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Peritoneal endometriosis, ovarian endometriosis, and adenomyotic nodules of the rectovaginal septum are three different entities

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Objective: To review the histogenesis of peritoneal, ovarian, and rectovaginal endometriotic lesions.

Design: The comparison of morphologic, morphometric, and histochemical data observed in each type of lesion.

Setting: A university hospital department of gynecology.

Patient(s): Patients complaining of infertility or pelvic pain with laparoscopically proved endometriosis.

Intervention(s): Laparoscopy was performed, and biopsy specimens from the endometriotic lesions were histologically studied.

Result(s): Three types of endometriotic lesions must be considered: peritoneal, ovarian, and rectovaginal. Morphologic and morphometric data show similarities between eutopic endometrium and red peritoneal lesions, suggesting that these lesions are the first stage of early implantation of endometrial glands and stroma. After partial shedding, the red lesions regrow constantly. The shedding induces an inflammatory reaction, provoking scarification, and the lesions become black. The subsequent fibrosis leads to areas of white opacification that are inactive. The pathogenesis of ovarian endometriomas is a source of controversy. Although there seems to be a consensus concerning the invagination theory, there is still a contradiction between the implantation theory and the metaplasia theory. We recently showed that the mesothelium covering the ovary can invaginate into the ovarian cortex, pushing back the primordial follicles. The presence of mesothelial invagination in continuum with endometriotic tissue suggests that metaplastic histogenesis of ovarian endometriotic lesions occurs. Rectovaginal endometriotic nodules must be considered adenomyomas, consisting of smooth muscle with active glandular epithelium and scanty stroma. Immunocytochemical results show poor differentiation and hormonal independence of these lesions and indicate a close relation with their mesodermal müllerian origin.

Conclusion(s): Peritoneal, ovarian and rectovaginal endometriotic lesions must be considered as three separate entities with different pathogeneses. (Fertil Steril® 1997;68:585–96. © 1997 by American Society for Reproductive Medicine.)

Key Words: Endometriosis, peritoneum, ovary, rectovaginal nodule, histogenesis

Several theories relating to the pathogenesis of endometriosis have been proposed since its first detailed description in 1860 by von Rokitansky (1). The most widely accepted theory, the transplantation theory, was proposed in 1927 by Sampson, (2) who observed that endometrial cells regurgitated through the fallopian tubes during menstruation. Three essential conditions must be met to consider retrograde menstruation as the explanation for the pathogenesis of pelvic endometriosis (3). First, endometrial cells must enter the peritoneal cavity through the fallopian tubes. Second, cells within the menstrual debris must be viable and able to be transplanted onto pelvic structures. Third, the ana-

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tomic distribution of endometriosis in the pelvic cavity must be correlated with the principles of transplantation for exfoliated cells.

Numerous studies have demonstrated that reflux of endometrial cells into the peritoneal cavity during menstruation is a common physiologic condition in women with patent tubes (4, 5). The viability of endometrial cells was demonstrated by culture of the menstrual effluent or peritoneal fluid (6, 7). Experimental studies also proved that endometriosis could be induced by exposure of the pelvis to increased amounts of menstrual discharge (8, 9). Implantation of endometrial tissue also experimentally induced endometriosis in rabbits (10, 11).

The second condition for the transplantation theory is that cells not only must be viable, but also must retain the capacity to adhere and proliferate. A large number of adhesive proteins and proteoglycans have been determined biochemically during the last decade. Our group has demonstrated that laminin and fibronectin are two major adhesion glycoproteins that play a key role in anchoring epithelial cells to basement membranes and stromal cells to the interstitial matrix, respectively (12, 13).

Integrins are cell-surface glycoproteins that act as receptors for extracellular matrix (ECM) proteins. The expression of some integrins has been described in normal endometrium, where they are important in the interactions between glandular and stromal elements (12, 14, 15). The first description of these glycoproteins in endometriotic tissue was given by Beliard et al. in 1992. The attachment of endometrial tissue fragments to the peritoneum could be explained by the detection of such cell adhesion molecules.

Bridges et al. (16) described cyclical changes in integrin expression, but observed no difference when comparing endometrial and endometriotic samples. Beliard et al. (13) did not find any difference in the expression of laminin and fibronectin in the two tissues. However, in their study, integrin expression was found to be present around the endometriotic glands when compared with the endometrium. Such a difference in the expression of fibronectin receptors between the endometrium and endometriosis was not found in the studies of Bridges et al. (16) or Van der Linden et al. (17).

After the adherence of endometriotic cells to the basement membrane (peritoneum), local degradation of the ECM is required. Recently, Marbaix et al. (18, 19) and Kokorine et al. (20) demonstrated that the marked decline in P concentration at the end of the menstrual cycle would initiate the synthesis and activation of matrix metalloproteinases (MMPs), causing ECM breakdown, tissue collapse, and menstruation. Thus, the presence of collagenases was proved during the menstrual period, and their probable presence in the peritoneal fluid, together with regurgitated endometrial cells, could be one of the elements in the local degradation of the peritoneal ECM.

Recently, Kokorine et al. (21) detected the presence of MMPs in red peritoneal lesions and in ovarian endometriomas independent of the menstrual cycle, suggesting that such lesions could represent shedding independent of the decline in P concentration. This hypothesis was bolstered by detection of the aminoterminal propeptide of type III procollagen in peritoneal fluid, which is a sign of increase in the metabolism of the ECM (22).

Recently, in vitro studies demonstrated that the invasion index of endometriotic cells was similar to that of bladder metastatic cell lines, suggesting that the invasiveness of endometriotic cells may contribute to the pathogenesis of endometriosis (23). The anatomic distribution of endometriosis in the pelvic cavity was described by Jenkins et al. (24) and correlated with the principles of transplantation for exfoliated cells. These data suggest that any exposure of the pelvic peritoneum to menstrual reflux would result in an increased risk of endometriosis. Because retrograde menstruation can be considered a physiologic occurrence in menstruating women with patent tubes (4), how can we explain the fact that not all women are found to have endometriosis at laparoscopy?

To explain the discrepancy between the occurrence of regurgitation and endometriosis, one must consider the volume of regurgitated menstrual debris, which can be determined by anatomic-mechanical predispositions. Ayers and Friedenstab (25) showed that uterotubal junction hypotonia occurred in patients with endometriosis but not in (infertile) control subjects. Their findings seem to be corroborated by Bartosik et al. (26), who found more endometrial cells in the abdominal cavity during flushing of the tubes in patients with endometriosis.

Recently, Salamanca and Beltran (27) demonstrated that in women with endometriosis, the propagation direction of the subendometrial myometrial contractive wave in the menstrual phase showed a predominantly retrograde pattern, whereas in the control group, it showed a normal antegrade pattern.

Short cycle lengths and long durations of menstruation with heavy flow, and therefore an increased exposure to retrograde menstruation, have been reported as risk factors for endometriosis (28). Moreover, there is a high prevalence of endometriosis in girls with congenital menstrual outflow tract obstruction (29, 30). However, even if volume is one

important factor, there is no doubt that other etiologic factors, such as hereditary contribution and immunologic deficiency, also account for implantation (31, 32).

