Deeply Infiltrating Endometriosis Is a Disease Whereas Mild Endometriosis Could Be Considered a Non-Disease

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INTRODUCTION

Endometriosis was described as a severe pathology necessitating radical surgery at the beginning of this century.[1-2] Defined morphologically as endometrial glands outside the uterine cavity both adenomyosis in the recto-vaginal septum, and chocolate cysts in the ovary were recognized as endometriosis.

Since the introduction of laparoscopy in the late sixties, the awareness that endometriosis is a very frequent disease has progressively increased. Initially typical lesions such as black puckered lesions and cystic ovarian endometriomas, which in their most severe forms were associated with extensive pelvic adhesions were described. In the early eighties, laparoscopic scrutiny led to the recognition of a whole variety of small white vesicles, red vesicles, flame-like lesions, polipoid lesions, and brown lesions as subtle forms of endometriosis.[3-4] Even a normal peritoneum was sometimes found to hide microscopical endometriosis.[5-6] In the late eighties CO_2-laser-excision techniques led to the observation that some typical lesions infiltrate deep into the subperitoneal stroma.[7-8] Although unexpected in the beginning, since it is found in women with a normal clinical examination, we rapidly realized that the most severe form of deep endometriosis presented clinically with extensive and painful nodularities in the pouch of Douglas. Now more subtle forms of deep endometriosis are being diagnosed.

Besides a brief review of deeply infiltrating endometriosis as a specific entity of severe endometriosis, an attempt will be made to consider the question whether endometriosis should always be regarded as a pathological condition or whether some forms of endometriosis could be considered a natural condition occurring in all women. In this concept only some forms of endometriosis should be considered pathological. This would not only change the question "Why do some women develop endometriosis?" into "Why does endometriosis develop in some women into a pathological condition?" but it could also stir up new ideas on prevention and treatment of endometriosis.

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Definition and Types of Deep Endometriosis

We defined deeply infiltrating endometriosis as endometriosis which infiltrates deeper than 5 mm under the peritoneum.[7-10] This choice of 5 mm was made because of morphological and epidemiological observations. Morphologically, superficial endometriosis (mostly subtle lesions) is an active disease in some 50% of lesions.[7] Lesions infiltrating only a few mm (mostly typical lesions) have frequently a burnt-out aspect, whereas lesions infiltrating deeper than 5 mm are morphologically the most active lesions. For infiltrating lesions a transition zone between morphologically active and inactive areas is estimated around 5–6 mm of depth. A second argument is derived from the frequency distribution of the depth of infiltration in women with pain and/or infertility, which is clearly biphasic with a nadir at 5–6 mm.[8] Both observations suggest that in the majority of women the endometriotic lesion infiltrates only superficially, and becomes inactive; however, when they infiltrate deeper than 5 mm, the disease becomes more active and aggressive, and develops into a much deeper lesion.

Laparoscopically endometriotic lesions defined as infiltrating deeper than 5 mm from the peritoneal cavity present most frequently as an area with mainly typical but also subtle lesions.[11,12] During excision this lesion which is easily recognized reveals itself as conical shaped becoming progressively smaller in its deeper parts. This lesion, type I, was therefore suggested to be caused by infiltration. Type II lesions are characterized by a small endometriotic lesion, surrounded by a massive bowel retraction. Sometimes at laparoscopy only the retraction is visible and during excision a large endometriotic nodule is revealed to be situated deeply under the bowel, which is retracted over it. In contrast to type I lesions, these lesions thus are characterized mainly by retraction. It is unclear whether type I and type II lesions are different entities or whether these differences are a consequence of the localization of these lesions in the pelvis. Type III lesions are generally laparoscopically small typical lesions, or sometimes even a normal peritoneum, overlying an induration. During excision, a massive spherical and deep lesion becomes apparent. Whereas type I lesions can be found in the uterovesical fold but most frequently in the pouch of Douglas, type III lesions are found exclusively in the pouch of Douglas or on the uterosacral ligaments. For this reason, and because of their morphological aspect type III lesions were suggested to be caused by adenomyosis externa.

