# Theories on the pathogenesis of endometriosis

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Although endometriosis has been known for over 100 years, its pathogenesis is still poorly understood. In this overview the literature regarding the pathogenesis of endometriosis is reviewed. The implantation or transplantation theory, that suggests implantation and subsequent growth of retrogradely shed viable endometrial cells, still remains the most widely accepted theory to explain the pathogenesis. The conditions that have to be met for the implantation theory are threefold: (i) retrograde menstruation has to occur; (ii) retrograde menstruation should contain viable endometrial cells; and (iii) adhesion to the peritoneum has to occur with subsequent implantation and proliferation. The scientific data to corroborate these conditions will be discussed. A short overview is given on cell adhesion molecules, in particular cadherins and integrins, the most important cell adhesion molecules involved in cell–cell adhesion and cell–extracellular matrix interaction. Special attention is given to the possible functional role of these cell adhesion molecules in the pathogenesis of endometriosis.
*Key words:* endometriosis/endometrium/pathogenesis/cell adhesion

## Introduction

Endometriosis is the presence of functional endometrial glands and stroma in ectopic locations outside the uterine cavity. Although endometriosis is one of the most commonly encountered problems in gynaecology, its pathogenesis is still poorly understood and remains controversial.

The first histological description of a lesion consistent with endometriosis was given by Von Rokitansky (1860). By 1896, Cullen (1896a,b) had suggested that endometriomas, or adenomyomas as he called these lesions, resembled the mucous membrane of the uterus.

## Three concepts

Among the theories concerning the pathogenesis of endometriosis three main concepts can be discerned (Table I). The oldest concept, that of in-situ develop-

**Table I.** Theories on the pathogenesis of endometriosis (modified from Hingst, 1926 and Ridley, 1968)

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| In-situ development |
| a. Germinal epithelium of the ovary (Waldeyer, 1870) |
| b. Embryonic cell rests |
| Mesonephric (Wolffian knob, Wolffian duct) (Von Recklinghausen, 1895, Breus, 1894) |
| Paramesonephric (Müllerian ducts) (Cullen, 1896, Russell, 1899) |
| c. Coelomic metaplasia (Iwanoff, 1898, Meyer, 1903, Lauche, 1923) |
| d. Metaplasia by inflammation (Hueter, 1918, Meyer, 1919, Tobler, 1923) |
| e. Metaplasia by hormonal stimulation (Novak, 1931) |
| f. Metaplasia by induction (omnipotent blastema) (Levander, 1941, Merril, 1966) |
| g. Secondary Müllerian system (Lauchlan, 1972) |
| Transplantation |
| a. Implantation, retrograde menstruation (Sampson, 1921) |
| b. Implantation, mechanical transplantation (Greenhill, 1942) |
| c. Benign lymphogenous metastasis (hystero–adenosis metastatica) (Halban, 1924/1925, Javert, 1949) |
| Combination of in-situ development and endometrial transplantation and implantation |

ment, is that endometriosis develops on the spot where it is found. Development may occur from the remnants of the Wolffian ducts or the Müllerian ducts, or alternatively from metaplasia of the peritoneal or ovarian tissue (Ridley, 1968; Lauchlan, 1972).

A second concept, the induction theory, is based on the assumption that endometriosis results from differentation of mesenchymal cells, activated (induced) by substances released by degenerating endometrium that arrives in the abdominal cavity (Levander and Normann, 1955; Merrill, 1966).

A third concept, the transplantation or implantation theory, is based on the transplantation and subsequent implantation of endometrial tissue as shown in Figure 1 (Sampson, 1927, 1940). This would include transportation of viable endometrial cells during menstruation via the Fallopian tubes into the abdominal cavity, implantation of these cells onto the peritoneum and the development of these cells into endometriosis.