In 1991, Oosterlynck et al. (33) reported defective natural killer cell activity in patients with endometriosis, also resulting in decreased cellular immunity. This finding could suggest that in patients with endometriosis, macrophages may not have sufficient capacity to clean the pelvic cavity of regurgitated debris (34). Recently, Rana et al. (35) reported a significantly higher basal or stimulated in vitro macrophage production of tumor necrosis factor-α (TNF-α) interleukin-8 (IL-8), and IL-10 in the peritoneal fluid of patients with endometriosis. Tumor necrosis factor-α and IL-8 are proinflammatory cytokines and are involved in the angiogenic process (36). Moreover, TNF-α could facilitate the in vitro adherence process of stromal cells to the mesothelium (37).

The role of trauma or inflammation of the mesothelium was suggested by Van der Linden et al. (38), who cultured endometrial cells on amniotic membranes. Adherence of endometrial cells to the epithelial surface of the amniotic membranes never was observed when the epithelium was intact. These investigators suggested that an intact epithelium could be an important defense mechanism in preventing initial adhesion of retrogradely shed endometrial fragments to peritoneum.

The celomic metaplasia hypothesis proposed by Meyer (39) states that the original celomic membrane undergoes metaplasia, forming typical endometrial glands and stroma. The celomic metaplasia theory is supported by the description of cases of endometriosis in which retrograde menstruation does not occur and cannot be explained by Sampson's (2) theory.

Endometriosis was described in the prostatic utricle of men with prostatic carcinoma who were undergoing high-dose estrogen therapy and in patients with Rokitansky-Küster-Hauser syndrome (40, 41), in whom there is no endometrium capable of being a source of endometriotic cells. The development of pelvic endometriosis by a process of metaplasia from the pelvic peritoneum is consistent with the supposed müllerian potential of this tissue, which has been referred to as a "secondary müllerian system" (42). Lauchlan (42) first used this term to refer to all müllerian-type epithelium (including endometriotic lesions) located outside the cavities of the original müllerian ducts. Moreover, common epithelial tumors of the ovary are considered to be derived from the surface epithelium (celomic epithelium or mesothelium) covering the ovary and from the underlying stroma (43).

Considering the metaplastic potential of the ovarian surface epithelium, ovarian endometriosis also could be explained by the metaplasia theory (44, 45). In spite of the histologic findings of Fujii (44) and of Nakamura et al. (45), which demonstrated the transformation of ovarian surface epithelium into other tissues (ciliated cells and endometrial-type epithelium), the metaplasia theory has not been supported widely until now; the transplantation theory of Sampson (2) has been the most widely accepted. In the pelvis, three different forms of endometriosis must be considered: [1] peritoneal endometriosis, [2] ovarian endometriosis, and [3] endometriosis of the rectovaginal septum (46).

PERITONEAL ENDOMETRIOSIS

According to morphologic data and morphometric evaluation of the stromal vascularization, there is an obvious similarity between proliferative eutopic endometrium and red peritoneal lesions (47–49). Morphologically, red peritoneal lesions are located systematically on the peritoneal surface and are characterized by numerous proliferative glands with a columnar or pseudostratified epithelium, as observed in proliferative eutopic endometrium. Hyperplastic areas, characterized by an increase in the number of endometrial glands in relation to the stroma, are observed in 12% of red lesions (48, 49). In such cases, making a distinction between peritoneal lesions and eutopic endometrium is difficult for the pathologist.

The glandular proliferative status of red lesions is similar to that observed in eutopic endometrium, revealing a similar degree of activity. The glandular proliferation index, immunohistochemically evaluated with the monoclonal antibody Ki-67, is similar in eutopic endometrium and red lesions during the proliferative phase (48, 49). The stromal vascularization, measured by relative surface areas of the capillaries and stroma, is similar in eutopic endometrium and red lesions (47).

An increase in the stromal vascularization is observed during the secretory phase in both tissues, corroborating the morphologic characteristics in eutopic endometrium that have been described by several investigators (50, 51). The gradual increase in the arborization and coiling of spiral arteries during the preovulatory phase is amplified in the postovulatory period.

When compared with eutopic endometrium, the lower expression of cytokeratin in the epithelium of peritoneal endometriosis could be interpreted as a lesser degree of differentiation or as a delay in differentiation (52). In hyperplastic endometrial lesions,

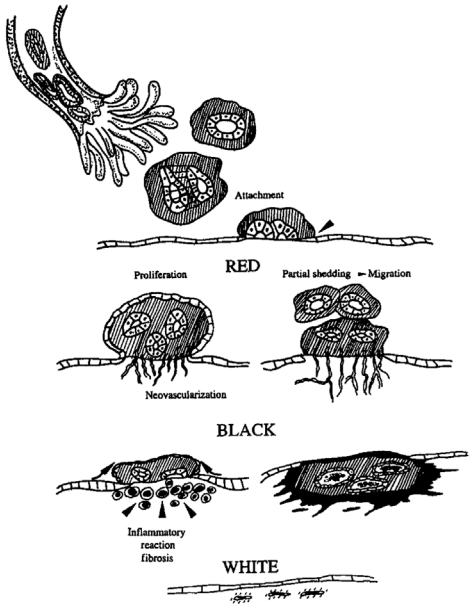

Figure 1 Hypothesis of the evolution of peritoneal endometriosis.

the loss of vimentin expression and the absence of secretory changes give rise to suspicion regarding their benign process (53). This also has been interpreted as a low degree of cell differentiation.

The loss of vimentin in eutopic endometrium during the secretory phase could be responsible for the cell disorganization associated with an ischemic process and could play a role in menstruation and implantation (54). It also may reflect a change in glandular function (52). A similar decrease throughout the cycle has been observed in eutopic endometrium and in ectopic peritoneal endometrium. The significantly lower vimentin expression in the epithelium of red lesions led us to suggest that it could be related to a trend toward hyperplasia.

Our morphologic and morphometric data allow us to suggest that eutopic endometrium and red peritoneal lesions are similar tissues, with red lesions being recently implanted regurgitated endometrial cells (48, 49). These data constitute an argument in favor of the transplantation theory for peritoneal endometriosis (Fig. 1). After endometrial tissue transplantation, the factors that regulate the attachment phase and thereafter initiate ectopic growth are not known. Red lesions are located consistently on the surface of the peritoneum, which consists histologically of a thin layer of loose connective tissue covered with a layer of mesothelium. There is a rich supply of subperitoneal blood vessels and lymphatics (55).

In red, flame-like lesions biopsied together with the normal peritoneum surrounding them, we recently observed an extensive vascular network between the stroma recently implanted onto the peritoneal surface and the peritoneal and subperitoneal layers, demonstrating the importance of angiogenesis in the early stages of development after implantation (48, 49). In our opinion, vascularization of endometriotic implants probably is one of the most important factors of growth and invasion of other tissue by endometrial glands (47, 56).

The three-dimensional representation of the vascular network located at the junction between the red lesions and the peritoneum revealed to us the main role of angiogenesis (48, 49). The high stromal vascularization suggested angiogenesis induced by recent implantation through growth factors or cytokines (57).

