Do we know what causes endometriosis?

Endometriosis is one of the most intensively investigated benign gynaecological disorders, but our understanding of its causation remains surprisingly incomplete. Several theories exist: coelomic metaplasia, induction, retrograde menstruation and implantation, Müllerian remnants and the archimetra concept. These hypotheses show various extents of plausibility and supporting scientific data.

While the theory of retrograde menstruation and implantation is the most widely accepted, no single concept explains all forms and appearances of endometriosis. Indeed, the wide variety in incidence and progression of the disease seem to defy an explanation by a single mechanism which may indicate that endometriosis is a heterogenous disease. In addition, there is considerable overlap between most of the proposed theories.

What is endometriosis?

Before evaluating the aetiological evidence, we must first classify the condition more accurately. Endometriosis is a common chronic condition, estimated to affect 3–8% of all reproductive age women (Halme et al, 1984). It is defined as the presence of endometrial glands and stroma outside of the uterus. The abnormal tissue is discontinuous with uterine endometrial tissue and is most often found in the following locations (in descending order of frequency): ovaries, uterine ligaments, rectovaginal septum, pelvic peritoneum, and rarely in laparotomy scars, in the umbilicus, vagina, vulva or appendix.

Endometriomas are ovarian cysts of variable size which are lined with functional endometrial tissue. Repeated cyclic shedding of endometrial cells and blood lead to accumulation of a dark brown viscous mass ('chocolate cysts'). Deep infiltrating endometriotic lesions are often associated with stromal hyperplasia and appear as nodules which are often found in the rectovaginal area.

Common symptoms of endometriosis are rather unspecific and include chronic pelvic pain, dysmenorrhoea, dyspareunia and reduced fertility. As a result, the correct diagnosis is often delayed by many years. It is important to distinguish endometriosis from adenomyosis which is characterized by the presence of endometrial glands and stroma within the myometrium.

Retrograde menstruation

In 1927 John Sampson published his observations that the presence of endometriotic lesions may be caused by flux of menstrual blood and tissue through the Fallopian tubes into the abdominal cavity where it attaches to the peritoneal surface.

The evidence for retrograde menstruation causing endometriosis is strong and includes: the distribution of abdominal lesions predominantly in the pelvis, the invasive viability of shed endometrium (so far only proven in tissue culture), the increased prevalence of endometriosis in women with a menstrual outflow obstruction, the microscopic identification of endometrial implants of apparently healthy peritoneum in cases of unexplained infertility, and the higher incidence in women with an increased exposure to menstruation (early menarche, nulliparity, short cycles, longer flow).

Early studies showed that endometriosis could be induced in women after they were given an intraperitoneal injection of their own menstrual blood (Ridley and Edwards, 1958). One hypothesis which has been suggested is that neurological dysfunction, sustained during childbirth or severe constipation, may cause disordered uterine motility and thereby increase retrograde menstruation.

The central argument against Sampson's theory is the fact that retrograde menstruation is a ubiquitous phenomenon with a likely prevalence of more than 90% in all women. In addition, there have been rare reports of endometriotic lesions outside the abdominal cavity, in prepubertal girls and in men. Therefore, further pathomechanisms must exist that are responsible for endometriotic growth.

Molecular mechanisms

Possible molecular mechanisms for successful ectopic implantation are currently being investigated. As the initial step, it is hypothesized that adhesion of endometrial tissue or cells is mediated, for example, via endometrial expression of surface markers such as CD44 and certain integrins, in particular $\alpha 6\beta 1$. Cells lacking the tumour suppressor E-cadherin are thought to represent the population that migrates to abnormal locations. The adherent tissue or cells are then believed to invade the mesothelial cells layer and basement membrane, which is thought to be linked to the upregulation of matrix metalloproteinases and the downregulation of tissue inhibitors of matrix metalloproteinases.

Hepatocyte growth factor may also aid invasion, possibly by promoting stromal cell proliferation and invasion of shed endometrial cells. The established tissue then requires sufficient supply of oxygen and nutrients to grow. It has been shown by the authors' group and others that blood vessel growth is an essential step in the development of endometriosis. A possible mechanism for this process called angiogenesis appears to be the overexpression of vascular endothelial growth factor (VEGF)-A. Raised levels of VEGF-A have been found in the peritoneal fluid of patients with endometriosis, and it has also been shown to be secreted by endometriotic lesions (McLaren et al, 1996).