### *In-situ development*

Von Recklinghausen offered several arguments in support of endometriosis originating from the Wolffian duct, or better the Wolffian knob (Hingst, 1926). He noted a great similarity in the structure of 'adenomyomas' and the mesonephros and emphasized that the mesonephros develops close to the uterus, the tubes and the ovaries. Others did not consider the mesonephros itself but its duct (Wolffian duct) as the tissue of origin for endometriosis. In particular, Meyer (1923) disputed the theories of von Recklinghausen. He did not find these similarities between endometriomas and the mesonephros and did not see any '*organ-*

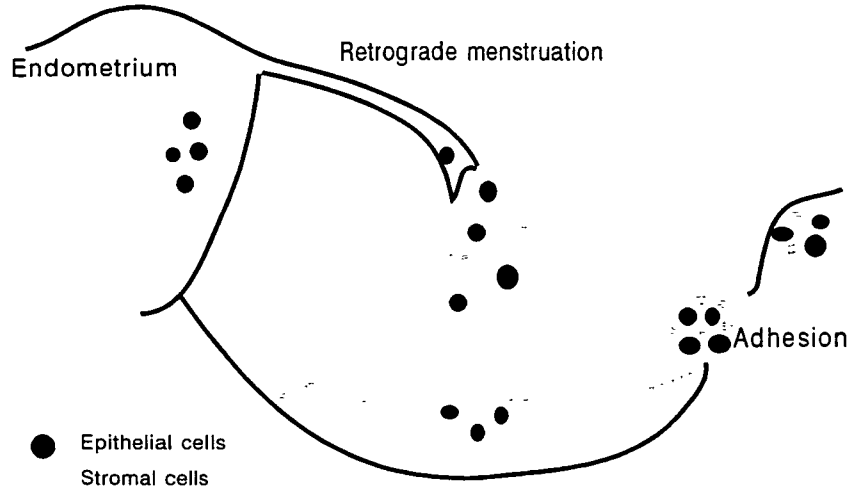


**Figure 1.** Pathogenesis of endometriosis. The implantation theory is based on the transplantation and subsequent implantation of endometrial tissue.

*ähnlichen Bau*'. Furthermore, a tumour originating from an organ that is segmentally present in the embryo, would not keep a similar shape during later developmental stages. Meyer also considered that the location of the mesonephros was not in accordance with the sites where the tumours were found. Russell (1899) surmised that endometriosis arose from Müllerian (paramesonephric) tissue. There are two major objections to Russell's theory. Firstly endometriosis is found in a much wider area than that of the course of the Müllerian ducts, and secondly endometriosis is not present in embryonic remnants of the Müllerian ducts in males. The theory that endometriosis originated from an embryonic organ did not meet with much opposition, as at that time endometriosis had been found either only in the uterine wall or in the Fallopian tubes and their immediate surroundings. Subsequently, however, endometriosis has been recognized on the serosal surface of the colon, the small intestines, the appendix and in scars of the abdominal wall. These findings rendered a purely embryonic derivation too restrictive. Lauche (1923) was one of the first to explain the development of endometriosis from a single origin, no matter where it developed. He deduced a common origin for different spots of endometriosis from the strict resemblance in histological morphology of these lesions. Endometriosis was supposed only to develop where peritoneum was found. According to this theory that was already suggested by Iwanoff (1898) and later was followed by Lauche (1923) and Meyer (1924), the histogenesis of endometriosis is explained by metaplasia of the original coelomic membrane. These metaplastic changes could occur secondary to inflammatory processes or hormonal influences (Meyer, 1919; Novak, 1931).

The theory of coelomic metaplasia still has some support, because it can explain the origin of endometriosis, regardless of the sites or the conditions of its occurrence (Suginami, 1991). Indeed, there is some circumstantial evidence in case reports of endometriosis occurring in young girls, even before menstru-

ation, and in reports of endometriosis at rare localities, such as pleura or diaphragma. The theory does not explain why endometriosis occurs exclusively in women, and typically during the reproductive years, or why endometriosis mainly affects the pelvic organs, or why it only occurs in women with functioning endometrium. Therefore, proof of this theory is lacking, either experimentally or clinically.

### *The induction theory*

Levander and Normann (1955) introduced the induction theory. This theory is based on the assumption that specific substances which are released by degenerating endometrium induce the development of endometriosis from omnipotent blastema, present in connective tissue. Merrill (1966) implanted filters that contained viable and ischaemic endometrial tissue subperitoneally in the rabbit. The suggestion was made that cell-free endometrial products were capable of inducing endometrial metaplasia. These changes do not meet the criteria for endometriosis, since no endometrial stroma has been found in the experiments reported so far.