One of these angiogenic growth factors, vascular endothelial growth factor, recently was detected in the peritoneal fluid of patients with endometriosis (57). Immunohistochemical studies have demonstrated the presence of angiogenic factors in eutopic and ectopic endometrium (58). In 1993, Ferriani et al. (60) detected fibroblast growth factor immunoreactivity in normal and endometriotic tissue, suggesting its role in the proliferation and angiogenesis of normal and ectopic human endometrium.

Hypervascularization permits further implantation in the subperitoneal fatty tissue (56). Once implantation has occurred, possibly facilitated by the natural killer cell defect according to the hypothesis of Oosterlynck et al. (33), further growth of the lesions depends on the formation of new capillaries. Soluble substances involved in angiogenesis have been detected in the peritoneal fluid of women with endometriosis (61).

It seems reasonable that the angiogenic factors, present in the peritoneal fluid of 58% of women with endometriosis, facilitate the growth of the endometriotic implants. These angiogenic factors could be produced by peritoneal macrophages, retrogradely menstruated endometrial cells, or the ectopic endometriotic lesions themselves (61).

The hypothesis that endometriotic implants secrete cytokines that recruit and activate peritoneal macrophages has been proposed (62). Khorram et al. (62) demonstrated that there were higher concentrations of cytokines in the peritoneal fluid of women with endometriosis than in that of normal control subjects. Activated peritoneal macrophages could be an important source of peritoneal fluid IL-8. Recently, Ryan et al. (63) pointed out a significant cor-

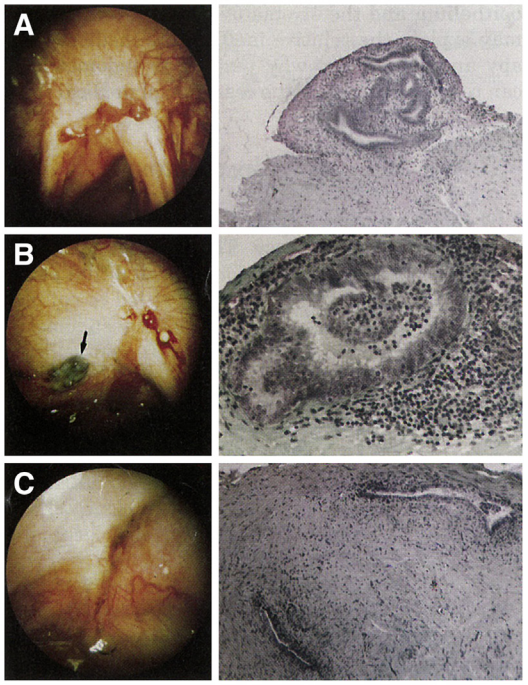

Figure 2 (**A**) Red, flame-like lesion at laparoscopy. Numerous glands with active epithelium with an abundant stroma are found on the peritoneal surface (stain, Gomori's trichome; original magnification, ×200). (**B**) Typical black lesion at laparoscopy (*arrow*). Combination of glands, stroma, and intraluminal debris (stain, Gomori's trichrome; original magnification, ×410). (**C**) White lesion at laparoscopy. Occasional retroperitoneal glandular structures and scanty stroma (stain, Gomori's trichrome; original magnification, ×200).

relation between the peritoneal fluid IL-8 concentration and the stage of endometriosis and suggested that IL-8 is an important angiogenic factor that contributes to the pathogenesis of endometriosis by promoting the neovascularization and proliferation of ectopic endometrial implants.

Further studies are needed to find a relation between high peritoneal fluid IL-8 concentrations and the presence of red peritoneal lesions. Red, flame-like lesions and glandular excrescences probably are the first stage of early implantation of endometrial glands and stroma (48, 49) (Fig. 2A). Their significantly higher stromal vascularization and epithelial mitotic index are responsible for the invasion of ectopic sites by glands and stroma.

Thereafter, detachment of glands from viable red endometrial implants, explained by the presence of MMPs, could initiate their implantation in other peritoneal sites, as in a "metastatic" process (21). Preliminary data from our group (21) revealed the presence of MMPs in the stroma of red lesions throughout the menstrual cycle, although in eutopic endometrium, MMPs are detected only during the marked decline in P.

After this partial shedding, the remaining red lesion always regrows constantly until the next shedding, but menstrual shedding finally induces an inflammatory reaction, provoking a scarification process that encloses the implant. The enclosed implant becomes a "black" lesion because of the presence of intraluminal debris (Fig. 2B). This scarification process is probably responsible for the reduction in vascularization, as proved by the significant decrease in the relative surface areas of the capillaries and stroma (47).

In some cases, the inflammatory process and subsequent fibrosis totally devascularize the endometriotic foci, and white plaques of old collagen are all that remain of the ectopic implant (48, 49). White opacification and yellow-brown lesions are latent stages of endometriosis (47) (Fig. 2C). They probably are inactive lesions that could be quiescent for a long time.

In agreement with Brosens (64), we regard red lesions as early endometriosis and black lesions as advanced endometriosis (47, 65). White lesions are believed to be healed endometriosis or quiescent or latent lesions (47). This hypothesis corroborates the clinical findings of Redwine (66) and of Goldstein et al. (67) that red lesions precede the others, and that with time, their presence decreases, being replaced by black and ultimately white lesions. Red petechial lesions are found in adolescents (67).

The shedding and implantation of endometrial cells is a process that occurs during the initial phase of reproductive life. The fact that this period is characterized by anovulatory cycles is in accordance with the hypothesis that anovulation, with a low P concentration in the peritoneal fluid, is the favored time for the implantation of endometriosis (68).

Black lesions rarely demonstrate typical progestational changes, although some investigators report that 70% of foci with a cyclic pattern undergo changes that are considered synchronous (±3 days) with the eutopic endometrium (48, 49, 69). This probably is because some basal vacuoles can be observed in some cells (<20%). Nevertheless, this cannot be interpreted as a typical secretory change because in order to be considered a secretory change it has to be demonstrated in >50% of the epithelial cells and because basal vacuoles also can be observed in anovulatory cycles or in the absence of P (50, 70).

The comparison of the steroid receptor content of endometriosis with that of eutopic endometrium and

their cyclic changes is a subject of controversy. The discrepancy between the results of different studies may result from the different assay methods used. In particular, biochemical assays that require a tissue homogenate obscure the heterogeneity of receptor content between glands and stroma and between endometriotic implants and nonendometrial tissue (71). It also could be explained by the selection of the endometriotic implants; in most studies, both peritoneal and ovarian lesion data have been considered together.

Metzger (72) found that the estrogen receptor (ER) and P receptor (PR) content of endometriotic implants correlated well with the receptor content of the corresponding endometrium, although only 13% of endometrial implants were found to be histologically synchronous with the corresponding intrauterine endometrium. The discrepancy between the apparent lack of histologic response and the apparently appropriate steroid receptor regulation suggests that histologic transformation is influenced by factors other than steroid receptor regulation.

In a quantitative immunohistochemical study, cyclic changes were observed in eutopic endometrium as well as in black lesions (73). The ER content of glandular epithelium and stroma decreased significantly during the secretory phase in the same way in both ectopic and eutopic endometrium. However, the ER content was lower in the glandular epithelium of black lesions than in eutopic endometrium. The PR content and its cyclic changes were similar in both endometrium and endometriosis, except in the glandular epithelium during the late secretory phase, where a persistently high PR content was observed in black lesions (48, 49).

