris[15]. Reactive fibrosis causes dense adhesions between the affected organ and adjacent structures. Hyperplasia of smooth muscles within the visceral wall is superimposed and therefore the lesion often resembles carcinoma.

The basic structures seen microscopically in endometriosis are endometrial glands and stroma and more rarely smooth muscle fibres[2]. The glands are lined by columnar, cuboidal or flattened epithelial cells, which may be ciliated, as found in the normal endometrium. The presence of endometrial stroma is more important in establishing the diagnosis even without glands[1]. In more advanced lesions, the microscopic features are less distinct although the presence of hemosiderin-laden macrophage may be helpful.

Table-II. The relative distribution of endometriosis*	
Site	**Frequency**
Ovary	57.6%
Pouch of douglas	34.2%
Posterior broad ligament	29.6%
Utero-vaginal septum	25.4%
Fallopian tubes	14.6%
Recto-vaginal septum	12.6%
Sigmoid colon	3.4%
Cervix	2.6%
Vulva	1.4%
Vagina	1%
Appendix	0.8%
Umbilicus	0.8%
Inguinal canal	0.8%
Laparotomy or episitomy scars	0.8%
Urinary bladder	0.7%
Caecum	0.6%
Round ligaments	0.4%
Small intestine	0.2%
** The total is more than 100% because of the presence of multiple lesions in the same patient.*	

Malignant transformation of endometriosis is rare. Again, the ovary is the most common site with an estimated 150 or more reported cases[16]. In contrast, only 45 cases of malignant extra-genital endometriosis have been found, the majority affecting the colon, rectum or omentum and in general the frequency of malignancy in a given site parallels that of endometriosis in this location. Pathologically, all malignant lesions have been adenocarcinoma which may be of endometroid or clear-cell type, adenoacanthoma, endometrial stromal sarcoma or carcinosarcoma. An important finding is that in almost 13% of patients with extra-ovarian endometriosis, clear-cell adenocarcinoma of the ovary without prior ovarian endometriosis may be present[17].

In summary, the ovary is the commonest organ affected by endometriosis. The pelvic peritoneum, the utero-sacral ligaments, the fallopian tubes, the recto-vaginal septum and the sigmoid colon are also frequently involved. Endometriosis is a nodular lesion in most sites although in the ovary it is often cystic. Extra-genital endometriosis is virtually serosal or muscular and therefore could cause mechanical obstruction and diminished capacity of the affected organ. The macroscopic and histological appearance of endometriosis is usually characteristic. Malignant transformation of endometriosis is extremely rare although ovarian adenocarcinoma is more commonly found in patients with endometriosis.

CLINICAL PRESENTATION & DIAGNOSIS

Active endometriosis is found almost exclusively in women of reproductive age with a mean age of 25-29 years at diagnosis[3]. The consequent adhesive disease may however be manifested in post-menopausal women[18]. Age of first pregnancy seems important and therefore infertile women and those less likely to get pregnant at a young age such as white women in the higher social classes are particularly vulnerable[5].

Genital or reproductive tract endometriosis in the female is associated with a wide variety of symptoms, although in many patients the disease is asymptomatic[3]. Some symptoms may strongly suggest the presence of endometriosis but none are pathognomonic of the disorder and although their severity depends on the site of growth, it does not correlate with the extent or severity of the disease. Similarly, only rarely are the physical findings specific for endometriosis. The common clinical features of endometriosis are summarized in Table III. It can be seen that the cyclic nature of symptoms is a most helpful diagnostic clue and that rectal examination is more informative than the conventional vaginal examination in patients suspected of having endometriosis. In 10% of patients, an endometriotic ovarian cyst may rupture producing an acute abdominal

condition which necessitates urgent abdominal exploration and treatment[19].

Since the clinical presentation is not characteristic of endometriosis, the diagnosis can only be made definitely by visualization and/or biopsy of the lesion at laparoscopy or laparotomy[1]. The role of non invasive procedures such as ultrasound scanning and magnetic resonance imaging is limited to the detection of ovarian endometriosis but the appearance is not pathognomonic[3]. Likewise, elevated serum CA-125 levels have been described in women with endometriosis but the low sensitivity and specificity of this test precludes its use both for diagnosis and therapeutic monitoring.