Lauchlan (1972) introduced the term 'secondary Müllerian system', which refers to all Müllerian-type epithelium located outside the course of the original Müllerian ducts. In this theory, the secondary Müllerian system is composed of cells similar to or identical with those lining the oviducts, uterus and endocervix. This layer of cells could then develop through metaplasia into four cell types, especially on the surface of the ovary; one of these cell types being endometrium-like. This could occur before or after invagination. One argument in favour of this theory is that endometriosis is not a simple ectopic focus of pure endometrium, because both serous and mucous epithelium can be found in endometriotic lesions (Lauchlan, 1972).

### *The implantation theory*

The conditions that have to be met for the implantation theory are threefold: firstly, retrograde menstruation has to occur; secondly, retrograde menstruation should contain viable endometrial cells; and thirdly, adhesion to the peritoneum has to occur with subsequent implantation and proliferation. The implantation theory was originally neglected for a long time, because menstrual effluent was considered to contain only non-viable endometrial tissue and retrograde menstruation was thought to be a rare phenomenon (Meyer, 1924; Novak, 1926). Although the theoretical concept was recognized by some authors, the problem remained to explain extraperitoneal localisations of endometriosis (Halban, 1924; Halban, 1925).

Retrograde menstruation and peritoneal adhesion of endometrial tissue is an essential element in the pathogenesis of endometriosis according to Sampson's theory (Sampson, 1927; Sampson, 1940; Haney, 1991). Sampson realized that for his concept the viability of endometrial tissue retrogradely shed into the

peritoneal cavity was crucial, or as he stated: '*If bits of Müllerian mucosa carried by menstrual blood escaping into the peritoneal cavity are always dead, the implantation theory, as presented by me, also is dead and should be buried and forgotten*' (Sampson, 1940).

## Viability

Menstrual effluent contains viable endometrial cells as shown in the classical study of Keettel and Stein (1951). They were able to culture cells from passively-collected menstrual effluent. Only in two out of seven cases was sufficient material obtained for culturing. After 24 h, an outgrowth of cells was noted. The cells were either fibroblastic or epithelioid. Cron and Gey (1927) had tried earlier to prove the viability of cast-off menstrual endometrium in culture, but they had used a curette to remove the endometrium. Geist (1933) suggested that desquamation of endometrium was not due to local necrosis, as he could demonstrate that menstrual effluent contained viable endometrial cells, that remained alive for at least 1 h. Ridley and Edwards (1958) demonstrated that endometrial cells obtained from the menstrual effluent could be implanted into the abdominal wall fascia. They selected 53 patients that were suitable for their experiments and of these 21 agreed to participate in the study. Only eight were actually included. An aliquot of shed endometrium was injected onto the abdominal fascia of these eight patients prior to an abdominal operation a few weeks later. Only in one case was evidence found for endometriosis developing at the site of injection.

The phenomenon of menstruation itself is something that has puzzled people for a long time. Menstrual effluent is composed of blood elements, endometrial cells and extracellular fluid. Menstruation is almost unique to woman and a few other primates. So far, only two non-primate species have been shown to menstruate naturally i.e. the elephant shrew (*Elephantulus myuras jamesoni*) and one bat (*Glossophaga soricina*) (Van der Horst and Gilman, 1941; Rasweiler, 1979). The uterine cycle of this bat is terminated by true menstruation, i.e. extensive necrosis and desquamation of a large part of the lamina functionalis with associated bleeding. The timing of this process is quite unusual; menstruation can be observed both immediately before and after ovulation (Rasweiler, 1979).

Only recently has menstrual shedding been associated with disorganization of the site-specific distribution of desmoplakin I/II, E-cadherin and α- and β-catenins (Tabibzadeh *et al.*, 1995). It has been suggested that particularly the fragmentation of endometrial glands during menstruation is related to this disorganization.

