Modern Approaches to Endometriosis

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Preface

Endometriosis provides a unique clinical and scientific challenge. It is being diagnosed with increasing frequency and yet we are unsure of the significance of this in many patients. Its appearance varies from a tiny focus of disease to a potently destructive phenomenon. We are still unsure of the relative value of medical or surgical treatment. The pathogenesis and control of the cellular function of the disease provide many scientific problems. The presence of a comparative normal epithelium, namely endometrium, provides a unique research opportunity. It is probable that only through basic science research will we be able to solve the clinical dilemmas that endometriosis presents.

We felt that it was important to create a book that explored the important scientific and clinical problems. We therefore invited acknowledged experts from both Europe and the United States of America to review their fields. The purpose of these reviews is not only to provide a resource for clinicians and scientists but also to stimulate thought and new ideas for research and treatment. To fulfil that aim we have asked that the authors be more speculative than normal for a volume such as this. We thank them for responding to their task so well and hope that you will feel as stimulated by their efforts as we have been.

Eric Thomas **John Rock**

Section A
Scientific Aspects of Endometriosis

1
The pathogenesis and aetiology of endometriosis

A. F. Haney

INTRODUCTION

Despite being one of the most frequently encountered gynaecological diseases requiring surgery and medical treatment, the pathophysiology of endometriosis remains controversial. Since the turn of the century, there has been substantial interest in this fascinating disease, but relatively little objective scientific data are available concerning its cause, natural history and, particularly, its relationship to infertility. It has been estimated that approximately 10–15% of all premenopausal women have endometriosis, albeit not all the women are symptomatic[1]. As a consequence, this represents a major clinical problem and consumes a significant proportion of the health care expenditures for gynaecological care. Until a better understanding of the pathophysiology of this disease is reached, effective therapy and, hopefully, prevention will elude us. This article attempts to review the relevant literature regarding the pathophysiology of endometriosis in an effort to identify those areas that may prove profitable for future research endeavors.

INCIDENCE

In order to obtain the true incidence of endometriosis in a population of unselected premenopausal asymptomatic women, the most sensitive diagnostic test, i.e. laparoscopy, would need to be performed prospectively. Obviously, such a trial is unethical and will never be completed. An alternative, although less accurate, approach is to estimate the incidence of this disease in women presenting with one of several symptoms justifying laparoscopy, i.e. pelvic pain, dysmenorrhoea and infertility. There are basically three types of studies

in this category. The first is that group of trials using women undergoing gynaecological procedures in general and identifying the subset that have endometriosis. Approximately 10–15% of women undergoing diagnostic laparoscopy for some symptom have this diagnosis confirmed. The second group of studies involves women undergoing laparoscopies for tubal ligation. These are obviously fertile women and thus have some selection bias. The incidence of the disease has been estimated to be 2–5% in this population[2]. The last group of studies involves women undergoing laparoscopies for infertility. They carry the highest probability of having endometriosis, varying from 30% to 40%[2–4]. These wide ranges probably reflect the heterogeneous population studied with inherent selection bias, including presenting symptomatology, educational level, socioeconomic status, cultural attitudes towards medical care, contraceptive use and delayed childbearing. Despite these considerations, it seems reasonable to estimate a gross clinical incidence of endometriosis in an unselected population of premenopausal women of approximately 2–5%.

EPIDEMIOLOGY OF ENDOMETRIOSIS

In an attempt to understand the nature of this disease, the first logical step is to identify the population at risk for having endometriosis, as that should provide insights into the pathophysiology of the process. To some extent, the questions asked by the epidemiologist will reflect the current understanding of the disease. As a result, the historical development of our understanding of endometriosis contains the biases of the investigators at the time of the studies.

An example of this bias involves the originally identified racial preponderance of the disease in white women. The initial studies demonstrated that only rarely was the disease identified in black women, and consequently it was thought that endometriosis had a racial predilection[5,6]. Initially, the potential confounding variables such as the availability of health care, access to contraception, cultural patterns of childbearing, and the attitudes toward menses were not considered[7–9]. It is now known that these factors significantly influence the likelihood of developing this disease. Once these variables were controlled for, the difference in the frequency between caucasian and black patients disappeared[10–12]. The only documented racial predilection of endometriosis, given comparable cultural and socioeconomic status, is that of the Japanese. Japanese women have twice the incidence of the disease of caucasian women[9].