The ectopic foci are more or less autonomous and are not governed by the normal control mechanisms governing the uterine endometrial glands and stroma. The exact reason why some implants or cells do not respond to hormonal therapy is not known, but at least four hypotheses have been proposed: [1] that the drug does not gain access to the endometriotic foci because fibrosis surrounding the foci prevents access locally; [2] that endometriotic cells may have their own genetic programming, whereas endocrine influence appears to be only secondary and dependent on the degree of differentiation of the individual cell; [3] that fewer ERs are present in ectopic peritoneal endometrium when compared with eutopic endometrium; and [4] that the different regulatory mechanisms of endometriotic steroid receptors may result in deficient endocrine dependency because the receptors, although present, are biologically inactive.

In our opinion, the persistence of PR in both the epithelium and the stroma of endometriotic lesions may explain the relative inefficacy of medical therapy and the reason why peritoneal endometriosis can recur quickly after the cessation of medical therapy (74).

OVARIAN ENDOMETRIOSIS

The pathogenesis of typical ovarian endometriosis is a source of controversy. The original article by Sampson (75) on this condition indicated that perforation of the so-called chocolate cyst led to spillage of adhesions and the spread of peritoneal endometriosis. The findings of Hughesdon (76) contradicted Sampson's (75) hypothesis and suggested that adhesions are not the consequence, but rather the cause, of endometrioma formation. Hughesdon demonstrated, by serial section of ovaries containing an endometrioma, that 90% of typical endometriomas are formed by invagination of the cortex after the accumulation of menstrual debris from bleeding of endometrial implants, which are located on the ovarian surface and adherent to the peritoneum.

The site of perforation, as described by Sampson (75), could represent the stigma of invagination. The observations of Brosens et al. (77), based on ovarioscopy and in situ biopsies, were in agreement with the hypothesis of Hughesdon (76). In 93% of typical endometriomas, the pseudocyst is formed by an accumulation of menstrual debris from the shedding and bleeding of active implants located by ovarioscopy at the site of inversion, resulting in a progressive invagination of the ovarian cortex (77).

Other investigators have suggested that large endometriomas may develop as a result of the secondary involvement of functional ovarian cysts in the process of endometriosis (78). We recently published a different hypothesis on the development of ovarian endometriosis (56, 79, 80). Celomic metaplasia of invaginated epithelial inclusions could be responsible for this pathogenesis (Fig. 3A). This hypothesis, based on the metaplastic potential of the pelvic mesothelium, already is a widely accepted theory on the pathogenesis of common epithelial ovarian tumors (43).

Although recent papers and debates have tried to classify endometriomas, there is still considerable uncertainty (77, 78). We believe that ovarian endometriosis is caused by metaplasia of the invaginated celomic epithelium (79, 80). Our arguments are as follows:

1. In our series, we found that 12% of endometriomas were not fixed to the broad ligament and that Hughesdon's (76) theory cannot explain the formation of the endometriomas in these cases.

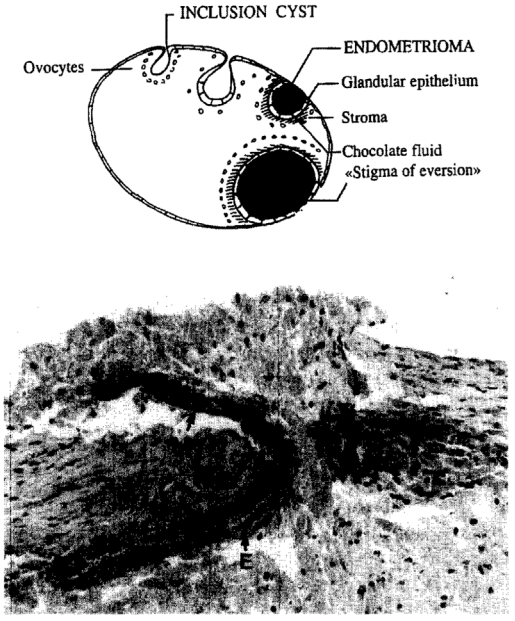

Figure 3 (**A**) Hypothesis of histogenesis of ovarian endometriomas. (**B**) Continuum between the flat cells of the ovarian surface mesothelium (*M*) and the endometrial-type epithelium (*E*) of the endometrioma (stain, Gomori's trichrome, original magnification, ×410).

2. It was not unusual to find multilocular endometriomas that could not be explained by the theory of adhesions and by bleeding of active superficial implants adherent to the peritoneum.

3. The epithelium covering the ovary, which is the mesothelium, can invaginate into the ovarian cortex. Invaginations of the mesothelial layer covering the ovarian tissue were described by Motta et al. (81) in animal and human fetal ovaries and also were visualized in human adult ovaries (48, 49). In our serial sections of the ovary, we frequently observed mesothelial inclusions. Under the influence of unknown growth factors, these inclusions could be transformed into intraovarian endometriosis by metaplasia.

4. The fact that primordial follicles were found surrounding the endometriotic cyst also is in agreement with our hypothesis. When the mesothelium invaginates deep into the ovary, the follicles located at the invagination site are pushed concomitantly with the mesothelium.

5. Our main argument is based upon the presence of epithelial invaginations in continuum with endometrial tissue, proving the metaplasia theory (48, 49, 79) (Fig. 3B).

6. Another major argument is related to the demonstration of the capacity of the endometrioma wall to invaginate secondarily into the ovarian cortex (48, 49, 79). Such secondary invaginations were observed in 33% of our cases and represent the so-called deep ovarian endometriosis that actually is just an extension of the endometrioma wall.

7. Arguments to support our hypothesis also can be found in the literature. First, endometriomas have been described in patients with Rokitansky-Küster-Hauser syndrome, who do not have a uterus and, therefore, do not have retrograde menstruation (41). Second, common epithelial tumors of the ovary are considered to be derived from the surface epithelium covering the ovary and from the underlying stroma (43).

Thus, our theory differs from the theories of Hughesdon (76) and of Brosens et al. (77), who consider that the pathogenesis of the typical ovarian endometrioma now has been clarified as a process originating from a free superficial implant that is in contact with the ovarian surface and is sealed off by adhesions, with the menstrual shedding and bleeding of this small implant resulting in progressive invagination of the ovarian cortex and formation of the pseudocyst.

In our opinion, the endometrioma must be considered as an invagination but not as the result of the bleeding of a superficial implant. Metaplasia of the celomic epithelium invaginated into the ovarian cortex was proved and explains the formation of the endometrioma (79, 80). The deep-infiltrating ovarian endometriosis described by our group is only the consequence of the invagination of endometriotic tissue into the ovary and probably is responsible for the recurrence of ovarian endometriosis after cyst excision or vaporization (48, 49, 82–85). These findings give us supplementary arguments favoring the surgical technique already proposed in 1987, which consists of vaporization of the internal wall of the cyst (83).

The depth of vaporization is shallow; only the glandular epithelium and the subjacent stroma have to be vaporized. There is no need to destroy the fibrotic capsule usually found surrounding the endometrioma. This technique avoids the removal of ovocytes, frequently observed when the endometriotic capsule is removed during ovarian cystectomy.