The functional reasons for the shedding of endometrium during menstruation in women remain unclear. The view that menstruation is a consequence of preparation of the endometrium for implantation was challenged by Profet (1993) with the argument that this waste of biologically-useful material would have been eliminated during evolution. The suggested role of menstruation in getting

rid of bacteria carried into the uterus during coitus, was again challenged by Finn (1994), who considered that menstruation was an integral part of the process of implantation. Most important seems to be that during the menstrual cycle the human endometrium develops into a more differentiated stage in the preparation of the endometrium for implantation than does the endometrium of nonmenstruating species. Consequently, when cells have become too differentiated, in order to perform a specific function, it is impossible to revert to their less differentiated state and therefore these cells will have to be discarded (Finn, 1987). This fundamental difference between the menstrual and oestrous cycles is presumably the basic reason for the bleeding and breakdown of tissue at menstruation. The menstruation occurs because the preparation of the endometrium has surpassed the point of return to its inactive state without massive degeneration and bleeding.

## Retrograde menstruation

After Sampson (1927), Watkins (1938) reported the occurrence of blood dripping from one or both Fallopian tubes, when a laparotomy was performed during menstruation. He detected red blood cells, leukocytes and endometrial cells in all specimens, whereas glandular structures were found in samples from two out of eight patients. The presence of blood in peritoneal fluid has been reported (Blumenkrantz *et al.*, 1981; Halme *et al.*, 1984). Passage and transfer of endometrial fragments to the peritoneal cavity through the Fallopian tubes also has become apparent from studies by Beyth *et al.* (1975). Peritoneal fluid contains endometrial tissue in up to 59% of patients with and without endometriosis undergoing laparoscopy at various stages of the menstrual cycle (Koninckx *et al.*, 1980; Badawy *et al.*, 1984; Bartosik *et al.*, 1986; Kulenthran and Jeyalashmi, 1989; Kruitwagen *et al.*, 1991). Recently, Kruitwagen *et al.* (1991) have found viable endometrial cells in peritoneal fluid. These authors succeeded in culturing these cells *in vitro*, and their data strongly suggest an endometrial origin of epithelial cells in peritoneal fluid. Furthermore, the anatomical distribution of endometriosis correlates very well with principles of transplant biology (Jenkins *et al.*, 1986). Blumenkrantz *et al.* (1981) observed blood-stained peritoneal fluid during menses in women undergoing chronic peritoneal dialysis. In these women, blood staining of peritoneal fluid preceded vaginal bleeding for one to several days. The presence of blood was detected by the observation of threads of sedimented red blood cells. The presence of endometrial tissue was not reported. Halme *et al.* (1984) found a red colour in 90% in the peritoneal fluid samples of women with patent tubes, suggesting the presence of blood. Only visual documentation of the colour of the peritoneal fluid samples was carried out. Oosterlynck *et al.* (1992) noted that the peritoneal fluid of women with endometriosis was bloodstained more frequently than peritoneal fluid from women without endometriosis. The samples, however, were obtained at different phases of the menstrual cycle.

Reti *et al.* (1983) suggested that the demonstration of blood in the Pouch of Douglas at laparoscopy was inadequate for the demonstration of retrograde menstruation since in their study only a weak correlation was found between blood staining of peritoneal fluid and the presence of endometrial cells. The presence of small clusters of cells resembling endometrial glands and stroma in the smear made from peritoneal fluid and stained according to Papanicolaou was taken as evidence for their endometrial origin by these authors.

Demonstration of the presence of endometrial cells in peritoneal fluid is an objective way to assess retrograde menstruation. Bartosik *et al.* (1986) reported no significant difference in the presence of endometrial tissue in peritoneal fluid between patients with and patients without endometriosis. In six out of 32 patients with endometriosis and in one out of nine patients without endometriosis, they were able to show endometrial tissue in peritoneal fluid. Badawy *et al.* (1984) described an increased prevalence of endometrial tissue in peritoneal fluid from patients with endometriosis. Their control group consisted mainly of patients with tubal factors, which may have biased their results. Furthermore, these authors did not associate the presence of endometrial cells with the phase of the menstrual cycle. Endometrial glands have been reported to occur in the peritoneal cavity after dilatation and curettage and after uterotubal irrigation (Beyth *et al.*, 1975; Bartosik *et al.*, 1986; Oosterlynck *et al.*, 1992; Willemsen *et al.*, 1985). Beyth *et al.* (1975) demonstrated that endometrial cells and tissue fragments could be found in a high percentage in the peritoneal cavity after flushing of the uterus and the tubes or after dilatation and curettage, irrespective of the phase of the cycle. In 12 out of 21 patients they found evidence of the presence of endometrial tissue in the peritoneal cavity before curettage. Willemsen *et al.* (1985) described the presence of proliferating endometrial epithelial cells in 67% of cultures prepared from peritoneal fluid obtained after uterotubal irrigation. Koninckx *et al.* (1980) found that endometrial tissue was more often refluxed into the peritoneal cavity after uterine irrigation in women with endometriosis as compared to women without endometriosis.