Another example involves the ascertainment bias of selection by presenting symptoms. If one simply selects those women with infertility[3,4], finding endometriosis is far more likely than in those women with more non-specific gynaecological signs or symptoms such as the presence of an adnexal mass, dyspareunia, dysmenorrhoea, dysfunctional uterine bleeding and pelvic pain[13–29]. Infertile women, by definition, have not fulfilled their childbearing desires and, as a consequence, typically have a lower number of children, are older when first seen, and have a higher probability of delayed childbearing either voluntarily or otherwise.

Because of the above considerations, it is unclear how seriously to consider the earlier epidemiological studies in the understanding of this disease. If one simply accepted an incidence of endometriosis in a fertile population at 2–5% and made an assumption that endometriosis was associated with delayed childbearing secondary to infertility by other aetiology, the incidence in an infertile population of 25–50% would neither be surprising nor necessarily be a reason to consider it aetiological in their infertility. The strongest data to suggest that endometriosis is associated with a lower probability of conception come from couples who are infertile because of azoospermia undergoing therapeutic donor insemination. When these women were evaluated prior to insemination and found to have endometriosis, their subsequent cycle fecundity with donor insemination was found to be substantially lower than in the women without endometriosis[30]. This constitutes the strongest data to date suggesting that some aspect of the pathophysiology of endometriosis is at least contributory, if not causal, in the patient's infertility.

PATHOGENESIS

Pathologists as well as gynaecologists have been interested in the phenomenon of ectopically implanted endometrium since its description in the mid-1800s. Several theories of pathogenesis were put forth prior to the era of objective scientific inquiry. Unfortunately, several of these theories have continued to enjoy popularity with clinicians despite the absence of scientific data. These misconceptions as to the nature of this disease have had a major effect on the therapeutic recommendations up to the present time. The unfortunate consequence has been the perpetuation of non-efficacious 'therapy' that compounds the problem by discouraging couples from participating in randomized clinical trials with appropriate untreated control arms. Until it is appreciated what constitutes efficacious treatment, appropriately controlled clinical trials that are at variance with the current unsubstantiated dogma will continue to be difficult to perform.

Before considering the various proposed mechanisms of development of endometriosis, it is appropriate to establish some criteria to evaluate these theories. First, there must be a uniformly accepted definition of the disease. The gold standard for diagnosis is having histologically documented endometrial glands and stroma outside the uterus, with evidence of menstrual cyclicity with haemosiderin-laden macrophages. This is an empirical definition arrived at by consensus in the early part of this century when only a minimal amount was known about the reproductive cycle in women and this description was used to ensure uniform reporting. Identification of glands and/or stroma as endometrial in origin, on the basis of morphology, is certainly tenuous. This is particularly true without specific biochemical markers of endometrium and in the presence of an inflammatory reaction that may substantially modify the histological appearance. With the emphasis today on endoscopy, the diagnosis of endometriosis is based almost exclusively on the visual appearance of the peritoneal implants. In the future, a more exacting definition may be

forthcoming, with antibodies directed against unique endometrial antigens being used to document unequivocally the tissue of origin.

The finding of endometrial glands and stroma deep within the myometrium, i.e. adenomyosis, constitutes a disease with entirely different epidemiology and clinical profile. This disease cannot be considered 'endometriosis' despite the old nomenclature of 'endometriosis interna', referring to adenomyosis, and 'endometriosis externa', referring to what we now consider endometriosis.

Second, the disease must be able to be re-created using an experimental design equivalent to an inoculum of endometrium. Obviously, some modification to adapt to the theories of autologous transplantation, congenital cell rests and coelomic metaplasia must be made. Lastly, the experimentally created disease must be equivalent in virtually all respects to the spontaneously developing entity both morphologically and functionally. While these criteria may seem overly stringent, they seem appropriate given the wide variance of the proposed pathophysiological mechanisms.

COELOMIC METAPLASIA

The first widely considered theory of histogenesis was that of coelomic metaplasia, and it was initially advocated by Dr Robert Meyer, the Dean of Gynaecologic Pathology, at the turn of the century. According to this proposal, under certain unspecified stimuli, cells might undergo a metaplastic process that changes their character and physiological function from that of peritoneal mesothelium to endometrium[31]. This concept underwent some expansion, with other investigators suggesting inductive influences on the coelomic membrane, and menstrual detritus and hormones have been most prominently mentioned. In the 1920s other theories of pathogenesis were proposed and a bitter debate raged. The disciples seemed to carry the intensity of the debate beyond that of the original proposer. There is clear evidence that Dr Meyer did not intend the coelomic metaplasia theory to exclude consideration of other ideas[31].