Table: III. The clinical feature of endometriosis

Symptoms	Signs
1- Progressive pelvic pain and dysmenorrhoea prior to onset of menstruation.	1- Fixed tender adnexal mass.
2- Dyspareunia	2- Tender nodules on the utero-sacral ligaments.
3- Infertility.	3- Scarring and fixation of the uterus to the rectum.
4- Pre-menstrual spotting of blood.	4- Induration of the pouch of douglas.
5- Painful defection and cyclic rectal bleeding if the sigmoid colon is involved.	5- Unusual abdominal masses, e.g. swelling of the umbilicus or laparotomy scars.
6- Cyclic dysuria and occasional haematuria if the urinary bladder is involved.	
7- Other cyclic symptoms according to affected site, e.g. pain and bleeding from the umbilicus or laparotomy scars.	

Laparoscopic diagnosis of endometriosis requires a methodical approach with inspection of the lateral walls of the pelvis, all surfaces of both ovaries and tubes, both sides of the broad ligament and the bladder and bowel surfaces. Unless a double-puncture technique using a probe is employed, both ovaries can not be properly manipulated and inspection of the ovarian fossa ; the most likely site of pelvic endometriosis; is often missed[20]. Pelvic inspection is not always straightforward and requires experience to identify the appearances associated with acute endometriosis; the white opacified peritoneum, the red flame-like lesions and the circular peritoneal defects termed pseudo-pouches besides the more obvious and characteristic "burnt out" areas of chronic disease. Laparoscopic biopsy is therefore becoming more important in equivocal cases and is mandatory when an ovarian endometrioma is found in order to exclude malignancy[1].

Various classifications have been used to stage laparoscopic and/or operative findings in the pelvis because the extent of endometriosis determines the prognosis, particularly for fertility, following treatment and because laparoscopic re-evaluation is used increasingly to monitor such treatment. The most popular classification (The American Fertility Society 1985) employs a scoring system of the extent and size of endometriotic deposits and the associated adhesions on the pouch of Douglas and on each tube and ovary[21]. Unlike genital endometriosis, extra-genital disease has never been categorized into stages, although recently a classification based on the organ involved, the size of the lesion and whether such lesion is serosal, muscular or mucosal has been suggested[22].

In summary, endometriosis is a protein, not a precise, disease. The diagnosis should be suspected whenever a woman of child-bearing age has cyclic symptoms of whatever nature. A ruptured endometriotic ovarian cyst is an important cause of acute abdominal manifestations in women of reproductive age. Laparoscopy is the standard diagnostic method of genital endometriosis since the symptoms and signs are not pathognomonic.

TREATMENT

Treatment of endometriosis is primarily focused on hormonal alteration of the menstrual cycle either medically or surgically, used alone or in combination. Management is usually individualized taking into account a number of aspects which include the patient's age, future fertility wishes, extent of the disease and severity of symptoms[23]. The efficacy of any particular form of treatment is measured by:

1. Rate of symptomatic relief during and following therapy.
2. Degree of resolution of endometriotic implants at laparoscopy or laparotomy.
3. The rate of recurrence of the disease over a specified period of follow up.
4. Pregnancy rate in those patients where infertility is a factor.

The rationale of medical therapy used in endometriosis is that hypo-oestrogenism consequent upon pituitary inhibition will result in atrophy of endometriotic implants. Such effect is produced indirectly using female sex steroids "pseudo-pregnancy regime" or directly using anti-gonadotrophic drugs "pseudo-menopause regime". Different agents have been tried over the years, those currently used and their mode of administration is presented in Table-IV.

Table- IV. Hormonal treatment of endometriosis

Pseudo-pregnancy regimes	Pseudo-menopause regimes
1- Combined oestrogen-progestogen pills: any preparation can be given continuously for 6-9 months.	1- Danazol: 400-800mg orally / day for 6-12 months.
2- Oral progestogens, e.g. medroxy progesterone acetate: 30-50 mg/ day for 6-9 months	2- GnRH analogues: monthly intramuscular depot injections or implants or daily subcutaneous injections or nasal spray for 6 months only*.
3- Injectable progestogens, e.g. medroxy progesterone acetate in depot form: 150 mg by intramuscular injection every month-3 months for 6-9 months.	3- Gestrinone: 5 mg orally twice / week for 6-12 months.