Most studies demonstrated the presence of endometrial cells in peritoneal fluid, using Papanicolaou staining (Koninckx *et al.*, 1980; Reti *et al.*, 1983; Badawy *et al.*, 1984). This has the disadvantage that only rather large clusters of cells, resembling endometrial glandular and stromal tissue, can be used for recognition and not single cells. Although epithelial markers could be demonstrated in cells of menstrual effluent, endometrium, peritoneal fluid as well as in endometriotic lesions, this is no strict evidence that endometriosis originates from endometrium by retrograde shedding of viable tissue fragments. Van der Linden *et al.* (1995a,b) have demonstrated the presence of endometrial cells in peritoneal fluid using immunohistochemistry. They compared the immunohistochemical staining properties of these fragments with those of cells present in endometrium, menstrual effluent, peritoneum and endometriotic lesions. The staining characteristics, based on the application of monoclonal antibodies against various epithelial markers in cells from menstrual effluent, endometrium, peritoneal fluid, and endometriotic lesions were remarkably similar. Their study

showed that peritoneal fluid contains single epithelial cells, rather than endometrial tissue fragments in women with patent tubes. Possibly endometrial epithelial cells after having left the uterine cavity, are modulated in the peritoneal cavity prior to developing into an endometriotic lesion.

As yet, the reason for implantation of endometrial tissue on the peritoneum or in other regions is unclear. It seems that cells, although present in the wrong place, possess the capacity to adhere and implant. In comparison, at least embryos are unfussy about where they attach as has been shown by the occurrence of abdominal, ectopic, pregnancies occasionally in women, and experimentally investigated using mice and mouse blastocysts (Kirby, 1963, 1967).

Also the question as to how retrogradely-shed endometrium can adhere to the peritoneal wall is still unanswered. In particular, studies on the initial contact between just one or a couple of endometrial cells and the peritoneal lining are still lacking. If retrograde menstruation is important in the pathogenesis of endometriosis, then at some point in time endometrial tissue, either glands or stroma, should adhere to the peritoneum. In theory, either the glandular epithelial cells or stromal cells or both cell types are directly involved in the contact with the epithelium of the peritoneum. Alternatively, both cell types mutual influencing each other to allow this first contact. Another possibility could be direct contact of endometrial cells with the extracellular matrix. Both implantation of viable endometrial tissue fragments and induction of coelomic metaplasia by these fragments will require adhesion of endometrial cells to the peritoneal lining. It is relevant therefore to study the mechanisms of cell adhesion in the development of endometriosis.

An important property of cells that allows them to form tissues, is their intrinsic adhesiveness. Cells usually form contacts through specialized membrane domains. In general, two major classes of adhesion can be distinguished, i.e. cell–cell and cell–extracellular matrix adhesion.

In the studies of van der Linden *et al.* (1994a,b), members of the integrin and cadherin family, important cell adhesion molecules, have been reported to be expressed in endometriotic lesions and in cells and tissues that are potentially involved in the development of endometriosis. These authors focussed their attention on cadherins and integrins. Cadherins are considered the most important cell adhesion molecules involved in cell–cell adhesion and integrins for cell–extracellular matrix (ECM) interactions. Cadherins belong to a group of calcium-dependent transmembrane glycoproteins (Figure 2) (Takeichi, 1988, 1990, 1991; Eidelman *et al.*, 1989). Cadherins mediate cell–cell interactions. Adhering processes, which involve cadherins are homophylic: cells adhere preferentially to cells which express the same cadherin (Nose *et al.*, 1988). Expression of cadherins changes dynamically during development, but cadherins are stably expressed in normally developed tissues throughout the cell cycle (Takeichi, 1991). Cadherins are important constituents of adherens junctions (zonula adherens) where they are responsible for cytoskeletal organization. Integrins are a family of cell membrane glycoproteins consisting of an α-and a β-subunit that mediate cell–cell and cell-matrix adhesion (Albelda and Buck, 1990; Ruoslahti,