Recently, Brosens et al. (86) also confirmed that ovarian cystectomy was not mandatory for the management of large endometriomas. Their study and our own strongly suggest destroying only the internal lining of the endometrioma, histologically represented by glandular epithelium, endometrial glands,

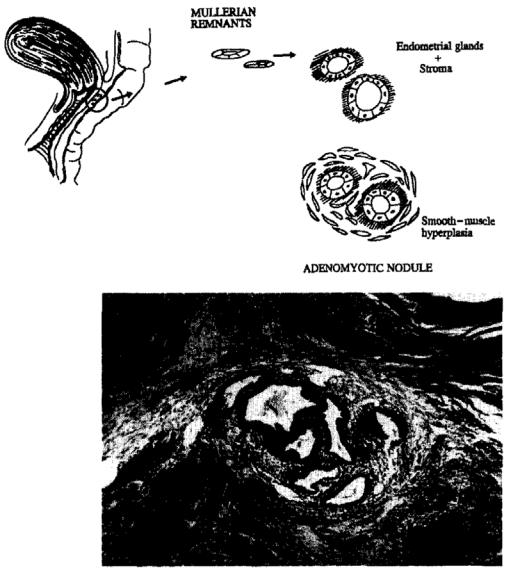

Figure 4 (**A**) Hypothesis of histogenesis of rectovaginal endometriosis. (**B**) Adenomyotic nodule. Scanty endometrial-type stroma and glandular epithelium disseminated in proliferative muscular tissue (stain, Gomori's trichrome; original magnification, ×200).

and stroma, to minimize ovarian trauma and avoid the risk of premature ovarian failure.

ADENOMYOTIC NODULES

Another form of the disease is deep-infiltrating endometriosis of the rectovaginal septum. In 1922, Sampson (87) defined cul-de-sac obliteration as "extensive adhesions in the cul-de-sac, obliterating its lower portion and uniting the cervix or the lower portion of the uterus to the rectum; with adenoma of the endometrial type invading the cervical and the uterine tissue and probably also (but to a lesser degree) the anterior wall of the rectum." The endometriotic nodule of the rectovaginal septum was considered by Koninckx and Martin (88) to be the consequence of deep-infiltrating endometriosis, and these investigators described three subtypes of deep endometriosis according to the depth of infiltration. The rectovaginal septum endometriotic nodule was considered to be the deepest form of endometriosis and to result from the natural evolution of peritoneal endometriosis in some women.

For us, the nodule of the rectovaginal septum is a different entity than peritoneal endometriosis that has another pathogenesis, and we strongly suggest that it corresponds to an adenomyotic nodule originating from müllerian rests by a process of metaplasia (46, 48, 49, 56, 89, 90) (Fig. 4A).

Deep vaginal endometriosis associated with pelvic endometriosis can take the form of nodular or polypoid masses, involving the posterior vaginal fornix (88, 89, 91). The differential diagnosis of vaginal endometriosis, particularly the superficial type, includes vaginal adenosis of the tuboendometrial variety, but the latter lacks endometrial stroma and the characteristic inflammatory response of endometriosis (92). In the uterus corpus, adenomyosis is a common condition characterized pathologically by the presence of endometrial glands and stroma within the myometrium.

Adenomyosis exhibits a varied functional response to ovarian hormones. Proliferative glands and stroma usually are observed in the first half of the menstrual cycle. Adenomyosis may not respond to physiologic levels of P, and secretory changes frequently are absent or incomplete during the second half of the menstrual cycle. Similar histologic observations can be made at the level of the endometriotic rectovaginal nodule, which is, like an adenomyoma, a circumscribed nodular aggregate of smooth muscle, endometrial glands, and, usually, endometrial stroma (46, 56, 90). This lesion originates from the tissue of the rectovaginal septum and consists essentially of smooth muscle with active glandular epithelium and scanty stroma (Fig. 4B).

The invasion of the smooth muscle by active glandular epithelium without stroma proves that the stroma is not mandatory for invasion and that the nodule is different from peritoneal endometriosis, in which epithelial glands are surrounded systematically by endometrial-type stroma (48, 49). The similarity of histologic descriptions of uterine adenomyosis have led us to suggest, like Brosens (64), that the so-called endometriotic nodule of the rectovaginal septum is the same as an adenomyoma or an adenomyotic nodule. Nevertheless, the coexpression of vimentin and cytokeratin indicates a close relation with their mesodermal müllerian origin (48, 49, 90).

The significantly lower vimentin expression in the epithelium of nodules, when compared with black lesions and eutopic endometrium, has led us to suggest, as we have for red peritoneal lesions, that a low expression of vimentin can be related to a trend toward hyperplasia (53, 90). The invasion of the smooth muscle of nodules by glandular cells without stroma is often seen clearly.

In recent studies, we described the differences observed between peritoneal and nodular lesions and suggested that the nodule is not the consequence of deep-infiltrating endometriosis but is the same as an

adenomyotic nodule, which develops from müllerian rests by metaplasia (46, 48, 49, 90). Smooth-muscle proliferation and fibrosis, consistently observed, are responsible for the nodular aspect of endometriosis located in the rectovaginal septum. The clinical diagnosis is made only when smooth-muscle proliferation is sufficient to be felt by vaginal examination.

At least two hypotheses could explain this smooth-muscle proliferation: [1] endometriotic foci involving smooth muscle typically are associated with striking proliferation of the smooth muscle, creating an adenomyomatous appearance similar to that of adenomyosis in the endometrium (93); and [2] the endometriotic stroma may exhibit smooth-muscle metaplasia, as has been demonstrated within the wall of ovarian endometriotic cysts (94).

We believe that the first hypothesis is the more tenable. The presence of smooth muscle in the organ affected by endometriosis is necessary for smooth-muscle proliferation. When endometriotic glands affect the rectovaginal septum, which contains smooth muscle, smooth-muscle proliferation can take place and the nodule thus develops. Hyperplasia of the smooth muscle present in the septum provokes perivisceritis visible at radiography because of the inflammatory process and secondary retraction of the rectal serosa. The absence of evolution of the rectal lesion after removal of the nodule supports our hypothesis concerning its pure rectovaginal septal origin (46, 89).

The variations in the ER and PR content of nodules throughout the cycle suggest that they probably are not regulated by steroids. In our study, the very low glandular epithelial and stromal ER content during the follicular phase can explain the absence of any secretory change in the glandular epithelium of the nodule (48, 58, 90). A recent study suggested that a low ER level was the key factor in explaining the out-of-phase endometrium despite normal P levels, but the reduction in PR also could cause resistance to P action and result in inadequate secretory transformation (95).

The absence of response to P levels suggests that the different regulatory mechanisms of endometriotic steroid receptors result in deficient endocrine dependency or that the receptors are present but biologically inactive (96, 97). The low mitotic activity, another low steroid receptor content observed in this pathology, can account for the relatively slow evolution of the adenomyoma and for the weak response to medical therapy, necessitating surgical excision (89, 98).

In cases of rectovaginal nodules, hyperplasia of the smooth muscle present in the septum provokes perivisceritis visible at radiography because of the inflammatory process and secondary retraction. This perivisceritis phenomenon is not an endometriotic rectal lesion or an invasion of the rectal wall by the endometriotic process, as has been suggested by many investigators. In our opinion, it is only the consequence of serosal retraction caused by the inflammatory process and fibrosis on the anterior wall of the rectum.