Experimental data supporting the coelomic metaplasia theory are meagre at best. The most prominently mentioned study is that of Merrill who noted 'endometrium-like' cells adjacent to Millipore filter chambers containing endometrium implanted in the peritoneum of rabbits[32,33]. These experiments were designed to investigate the inductive influence of menstrual detritus on the peritoneal mesothelium. Despite some morphological similarity to endometrial glands, no evidence of endometrial stroma or functional characteristics of endometrium could be appreciated. Other inductive influences have been postulated, such as gonadal steroids and follicular fluid contents, all without experimental evidence.

A firm scientific basis for the concept of coelomic metaplasia has yet to be established. There are several questions that need to be addressed if this pathophysiological mechanism is to be seriously entertained. The first would be that endometriosis could develop in the absence of endometrium, i.e. in women with congenital absence of the uterus. Although there are case reports purporting to demonstrate endometriosis in these women[34], the situation is

confusing. There are invariably fallopian tube remnants present and occasionally small blind uterine horns that may be the source of endometrium. Second, if peritoneal epithelium has the potential to undergo metaplasia, this phenomenon would be expected to occur in men as well as women. While there are case reports of endometriosis in men, each involves the treatment of metastatic prostate cancer with high-dose oestrogens[35–38]. This probably represents hyperplasia of the endometrial cell rests in the prostatic utricle, the remnant of the Mullerian ducts in men. Third, coelomic metaplasia should occur in those sites where the coelomic membranes are present. While there is embryological evidence that the coelomic membrane covers both the abdominal and thoracic cavities[39,40], endometriosis is rare outside the pelvis or its contiguous structures. Lastly, if coelomic metaplasia is similar to metaplasia elsewhere, it should occur with increasing frequency with advancing age. The clinical pattern of endometriosis is distinctly different, with an abrupt halt in the disease with cessation of menstruation. While endometriosis has been observed in postmenopausal women[41,42], it is probably associated with oestrogen replacement therapy or an endogenous oestrogen source.

Until the above-noted concerns are addressed, there is little justification for considering coelomic metaplasia as a serious candidate as the aetiology of endometriosis.

EMBRYONIC CELL RESTS

It has been speculated that embryonic cell rests could explain the presence of ectopic endometrium. This is based on the assumption that in areas adjacent to the Mullerian ducts, rudimentary duplications of the Mullerian system might be present, allowing cells of Mullerian origin to develop into functioning endometrium, particularly in peritoneal pockets or defects at the base of the broad ligaments[43].

There are disconcerting questions regarding this concept. First, the embryonic distribution of the urogenital ridges is from the pelvis into the thoracic activity. The distribution of ectopic endometrium would be expected to correspond to the distribution of these putative precursors[39,40]. Such incidental cell rests have not been identified in the pelvis or thoracic cavity. Furthermore, the rare endometriosis found in the thoracic cavity is in the distribution of the vasculature, consistent with blood-borne transplanted endometrial cells[31]. Second, if the embryonic cell rest hypothesis is to be seriously entertained, one would anticipate finding the endometriosis immediately after menarche, when hormonal stimulation is initiated. By contrast, endometriosis has its greatest incidence in the fourth decade of life[3,44]. On the basis of these considerations the likelihood that endometriosis has its origin in remnants of embryonic structures is highly improbable.

TRANSPLANTATION OF EXFOLIATED ENDOMETRIUM

A scientific approach to understanding the aetiology of endometriosis began with the pioneering efforts of a private practitioner from Albany, New York,

Dr J. A. Sampson. Based on his clinical experience, he proposed that the menstrual effluent contained viable endometrial cells that could be transplanted to ectopic sites[45–48]. He reasoned that since the oviducts communicate freely between the peritoneal and uterine cavities, regurgitation of menstrual debris through the oviducts was the likely source of these cells in the vast majority of patients. A substantial clinical data base exists to support this hypothesis. Several other routes of dissemination have been observed, including lymphatic and vascular channels and by iatrogenic deposition. Transtubal dissemination appears to be the most common route of dissemination, by far, with the preponderance of endometriosis being found on the peritoneal surfaces of the pelvis and on the pelvic viscera.

Specific scientific evidence that supports the ability of endometrial cells to be transplanted, regardless of route, includes:

1. Viable endometrial cells have been demonstrated in the menstrual effluent[49,50].
2. Endometrium can be implanted experimentally and grow within the peritoneal cavity[51].
3. Endometrial cells obtained from the menstrual effluent are transplantable to the abdominal wall fascia[31,52].
4. Neither oestrogen nor progesterone is required for implantation and early growth of endometrial cells, although there does appear to be some long-term necessity for these gonadal hormones to maintain the viability of endometrial implants[53].