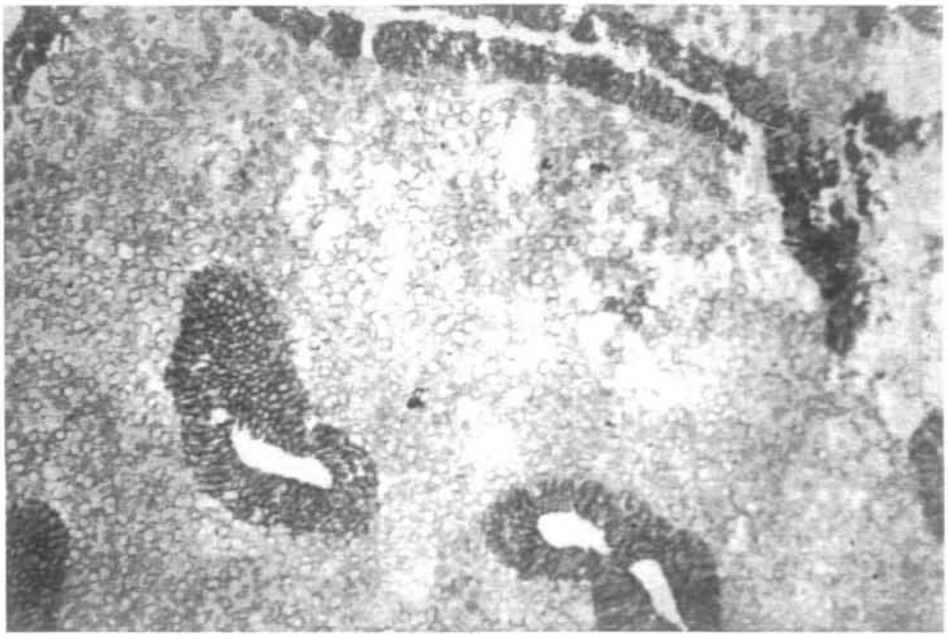

**Figure 2.** Immunohistochemical staining for E-cadherin, using monoclonal antibody HECD-1, in cryostat section of endometrium.

1991; Albelda, 1993). Integrins appear to be the primary mediators of cell–extracellular matrix interactions (Figure 3). The name integrin was given to underline the presumed role of these proteins in integrating the intracellular cytoskeleton with the extracellular matrix. Currently more than 20 integrin heterodimers are known, which are composed of one of at least 14 different $\alpha$ and one of eight different $\beta$ chains (Hynes, 1992). Some $\alpha$ subunits can combine with more than one $\beta$ subunit.

Integrins $\alpha_2\beta_1$, $\alpha_3\beta_1$, $\alpha_4\beta_1$, $\alpha_5\beta_1$, and $\alpha_6\beta_1$ and E-cadherin have been shown to be expressed in endometriotic lesions as well as in cells and tissues that are potentially involved in the development of endometriosis (van der Linden *et al.*, 1994a). Regurgitated cells obtained from peritoneal fluid showed expression of cell adhesion molecules, particularly E-cadherin and some $\beta_1$-integrins, but to a lesser extent than the cells from the tissues, they are supposed to stem from. The expression pattern of cell adhesion molecules suggests that the loss of cell adhesion properties could be involved in the shedding of endometrial tissue during menstruation and the attachment of endometrial tissue fragments to the peritoneum. The demonstration of cell adhesion molecules in menstrual effluent, endometrium, peritoneal fluid, as well as in endometriotic lesions, is no strict evidence that endometriosis originates from endometrium by retrograde shedding of viable tissue fragments. However, all cells potentially involved in the pathogenesis of endometriosis, express members of the integrin and cadherin families of cell adhesion molecules. Effective cellular adhesion requires that a cell coordinates the action of its various adhesion molecules. It is, therefore, not to be expected that in the pathogenesis of endometriosis the processes of adhesion