Metaplasia

Another theory argues that a metaplastic process can be induced by appropriate stimuli. Inflammation, growth factors, hormonal changes or mechanical stress may result in the development of endometrium-like cells from undifferentiated coelomic tissue (Meyer, 1903). The theory is attractive as it can explain endometriosis in the absence of menstruation. It is supported by animal experiments in which endometrium-like epithelium and glands were induced. However, a metaplastic aetiology would make the following predictions: endometriosis should

exist in any location where tissue is derived from coelomic epithelium, it should occur even in the absence of endometrium, and its prevalence should increase with age. None of these predictions are supported by scientific evidence. Also, to date no direct evidence exists showing the formation of endometrial stroma at the end of the metaplastic process.

Role of the immune system

The immune system may be a common factor in the pathogenesis of endometriosis. Tumour necrosis factor-alpha (TNF-α) has been reported to be responsible for the upregulation of matrix metalloproteinases and downregulation of tissue inhibitors of matrix metalloproteinases resulting in enhanced invasiveness (Sillem et al, 2001). Endometrial stromal cells have been reported to secrete thrombin, which is intimately involved with an inflammatory response.

Immune deficiencies may also permit disease progression. Reduced natural killer cell activity and phagocytotic capability of peritoneal macrophages may be partially responsible. Diminished cytotoxic T-cell activity may also allow endometrial implantation, and it has been suggested that this might be mediated by a TH2 immune shift. Endometrial cells evade immunosurveillance by abnormal expression of Fas-ligand and by secretion of soluble intercellular adhesion molecule (ICAM)-1 (thereby preventing lymphocytes and natural killer cells binding).

Interleukin-6 (IL-6) secreted by endometrial cells may also upregulate soluble ICAM-1 secretion by macrophages. Auto-antibodies recognizing T-like antigens have been reported to be present in increased amounts in women with endometriosis. These antibodies may upregulate expression of IL-1, IL-6 and TNF-α, which may in turn increase aromatase expression necessary for oestrogen production.

Archimetrial impairment

More recently, another theory has suggested that endometriosis may be caused by an impaired archimetra (the epithelial and stromal endometrium and the stratum subvasculare of the myometrium) (Leyendecker et al, 1998). This hypothesis describes anatomical and structural defects as well as local alterations of the biochemical environment. The authors also discuss a possible hyper- and dysperistalsis of the stratum subvasculature. This may be a result of elevated endometrial oestrogen levels in patients with endometriosis. The altered peristalsis may also partially explain the increased incidence of infertility in endometriosis patients.

The archimetra concept is interesting as it combines established hypotheses and scientific biochemical data. For example, there are convincing data demonstrating increased oestrogen levels in endometriotic lesions (Bulun et al, 2000). This may be because endometrium of affected women over-expresses aromatase, the enzyme responsible for the conversion of androgens into oestrogen. Additionally, the expression of another enzyme, 17β-HSD type 2, is suppressed, which results in unilateral production of oestradiol. Also, it has been shown that steroidogenic factor-1 (necessary for the cellular uptake of cholesterol) is over-expressed in ectopic endometrium. This allows the endometriotic tissue to function as an independent oestrogen-producing system.

Conclusions

Our understanding of endometriosis remains incomplete but is rapidly evolving. It remains particularly difficult to draw conclusions about whether increased levels of various substances found in women with endometriosis are causes or effects of the condition. It is to be hoped that future progress in the field can urgently be translated into improved prevention, diagnosis and management of this common but currently poorly-treated condition. **BJHM**

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KEY POINTS

- Several theories currently exist to explain the pathogenesis of endometriosis.
- The disease is probably caused by some combination of these mechanisms.
- Retrograde menstruation is the most widely supported theory.
- Other theories include metaplastic processes and archimetral impairment.
- Immune deficiencies, angiogenesis and inflammation are hypothesized to be intimately involved.