The absence of evolution of the rectal lesion after removal of the nodule supports our hypothesis concerning its rectovaginal septal origin and strongly suggests that it is not necessary to excise the anterior wall of the rectum in such circumstances. However, excision of the nodule and the vaginal mucosa located in front of it is essential because of the presence of endometriotic glands in contact with the vagina.

CONCLUSION

Peritoneal endometriosis, the different aspects (black, red, and white) of which represent distinctive steps in the evolutionary process, can be explained by the transplantation theory. Red lesions are the most active and most highly vascularized lesions and are considered to be the first stage of peritoneal endometriosis.

According to our histologic findings, celomic metaplasia of invaginated epithelial inclusions could be responsible for the development of ovarian endometriosis. The epithelium covering the ovary, which originally derives from the celomic epithelium, has great metaplastic potential and provokes epithelial inclusion cysts by invagination. Under the influence of unknown growth factors, these inclusions could be transformed into intraovarian endometriosis by metaplasia.

The rectovaginal endometriotic nodule is an adenomyotic nodule whose histopathogenesis is not related to the implantation of regurgitated endometrial cells but to metaplasia of müllerian remnants located in the rectovaginal septum. Metaplastic changes of müllerian rests into endometriotic glands involving the rectovaginal septum are responsible for the striking proliferation of the smooth muscle, creating an adenomyomatous appearance similar to that of adenomyosis in the endometrium.

REFERENCES

1. von Rokitansky C. Ueber Uterusdrusen-Neubildung in Uterus and Ovarialsarcomen (Uterine gland proliferation in uterine and ovarian sarcomas). Zeitschrift Gesellschaft für Aerzte zu Wien 1860;37:577.
2. Sampson JA. Peritoneal endometriosis due to menstrual dissemination of endometrial tissue into the peritoneal cavity. Am J Obstet Gynecol 1927;14:422–69.

3. Donnez J, Nisolle M, Casanas-Roux F, Grandjean P. Endometriosis: pathogenesis and pathophysiology. In: Shaw RW, editor. Endometriosis. Carnforth: Parthenon Publishing, 1990: 11–29.
4. Halme J, Hammond MG, Hulka JF, Raj S, Talbert LM. Retrograde menstruation in healthy women and in patients with endometriosis. Obstet Gynecol 1984;64:151–4.
5. Liu DTY, Hitchcock A. Endometriosis: its association with retrograde menstruation, dysmenorrhea and tubal pathology. Br J Obstet Gynaecol 1986;93:859–62.
6. Keettel WC, Stein RJ. The viability of the cast-off menstrual endometrium. Am J Obstet Gynecol 1951;61:440–2.
7. Kruitwagen RF, Poels LG, Willemsen WN, De Ronde IJ, Jap PH, Rolland R. Endometrial epithelial cells in peritoneal fluid during the early follicular phase. Fertil Steril 1991;55:297–303.
8. Te Linde RW, Scott RB. Experimental endometriosis. Am J Obstet Gynecol 1950;60:1147–73.
9. Scott RB, Te Linde RW, Wharton LR Jr. Further studies on experimental endometriosis. Am J Obstet Gynecol 1953; 66:1082–103.
10. Schenken RS, Asch RH, Williams RF, Hodgen GD. Etiology of infertility in monkeys with endometriosis: luteinized unruptured follicles, luteal phase defects, pelvic adhesions, and spontaneous abortions. Fertil Steril 1984;41:122–30.
11. Donnez J, Wayembergh M, Casanas-Roux F, Karaman Y, Willems T, Ferin J. Effect on ovulation of surgically induced endometriosis in rabbits. Gynecol Obstet Invest 1987;24: 131–7.
12. Foidart J-M, Béliard A, Donnez J. Endometriosis and invasion. In: Brosens I, Donnez J, editors. The current status of endometriosis research and management. Carnforth: Parthenon Publishing, 1993:35–9.
13. Béliard A, Donnez J, Nisolle M, Foidart J-M. Localization of laminin, fibronectin, E-cadherin, and integrins in endometrium and endometriosis. Fertil Steril 1997;67:266–72.
14. Lessey BA, Damjanovich L, Coutifaris C, Castelbaum A, Albelda SM, Buck CA. Integrin adhesion molecules in the human endometrium: correlation with the normal and abnormal menstrual cycle. J Clin Invest 1992;90:188–95.
15. Tabibzadeh S, Sun XZ. Cytokine expression in human endometrium throughout the menstrual cycle. Hum Reprod 1992; 7:1214–21.
16. Bridges JE, Prentice A, Roche W, Englefield P, Thomas EJ. Expression of integrin adhesion molecules in endometrium and endometriosis. Br J Obstet Gynaecol 1994;101:696–700.
17. Van der Linden PJ, De Goeij AF, Dunselman GA, Erkens HW, Evers JL. Expression of cadherins and integrins in human endometrium throughout the menstrual cycle. Fertil Steril 1995;63:1210–6.
18. Marbaix E, Kokorine I, Henriet P, Donnez J, Courtoy PJ, Eeckhout Y. The expression of interstitial collagenase in human endometrium is controlled by progesterone and by estradiol and is related to menstruation. Biochem J 1995;305: 1027–30.
19. Marbaix E, Kokorine I, Donnez J, Eeckhout Y, Courtoy P. Regulation and restricted expression of interstitial collagenase suggest a pivotal role in the initiation of menstruation. Hum Reprod 1996;11(2 Suppl):134–43.
20. Kokorine I, Marbaix E, Henriet P, Okada Y, Donnez J, Eeckhout Y, et al. Focal cellular origin and regulation of interstitial collagenase (matrix-metalloproteinase-1) are related to menstrual breakdown in the human endometrium. J Cell Sci 1996;109:2151–60.
21. Kokorine I, Nisolle M, Donnez J, Eeckhout Y, Courtoy PJ, Marbaix E. Expression of interstitial collagenase (matrix metalloproteinase-1) is related to the activity of human endometriotic lesions. Fertil Steril 1997;68:246–51.
22. Spuijbroek MD, Dunselman GA, Menheere PP, Evers JL. Early endometriosis invades the extracellular matrix. Fertil Steril 1992;58:929–33.
23. Gaetje R, Kotzian S, Hermann G, Baumann R, Starzinski-Powitz A. Invasiveness of endometriotic cells in vitro. Lancet 1995;346:1463–4.
24. Jenkins S, Olive DL, Haney AF. Endometriosis: pathogenetic implications of the anatomic distribution. Obstet Gynecol 1986;67:335–8.
25. Ayers JW, Friedenstab AP. Utero-tubal hypotonia associated with pelvic endometriosis. The American Fertility Soc 1985; 131(supplement).
26. Bartosik D, Jacobs SL, Kelly LJ. Endometrial tissue in peritoneal fluid. Fertil Steril 1986;46:796–800.
27. Salamanca A, Beltran E. Subendometrial contractility in menstrual phase visualized by transvaginal sonography in patients with endometriosis. Fertil Steril 1995;64:193–5.
28. Cramer DW, Wilson E, Stillman RJ, Berger MJ, Belisle S, Schiff I, et al. The relation of endometriosis to menstrual characteristics, smoking, and exercise. J Am Med Assoc 1986; 255:1904–8.
29. Sanfilippo JS, Wakim NG, Schikler KN, Yussman MA. Endometriosis in association with uterine anomaly. Am J Obstet Gynecol 1986;154:39–43.
30. Olive DL, Henderson DY. Endometriosis and müllerian anomalies. Obstet Gynecol 1987;69:412–5.
31. Simpson JL, Elias S, Malinak LR, Buttram VC. Heritable aspects of endometriosis. I. Genetic studies. Am J Obstet Gynecol 1980;137:327–31.
32. Steele RW, Dmowski WP, Marmer DJ. Immunologic aspects of human endometriosis. Am J Reprod Immunol 1984;6:33–6.
33. Oosterlynck D, Cornillie FJ, Waer M, Vandeputte M, Koninckx PR. Women with endometriosis show a defect in natural killer cell activity resulting in a decreased cytotoxicity to autologous endometrium. Fertil Steril 1991;56:45–51.
34. Dunselmann GA, Hendricx MG, Bouckaert PX, Evers JL. Functional aspects of peritoneal macrophages in endometriosis of women. J Reprod Fertil 1988;82:707–10.
35. Rana N, Braun DP, House R, Gebel H, Rotman C, Dmowski WP. Basal and stimulated secretion of cytokines by peritoneal macrophages in women with endometriosis. Fertil Steril 1996;65:925–30.
36. Koch AE, Polverini PJ, Kunkel SL, Harlow LA, Di Pietro LA, Einer VM, et al. Interleukin 8 as a macrophage derived mediator of angiogenesis. Science 1992;258:1798–801.
37. Zhang R, Wild R, Ojago J. Effect of tumor necrosis factor-α on adhesion of human endometrial cells to peritoneal mesothelial cells: an in vitro system. Fertil Steril 1993;59:1196–201.
38. Van der Linden PJ, de Goeij AF, Dunselman GA, Erkens HW, Evers JL. Endometrial cell adhesion in an in vitro model using intact amniotic membranes. Fertil Steril 1996;65:76–80.
39. Meyer R. Ueber den Stand der Frage der Adenomyositis und Adenomyome in Algemeinen und Insbesondere ueber Adenomyositis seroepithelialis und Adenomyometritis sacromatosa (The current question of adenomyositis and adenomyomas in general and particularly seroepithelial adenomyositis and sarcomatoid adenomyometritis). Zentralbl Gynakol 1919;43: 745–50.
40. Melicow MM, Pachter MR. Endometrial carcinoma of the prostatic utricle (uterus masculinus). Cancer 1967;20:1715–22.