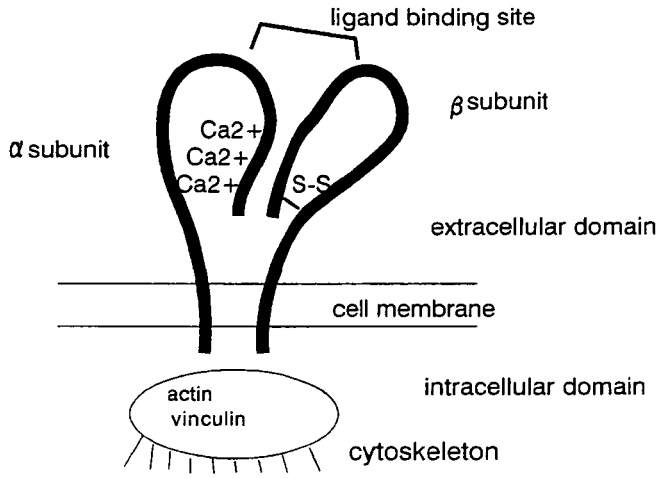


**Figure 3.** Basic structure of integrins.

of shed endometrial tissue can be explained by the mere presence or absence of one single cell adhesion molecule.

E- and P-cadherin are presumably functionally involved in the maintenance of epithelial structures in endometrium and endometriosis, both during the proliferative and the secretory phase of the cycle (van der Linden *et al.*, 1994b). E- and P-cadherin expression was detected in all cycle phases in endometrial samples and did not vary throughout the menstrual cycle (van der Linden *et al.*, 1995). If these adhesion molecules are functionally involved in the cyclic menstrual shedding, the loss of expression is limited to a short period of time. Of the $\beta_1$ integrins, only $\alpha_2\beta_1$ expression was modulated during the menstrual cycle, as it was only absent in the midluteal phase. No relation was found between the expression of cell adhesion molecules and the expression of oestrogen receptor (ER) and progesterone receptor (PR) or the serum concentrations of progesterone and oestradiol (van der Linden *et al.*, 1995).

Since cadherins and $\beta_1$-integrins could be detected in late luteal phase endometrium, these cell adhesion molecules could be involved in the attachment of endometrial fragments to the peritoneal lining as a result of retrograde menstruation. The functional involvement of these cell adhesion molecules remains to be clarified.

In conclusion, the transplantation theory (suggesting the implantation and subsequent growth of retrogradely-shed viable endometrial cells) still remains the most widely-accepted theory to explain the pathogenesis of endometriosis, although the development of endometriosis is probably a multifactorial event. A plausible alternative could well be the induction theory (transformation of mesothelium to endometrium-like tissue under the influence of products of regurgitated endometrium). Both theories require retrograde menstruation and adhesion of shed endometrial cells to the peritoneal lining.

Both growth and clinical symptoms of endometriosis are largely regulated by steroidal hormones. Most studies published on steroid receptors in endometriotic

tissue have shown lower levels of oestrogen and progesterone receptors in ectopic tissue than in endometrium (Bergqvist, 1995). Recently these findings were challenged. Jones *et al.* (1995) found that the oestrogen receptor expression both in epithelium and stroma of ectopic tissue was significantly higher than in eutopic endometrium throughout the cycle. It was suggested that the lower oestrogen- and progesterone receptor indicate that endometriotic tissue, ones it is formed, is not as well regulated by oestrogen and progesterone as is the endometrium (Bergqvist, 1995). Furthermore, it seems that steroids are not needed for the early stages of development such as the adhesion processess, but are important for the proliferation and the growth of endometriotic tissue. Recent concepts on the further development of endometriosis consider minimal endometriosis as a normal condition occurring intermittintly in normal women, in contrast to endometriotic disease occurring as deeply infiltrating endometriosis, and cystic ovarian endometriosis (Muyldermans *et al.*, 1995).

Future research should be directed towards finding how the processes involved in the pathogenesis of endometriosis can take place, instead of why.

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