Retrograde menstruation

Dr Sampson concluded that from his clinical experience it was most likely that endometrial cells were regurgitated through the fallopian tubes at the time of menses. In order to understand this situation, one must consider the physiology of menstruation. Following ovulation, unique histological and functional changes occur in the endometrium in preparation for implantation. In a non-conceptive menstrual cycle, luteolysis is marked by declining oestrogen and progesterone levels, resulting in a breakdown of the surface layer of the endometrium. The menstrual effluent is thus composed of extracellular fluid, blood, and clusters of shed endometrial cells[54,55]. This decline in gonadal steroids triggers the release of uterine prostaglandins[56], which appear to be involved in arterial spasm in the superficial layers of the endometrium as well as in stimulating rhythmic uterine contractions, elevating the pressure within the uterus and aiding in the expulsion of menses[56].

There are three possible routes of egress for the menstrual effluent from the uterine cavity — the cervix and both fallopian tubes. As the cervical canal generally has the largest calibre and the lowest resistance, the majority of flow is in that direction. There is a paucity of information on the physiology on the uterotubal junction in humans with respect to directional flow of the menstrual debris. The rarity of spontaneous endometriosis in monkeys may be related to the small calibre of the uterotubal junction[57,58] and the difficulty

in demonstrating reflux of dye through the uterotubal junctions with hysterosalpingography[51]. Unfortunately, little is known of the physiology of the uterotubal junction in humans. Uterotubal junction 'spasm' is thought to occur in response to irritating solutions, stress, smoking and even general anaesthesia. Paradoxically, the general anaesthetic halothane, as well as glucagon (known to relax smooth muscles), is used in an attempt to overcome uterotubal junction 'spasm'[59–61]. Evidence to support an 'incompetent' uterotubal junction allowing increased menstrual regurgitation in women with endometriosis comes from Ayers and Friedenstab, who observed relative hypotonia of the uterotubal junction in women with endometriosis[62]. Similarly, cervical stenosis has been suggested to increase the probability of endometriosis by creating relative uterine outflow obstruction, allowing the normal uterine pressure to overcome the uterotubal junction during menses, although there are no data aside from those for women with congenital anomalies[14,63,64].

Some degree of regurgitation of menses via the oviducts appears to be a universal event in women in virtually every menstrual cycle. This is supported by evidence of bloody peritoneal dialysates at the time of menses in women undergoing peritoneal dialysis[65] and bloody peritoneal fluid observed at laparoscopy during menses[66,67]. Even on non-menstrual days, the aspiration of peritoneal fluid reveals a greater probability of having endometrial tissue in women with endometriosis than in control women[68]. While a slower clearance of 'normally' regurgitated menses cannot be excluded, these data do support the concept of increased retrograde menstruation in women with endometriosis.

In order to consider retrograde menstruation the prime mechanism for development of the bulk of endometriosis, several observations must be present. First and foremost, viable endometrial cells must be present in the fallopian tubes. Second, viable endometrial cells must be present in the menstrual debris and have the ability to be transplanted. Third, the anatomic distribution of the disease should be compatible with the tenets of transplantation biology and be more common at the site of entry into the pelvis, i.e. the fimbrial ostia. The following evidence exists to support these points:

1. Viable endometrial cells have been demonstrated in the fallopian tube by perfusing excised segments of the human oviducts[69] as well as in histological segments of the fallopian tubes during menses[70].

2. Endometrial cells have been noted by cytology of the peritoneal fluid with the peritoneal fluid being collected either by culdocentesis[71] or laparoscopy[68].

3. The natural position of the fallopian tube ostia is near the insertion of the uterosacral ligament into the uterus at the base of the broad ligament. This is an extremely common site of endometriosis[72].

4. Gravity should affect free-floating endometrial cells in the peritoneal cavity. When either supine or upright, the pelvic cavity is the most dependent portion of the abdominal cavity and represents, by far, the most common site of endometriosis. In addition, when the pelvic cavity is bisected by an anteflexed uterus, endometriosis is commonly found in

both the anterior and posterior dependent compartments, i.e. the uterovesicle fold in the cul de sac. When the uterus is retroflexed and does not bisect the pelvic cavity and no dependent anterior compartment exists, implants on the uterovesicle fold are extremely uncommon[72].