41. Rosenfeld DL, Lecher BD. Endometriosis in a patient with Rokitansky-Kuster-Hauser syndrome. Am J Obstet Gynecol 1981;139:105–7.
42. Lauchlan SC. The secondary müllerian system. Obstet Gynecol Surv 1972;27:133–46.
43. Serov SF, Scully RE, Sobin LH. Histological typing of ovarian tumors. Geneva: World Health Organization, International histological classification of tumors. No. 9. 1973:17–21.
44. Fujii S. Secondary Müllerian system and endometriosis. Am J Obstet Gynecol 1991;162:219–25.
45. Nakamura M, Katabuchi H, Tohya TR, Fukumatsu Y, Matsuura K, Okamura H. Scanning electron microscopic and immunohistochemical studies of pelvic endometriosis. Hum Reprod 1993;8:2218–26.
46. Donnez J, Nisolle M, Casanas-Roux F, Brion P, Da Costa N. Stereometric evaluation of peritoneal endometriosis and endometriotic nodules of the rectovaginal septum. Hum Reprod 1995;11:224–8.
47. Nisolle M, Casanas-Roux F, Anaf V, Mine JM, Donnez J. Morphometric study of the stromal vascularization in peritoneal endometriosis. Fertil Steril 1993;59:681–4.
48. Nisolle M. Peritoneal, ovarian and rectovaginal endometriosis are three distinct entities [Thèse d'Agrégation de l'Enseignement Supérieur]. Louvain (Belgium): Université Catholique de Louvain, 1996.
49. Nisolle M, Donnez J, editors. Peritoneal, ovarian and rectovaginal endometriosis: the identification of three separate diseases. Carnforth: Parthenon Publishing, 1996.
50. Ferenczy A. Anatomy and histology of the uterine corpus. In: Kurman RJ, editor. Blaustein's pathology of the female genital tract. New York: Springer-Verlag, 1987:257–91.
51. Peek M, Landgren BM, Johannisson E. The endometrial capillaries during the normal menstrual cycle: a morphometric study. Hum Reprod 1992;7:906–11.
52. Nisolle M, Casanas-Roux F, Donnez J. Coexpression of cytokeratin and vimentin in eutopic endometrium and endometriosis throughout the menstrual cycle: evaluation by a computerized method. Fertil Steril 1995;64:69–75.
53. Nakopoulou L, Minaretzia D, Tsionou C, Mastrominas M. Value of immunohistochemical demonstration of several epithelial markers in hyperplasia and neoplastic endometrium. Gynecol Oncol 1990;37:346–53.
54. Norwitz ER, Fernandez-Shaw S, Barlow DH, Starkey PM. Expression of intermediate filament in endometrial glands changes with the onset of pregnancy and in endometriosis. Hum Reprod 1991;6:1470–3.
55. Bloom W, Fawcett DN. A textbook of histology. Philadelphia: WB Saunders, 1978:186–7.
56. Donnez J, Nisolle M. L'endométriose péritonéale, le kyste endométriotique ovarien et le nodule de la lame rectovaginale sont trois pathologies différentes [editorial]. Références en Gynécologie Obstétrique 1995;3:121–3.
57. Smith SK. Vascular endothelial growth factor and the endometrium. Hum Reprod 1996;11(2 Suppl):56–61.
58. Haining RE, Cameron IT, Van Pajendorps C, Davenport AP, Prentice A, Thomas EJ, et al. Epidermal growth factor in human endometrium: proliferative effects in culture and immunocytochemical localization in normal and endometriotic tissues. Hum Reprod 1991;6:1200–5.
59. Ferriani RA, Charnok-Jones DS, Prentice A, Thomas EJ, Smith SK. Immunohistochemical localization of acidic and basic fibroblast growth factors in normal human endometrium and endometriosis and the detection of their mRNA by polymerase chain reaction. Hum Reprod 1993;8:11–6.
60. Oosterlynck DJ, Meuleman C, Sobis H, Vandeputte M, Koninckx PR. Angiogenic activity of peritoneal fluid from women with endometriosis. Fertil Steril 1993;59:778–82.
61. Halme J, White C, Kauna S, Ester J, Haskill S. Peritoneal macrophages from patients with endometriosis release growth factor activity in vitro. J Clin Endocrinol Metab 1988;66:1044–9.
62. Khorram O, Taylor RN, Ryan IP, Schall TJ, Landers DV. Peritoneal fluid concentrations of the cytokine RANTES correlate with the severity of endometriosis. Am J Obstet Gynecol 1993;169:1545–9.
63. Ryan IP, Tseng JF, Schriock ED, Khorram O, Landers DV, Taylor RN. Interleukin-8 concentrations are elevated in peritoneal fluid of women with endometriosis. Fertil Steril 1995;63:929–32.
64. Brosens IA. Is mild endometriosis a disease? Is mild endometriosis a progressive disease? Hum Reprod 1994;9:2209–11.
65. Donnez J, Casanas-Roux F, Nisolle M. Peritoneal endometriosis: new histological aspects. In: Brosens IA, Donnez J, editors. The current status of endometriosis. Research and management. Carnforth: Parthenon Publishing, 1993:75–87.
66. Redwine DB. Age-related evolution in color appearance of endometriosis. Fertil Steril 1987;48:1062–3.
67. Goldstein MP, de Cholnoky C, Emans SJ, Leventhal JM. Laparoscopy in the diagnosis and management of pelvic pain in adolescents. J Reprod Med 1980;44:251–8.
68. Brosens IA, Koninckx PR, Corveleyn PA. A study of plasma progesterone, oestradiol-17 beta, prolactin and LH levels and of the luteal phase appearance of the ovaries in patients with endometriosis and infertility. Br J Obstet Gynaecol 1978;85:246–50.
69. Bergqvist A, Ljunberg O, Myhre E. Human endometrium and endometriotic tissue obtained simultaneously: a comparative histologic study. Int J Gynecol Pathol 1984;3:135–45.
70. Mazur T, Kurman RJ. Normal endometrium and infertility evaluation. In: Mazur T, Kurman R, editors. Diagnosis of endometrial biopsies and curettings. A practical approach. New York: Springer-Verlag, 1995:7–32.
71. Bergqvist A, Ferno M. Estrogen and progesterone receptors in endometriotic tissue and endometrium: comparison of different cycle phases and ages. Hum Reprod 1993;8:2211–7.
72. Metzger DA. Cyclic changes in endometriosis implants. In: Brosens IA, Donnez J, editors. The current status of endometriosis. Research and management. Carnforth: Parthenon Publishing, 1993:89–108.
73. Nisolle M, Casanas-Roux F, Wyns CH, De Menten Y, Mathieu PE, Donnez J. Immunohistochemical analysis of estrogen and progesterone receptors in endometrium and peritoneal endometriosis: a new quantitative method. Fertil Steril 1994;62:751–9.
74. Evers JL. The second-look laparoscopy for evaluation of the result of medical treatment of endometriosis should not be performed during ovarian suppression. Fertil Steril 1987;47:502–4.
75. Sampson JA. Perforating haemorrhagic (chocolate) cysts of the ovary. Arch Surg 1921;3:245–323.
76. Hughesdon PE. The structure of endometrial cysts of the ovary. Journal of Obstetrics and Gynaecology British Empire 1957;44:69–84.
77. Brosens IA, Puttemans PJ, Deprest J. The endoscopic localization of endometrial implants in the ovarian chocolate cyst. Fertil Steril 1994;61:1034–8.
78. Nezhat F, Nezhat C, Allan CJ, Metzger DA, Sears DL. A clinical and histological classification of endometriomas: implications for a mechanism of pathogenesis. J Reprod Med 1992;37:771–6.
79. Donnez J, Nisolle M, Gillet N, Smets M, Bassil S, Casanas-