The definition of deeply infiltrating endometriosis as endometriosis infiltrating deeper than 5 mm does not rule out that different physiopathological mechanisms could lead to this condition. However, it stresses the concept that once endometriosis is situated deeper than 5 mm under the peritoneum, it becomes a different condition. It is morphologically more active; it starts to grow and forms large nodules with massive pelvic distortion and severe pain.

This concept also emphasizes the differences in physiology between superficial and deep endometriotic lesions. Whereas superficial pelvic endometriosis secrete CA125 and PP14 mainly towards the peritoneal cavity, deep endometriotic nodules secrete CA125 and PP14 mainly towards the blood stream.[13] Similarly it seems logical to postulate that superficial pelvic endometriosis is hormonally influenced mainly by the peritoneal fluid microenvironment, whereas deep endometriosis is mainly influenced by plasma hormone concentrations. A transition zone at a depth of some 5 mm where diffusion from the peritoneal cavity would become less important, seems theoretically acceptable. Deep endometriosis would thus become endometriosis which has escaped from the direct influence of peritoneal fluid (FIG. 1).

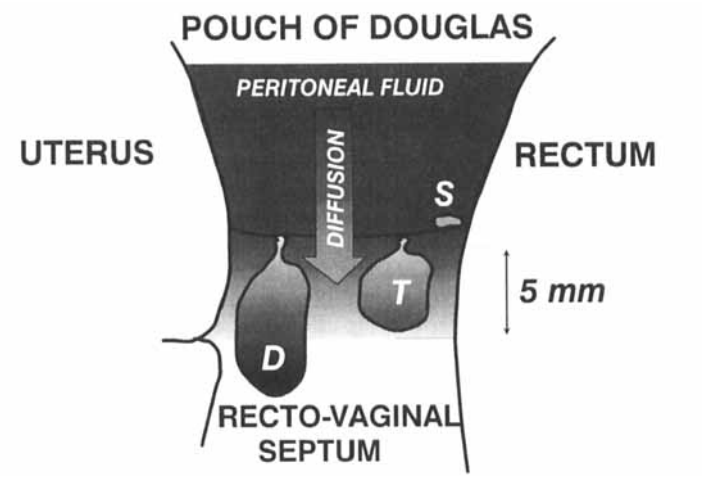

FIGURE 1. Deeply infiltrating endometriosis is defined as endometriosis infiltrating deeper than 5 mm under the pelvic peritoneum (D). It is suggested that subtle (S) and typical (T) lesions are mainly controlled by peritoneal fluid, whereas deep lesions are influenced by plasma hormones. Medical therapy could shrink deep lesions and bring them back under peritoneal fluid control.

Diagnosis of Deep Endometriosis[11]

Severe forms of deeply infiltrating endometriosis are clinically obvious. Extensive nodularities in the pouch of Douglas are felt by bimanual clinical examination. During laparoscopy large areas of pelvic endometriosis presenting as a white plaque with dark brown spots and/or subtle lesions are easily recognized as type I lesions because of the massive induration underneath. Also type II lesions are easily recognized as a small lesion surrounded by bowel retraction and pelvic distorsion. Type III lesions can easily be missed if the laparoscopist is not aware of the nodule felt during the clinical examination, or by palpation during laparoscopy.

Mild forms of deep endometriosis on the contrary are easily missed. At clinical examination the endometriosis cannot be felt except during menstruation.[10] Therefore, a routine examination during menstruation is recommended in all women suspected of having deep endometriosis. Sometimes at laparoscopy mild forms of deep endometriosis can only be detected when an induration is felt by palpation under an endometriotic lesion or even when an induration is felt in an otherwise completely normal pouch of Douglas. A preoperative clinical examination preferentially during menstruation can be extremely helpful in recognizing and localizing these lesions.