5. Attachment of free-floating endometrial cells is influenced by the mobility of the pelvic structures. Those that are fixed in the pelvis have a much higher rate of transplantation than mobile structures. The actively peristalsing small bowel and mobile fallopian tube are rarely involved, in contrast to the non-mobile structures such as the ovary, pelvic peritoneum and fixed portion of the sigmoid colon[72].
6. Transplantation is predictable on the basis of the suitability of the surface epithelium, vascularity, and the local hormone environment. The pelvic peritoneum would seem ideal, being thin, well vascularized and bathed in high levels of gonadal steroids after ovulation. This is in distinct contrast to the remainder of the epithelium in the genital tract, with ciliated fallopian tube epithelium, mucus secreting endocervical epithelium, and squamous epithelium of the exocervix, vagina and vulva. As the endometrium is dependent upon ovarian hormones and the ovary is adjacent to the fallopian tube ostia, it is no surprise that the most common site of endometriosis is the ovary[6,72].

It is obvious from the above that a substantial amount of hard evidence supports the pathophysiological process of retrograde menstruation and transplantation of endometrial cells on the peritoneum of the pelvis. No comparable data base exists for any other proposed mechanism of development.

Lymphatic and haematogenous dissemination

Dissemination of endometrial cells through lymphatic or vascular channels has long been considered. This would account for the rare finding of endometrial tissue at sites distant from the pelvis. Endometrial tissue in lymphatic spaces was first noted by Halban in 1925 when he reported five cases with lymphatic spread[73]. Endometrial tissue has been noted microscopically in lymphatic channels[74] and lymph nodes[73,74] as well as the umbilicus[75], known to be rich in the lymphatics of pelvic origin.

Dissemination through the vascular system was initially suggested by Sampson[47] and subsequently confirmed by Javert[74]. There have been many reports since, demonstrating endometriosis in well-vascularized organs such as the lungs, skin and muscles[31]. The circumstances leading to the shedding of endometrial cells in the venous system are unknown. This must be an extremely unusual event or, alternatively, the viability of cells within the vascular system is extremely low.

Iatrogenic dissemination

It has long been appreciated that gynaecological surgical procedures, particularly when the endometrial cavity is entered, have been associated with

iatrogenic transplantation of endometrial cells. Typically, these are caesarean sections, myomectomies, and hysterotomies for non-obstetric indications[76,77]. As the development of endometriosis involves the transplantation of autologous cells, the exfoliated cells would be expected to have a relatively high transplantation rate. This is supported by the experiments transplanting human endometrial tissue to the upper vagina[72] and anterior abdominal wall[52].

The squamous epithelium of the lower genital tract (exocervix, vagina and vulva) probably protects these areas from implantation of endometrial cells. Whether the likelihood of transplantation varies with the time of the cycle in which the surgery is performed remains unclear. It has been suggested that the probability of attachment is highest in the interval phase of the menstrual cycle, diminishing in the secretory luteal and premenstrual phase, and being least likely during pregnancy[78]. In the monkey, the survival of endometrial grafts derived from the basalis region is much higher than that of the functionalis region (80% vs 20%)[54,79]. This may explain the relatively low iatrogenic dissemination rate, as infrequently will the full thickness of the endometrium be surgically dislodged.

Summary of the transplantation hypothesis

From the above information, it is apparent that the aetiology of endometriosis involves transplantation of exfoliated endometrial cells. There is a substantial data base to support this with the vast majority of disease being accounted for by retrograde menstruation and intraperitoneal implantation. While lymphatic and haematogenous or iatrogenic routes have been demonstrated, the clinical pattern strongly supports the retrograde menstrual process in the vast majority of patients.

OTHER FACTORS

While virtually all cycling women menstruate retrogradely to some degree, not all develop endometriosis. The prevalence of the disease in the general female population of reproductive age is difficult to establish. Only women with clinical problems or desirous of voluntary sterilization have their pelvis visualized. Even with this selection bias, it becomes apparent there are some factors that influence any individual's probability of developing the disease.

Genetics

A familial probability of developing endometriosis has long been suspected on the basis of case reports[80] and retrospective reviews[81]. More formal genetic studies have demonstrated endometriosis in approximately 7% of first-degree female relatives of affected individuals[82,83] with a 2% risk for second-degree female relatives[82]. This appears to be through a maternal inheritance pattern[82], and those women with a first-degree relative with endometriosis are more likely to have severe disease[84]. The pattern appears to be one of polygenetic

or multifactorial inheritance, and no relationship to HLA cell surface antigens has been noted[85,86].