*See text

All drugs must be administered continuously and will therefore result in hypo-oestrogenic amenorrhoea. Medical treatment is mainly indicated for symptomatic relief and is associated with a subjective and objective improvement of endometriosis in up to 60% of patients[3]. However, this treatment has not been effective in improving fertility and besides cost, dose-related side-effects are common and unacceptable to most patients[23]. Female sex hormones may cause breakthrough bleeding, nausea, fluid retention, depression, breast tenderness but most importantly progestogens can alter lipoproteins adversely. Hypo-estrogenic manifestations namely decreased breast size, hot flushes, irritability and mood changes can occur with all pseudo-menopause regimes but are more pronounced with gonadotropin hormone-releasing hormone (GnRH) analogues. Consequently, the use of these analogues in women may lead to a reduction in bone mass which despite being reversible, limits the duration of therapy. Danazol is androgenic and may also cause weight gain, muscle

cramps, oedema, rash, headaches and alterations in liver function and lipoprotein metabolism. Gestrinone is androgenic but has a longer half-life and causes less side-effects compared to danazol.

Surgical treatment of endometriosis is either conservative or radical. Conservative surgery performed either by laparoscopy or laparotomy is mainly considered when the ability to conceive is retained aiming to restore normal pelvic anatomy, conserve as much ovarian tissue as possible and eliminate all active disease. Amongst the various techniques used, laparoscopic surgery using the carbon dioxide or neodymium yttrium-alumium-garnet laser is claimed to be superior because the precision and vaporising effect of laser results in minimal fibrosis and scar tissue formation[20]. Like medical treatment, the results of conservative surgery has been disappointing both in terms of recurrence and pregnancy rates[3]. In fact, recurrence of endometriosis will eventually occur in up to 50% of cases following treatment modalities short of surgical castration[23].

The permanent cure of endometriosis will be only achieved by a radical surgical approach that entails bilateral oophrectomy often combined with salpingectomy and hysterectomy. Radical surgery is usually indicated nearer to the menopause but even in young women. Failure to castrate in the presence of extensive endometriosis in a futile attempt to preserve fertility is undoubtedly the most hazardous of all surgical attempts[1]. Equally important is that the endometriotic tissue is not likely to respond to hormonal manipulation at the stage of fibrosis and surgical excision is therefore safer in adhesive disease[24]. Because extensive pelvic endometriosis may present many technical problems, surgical principles in difficult cases include sharp dissection of adhesions, identification of the ureters, mobilization of the recto sigmoid and drainage[1]. Every attempt should be made to ensure complete removal of both ovaries, without which the disease will continue producing the ovarian remnant syndrome[24]. The post-operative use of hormone replacement therapy in young patients is controversial but may be safely prescribed provided that the pelvis is cleared of all visible endometriotic implants[1,8,20,23].

The combination of medical and surgical therapy was a logical extension of the potential advantages of either modality when used alone. On the whole, this therapy appears to be more effective in advanced or extensive disease although it is not clear whether medical treatment should be given before, after or both before and after operation[23]. Endometriosis-associated pelvic pain may respond to treatment with non-steroidal anti-inflammatory drugs without the resort to hormones and their inherent side-effects[3]. Laparoscopic utero-sacral nerve ablation or presacral neurectomy have also been used successfully.

In summary, endometriosis is treated by inhibition of ovarian function which is necessary for continued activity of the disease. In most cases, medical treatment is used first and usually results in temporary relief of symptoms at the expense of frequent side effects. Radical surgery is indicated in patients not responding to, or relapsing after, medical treatment with the aim of both total disease clearance and complete castration otherwise recurrence is inevitable. If this manoeuver is hazardous or impossible then hormonal treatment should be given post-operatively to control residual disease.

Conservative surgery is employed when infertility is the primary reason for treatment and the aim here, in contrast to radical surgery, is to preserve and restore reproductive function. Unfortunately, it is obvious that there is still no single operation or drug that is 100% effective for all patients with all stages of endometriosis.

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Learning is a fascinating experience

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