Roux F. Large ovarian endometriomas. Hum Reprod 1996; 11:641–6.
80. Nisolle M, Donnez J. It is time to reassess the pathogenesis of ovarian endometriomas. Lancet (Submitted).
81. Motta PM, Van Blerkom J, Mekabe S. Changes in the surface morphology of ovarian germinal epithelium during the reproductive life and in some pathological conditions. Submicroscopy Cytology 1992;99:664–7.
82. Canis M, Wattiez A, Pouly JL, Bassil S, Bouquet J, Chapron C, et al. Laparoscopic treatment of endometriosis. In: Brosens IA, Donnez J, editors. The current status of endometriosis. Research and management. Carnforth: Parthenon Publishing, 1993:407–17.
83. Donnez J. CO_2 laser laparoscopy in infertile women with endometriosis and women with adnexal adhesions. Fertil Steril 1987;48:390–4.
84. Donnez J, Nisolle M, Casanas-Roux F. Classification and endoscopic treatment of ovarian endometriosis. In: Popkin E, editor. Woman's health today. Carnforth: Parthenon Publishing, 1994:112–5.
85. Nisolle M, Donnez J. Conservative laparoscopic treatment of ovarian endometriosis. In: Shaw RW, editor. Endometriosis: current understanding and management. London: Blackwell Science Ltd, 1995:237–47.
86. Brosens IA, Van Ballaer P, Puttemans P, Deprest J. Reconstruction of the ovary containing large endometriomas by an extraovarian endosurgical technique. Fertil Steril 1996;66: 517–21.
87. Sampson JA. Intestinal adenomas of endometrial type. Arch Surg 1922;5:21–7.
88. Koninckx PR, Martin D. Deep endometriosis: a consequence of infiltration or retraction or possible adenomyosis externa? Fertil Steril 1992;58:924–8.
89. Donnez J, Nisolle M, Casanas-Roux F, Bassil S, Anaf V. Rectovaginal septum, endometriosis or adenomyosis: laparoscopic management in a series of 231 patients. Hum Reprod 1995;2:630–5.
90. Donnez J, Nisolle M, Smoes P, Gillet N, Beguin S, Casanas-Roux F. Peritoneal endometriosis and "endometriotic" nodules of the rectovaginal septum are two different entities. Fertil Steril 1996;66:362–8.
91. Reich H, McGlynn F, Salvat J. Laparoscopic treatment of cul-de-sac obliteration secondary to retrocervical deep fibrotic endometriosis. J Reprod Med 1991;36:516–22.
92. Zaloudek C, Norris HJ. Mesenchymal tumors of the uterus. In: Kurman R, editor. Blaustein's pathology of the female genital tract. New York: Springer-Verlag, 1987:373–408.
93. Scully RE, Richardson GS, Barlow JF. The development of malignancy in endometriosis. Clin Obstet Gynecol 1966;9: 384–411.
94. Scully RE. Sex cord–mesenzyme tumors: pathologic classification and its relation to prognosis and treatment. In: Junqeira AC, Gentile F, editors. Ovarian cancer. Heidelberg: Springer-Verlag, 1968, vol II, 40–56.
95. Hirama Y, Ochiai K. Estrogen and progesterone receptors of the out-of-phase endometrium in female infertile patients. Fertil Steril 1995;63:984–8.
96. Laatikainen T, Andersson B, Karkkainen J, Wahlström T. Progestin receptor levels in endometriomas with delayed or incomplete changes. Obstet Gynecol 1983;62:592–5.
97. Spirtos NY, Yurewicz EC, Moghissi KS, Magyar DM, Sundareson AS, Bottoms SF. Pseudocorpus luteum insufficiency: a study of cytosol progesterone receptors in human endometrium. Obstet Gynecol 1985;65:535–40.
98. Donnez J, Nisolle M, Smets M, Bassil S, Casanas-Roux F. Recto-vaginal septum adenomyotic nodule: a distinct entity. A series of 500 cases. Br J Obstet Gynaecol (in press).