Race

As noted earlier, endometriosis was originally believed to have a strong racial preponderance. However, once the confounding variables, such as availability of health care, access to contraception, cultural differences regarding childbearing patterns, and attitudes toward dysmenorrhoea and menses were considered, these differences disappear. Only in Japanese women does an increase in the incidence of endometriosis persist when corrected for confounding variables[9].

Menstrual factors

While no cases of endometriosis have been reported prior to the onset of puberty, the disease has certainly been noted in the teenage years[87]. There is a disproportionally large number of cases of endometriosis in this early interval attributable to Mullerian anomalies with absolute or relative uterine outflow obstruction. As our diagnostic tools have improved (e.g. laparoscopy), increasing numbers of young women have been detected with endometriosis, urging further efforts in preventing and controlling the disease in an attempt to minimize the effect on future fertility.

As retrograde menstruation is the predominant mechanism of development of endometriosis, women with menstrual patterns offering a greater opportunity for contamination of the peritoneal cavity by menstrual debris are likely to be at greater risk for development of the disease. This concept is supported by a controlled study of women with endometriosis-associated infertility, in which women with short menstrual lengths (less than 27 days) and longer menstrual flow (more than 7 days) had twice the risk of developing endometriosis compared with women with longer cycle lengths and shorter durations of flow[88]. Essentially, the more days of menstrual bleeding per year, the greater the probability of developing the disease. A greater incidence of menorrhagia and earlier average age of menarche have also been associated with endometriosis[89], but this has also been disputed[67], so no clear consensus is apparent.

The symptom of dysmenorrhoea has long been associated with endometriosis and has been proposed to be a consequence of the disease. Alternatively, prostaglandin-induced elevations in uterine pressure are thought to cause dysmenorrhoea[90] and may increase uterine pressure sufficiently to alter the volume of retrograde menstruation. This is particularly true if relative uterine outflow obstruction is present, and nulliparous women may be considered to have some degree of outflow obstruction in the absence of a vaginal delivery. According to this concept, dysmenorrhoea may be a clinical characteristic associated with higher pressures and increased tubal regurgitation rather than a consequence of the disease. While dysmenorrhoea has been reported to increase the risk of endometriosis, fertile women undergoing tubal sterilization have paradoxically been found to have no significant differences in the

occurrence of dysmenorrhoea whether or not they had endometriosis[67]. Until further information is available about the pressure relationships between the uterotubal junction and cervix, this will remain a clouded area.

Delayed childbearing

Childbearing has long been recommended as a protective measure against the development of endometriosis[5]. Delayed childbearing, either by choice or as the result of infertility, has been implicated as a risk factor for the development of the disease. The finding to support this concept is that the risk of developing the disease correlates with a cumulative menstrual exposure (menstrual frequency and volume over time)[88,91]. Whether the protective hormones produced during pregnancy or an irreversibly enlarged cervix after a vaginal delivery alters the ultimate likelihood of retrograde menstruation remains to be clarified.

Uterine outflow obstruction

Development of endometriosis in the first few years after menarche has been associated with a high rate of obstructing genital tract anomalies including non-communicating rudimentary uterine horns, cervical stenosis, cervical atresia, vaginal agenesis, or an imperforate hymen[87]. As a general rule, those lesions at the level of the cervix have a higher incidence of the endometriosis than those lower in the genital tract (imperforate hymen). This explains the observation that in women with Mullerian anomalies, those with outflow obstruction were more likely to have endometriosis than those without outflow obstruction (77% vs 37%)[92,93].

Modest degrees of relative uterine outflow obstruction may play a role in development of endometriosis, but empiric cervical dilatation has never been shown to be preventative or therapeutic. Until better diagnostic methods are available to determine the direction of menstrual flow, this will remain a controversial issue. It has been suggested that contraceptive methods such as diaphragms or the use of tampons may obstruct outflow of the genital tract[13]. No convincing demonstration of an increased risk of endometriosis with the use of tampons, douching, cervical caps, or coitus during menses has been forthcoming.

Dependence on reproductive hormones

While endometriosis is found virtually exclusively in menstruating women, a clear picture of the hormonal dependence of these implants is still not available. While menopausal women may develop the disease[41,42], it is probably related to activation of pre-existing disease by oestrogen replacement therapy or increased endogenous hormone production because of obesity. The vast majority of women after menopause will have atrophic implants, consistent with the loss of gonadal hormone support. The specific hormonal conditions required for maintenance of endometrial implants has yet to be clearly defined.