The extent and depth of both severe and mild forms of deep endometriosis becomes apparent only during excision. Therefore, we recommend that all suspected lesions be excised.[9] During excision the border between endometriosis and normal healthy tissue is scrupulously followed by combining palpation of induration and visual appearance. Since tissue damage and bleeding is minimal using a CO_2-laser, preferentially in superpulse mode to avoid carbonization, this is the method of choice to excise deep endometriosis. Scissors give a good feeling of induration and plane of cleavage, but the tissue damage accompanying electroco-

agulation, frequently blurs visual inspection. Since depth and lateral spread cannot be judged from the visual appearance, and since deep endometriosis often remains an almost "unexpected" finding during excision, coagulation or vaporization should not be used in any endometriotic lesion which could hide a deeper infiltrating lesion.

Because of the difficulty of making a diagnosis—clinically often unnoticed, laparoscopically sometimes invisible, really apparent only during excision—the clinical usefulness of ultrasound and magnetic resonance imaging (MRI) was investigated. Both techniques failed to detect reliably mild forms of deep endometriosis. Severe endometriosis was seen at MRI but the lateral spread and depth of invasion could not be predicted accurately.[14] CA125 plasma concentrations using a cut off concentration of 25 U/ml was shown to predict deep endometriosis with a sensitivity of 67% and a specificity of 90%.[13] Therefore, CA125 is recommended as a marker to be used in all women suspected of having deep endometriosis. Its clinical utility could become even more important when CA125 concentrations would be assayed during menstruation, or when the ratios between menstrual and follicular concentrations would be used, or when the CA125 concentrations would be used to diagnose type III lesions, which are clinically the most easily missed.

Treatment of Deep Endometriosis

The diagnosis and more specifically the depth of infiltration and the lateral spread of deep endometriosis can only be made during excision. While this is the treatment of choice, our experience over the last five years also shows that the recurrence rate after complete excision is very low. Overall recurrence seems to be less than 10%, and practically speaking in all these women the previous excision could be traced as incomplete. Incomplete excision has been the consequence of inexperience, especially at the beginning of our investigation of deep endometriosis. The proximity of the ureter and the bowel can make a complete excision technically impossible but this has changed with time. Whereas a few years ago we preferred to leave some endometriosis in the bowel wall, we now prefer to perform a complete excision and to suture the bowel endoscopically if necessary. Also the dissection of endometriosis from the ureter is progressively done more completely since ureter lesions and even transsection can be treated endoscopically using a double J.[16-17] Complete excision, for which the CO_2-laser is technically the method of choice, thus is the only method for diagnosing and curing deep endometriosis. It is obvious that a complete bowel preparation is mandatory in all women scheduled for excision of deep endometriosis.

Women with deep endometriosis present clinically with pelvic pain or infertility or both.[7-8] Women with pain generally have larger and deeper lesions than women with infertility only: lesions infiltrating deeper than 10 mm almost invariably cause severe pain. The results of complete excision of deep endometriosis in women with pain are excellent, more than 80% of women being and remaining pain free for at least five years, the duration of our actual follow-up period. Also in women with infertility cumulative pregnancy rates of 67% are obtained after six months. Using Cox's multivariate life table analysis, it was demonstrated that in women with a regular cycle, with a normal fertile husband, and without tubal occlusion, when the duration of infertility was taken into account, endometriosis was the main predictor of a subsequent pregnancy. In the group of women with endometriosis, both the presence of deep endometriosis and of cystic ovarian endometriosis

emerged as independent variables, whereas mild and moderate endometriosis were no longer significant as predictors.

Medical therapy of endometriosis has repeated been shown to give excellent results in alleviating pain in women with endometriosis.[18,19] Moreover, a large number of women remain pain free for longer periods following medical treatment by danazol, or GnRH agonists. On the other hand, medical treatment has been demonstrated to inactivate endometriosis, not to destroy endometriotic lesions.[20] Knowing that pelvic pain in women with endometriosis without cystic ovarian endometriosis is mainly caused by deep endometriosis, we suggest the following hypothesis. By inactivating endometriosis medical therapy will shrink the endometriotic nodule. If the remaining nodule would become less than 5–6 mm in depth, the endometriotic nodule would again become influenced by substances—hormones diffusing from the peritoneal fluid (FIG. 1). This could explain why many women remain pain free after medical treatment has been stopped. The importance of this concept would be that medical treatment should eventually be given intermittently in order to keep deep endometriosis under the influence of the peritoneal fluid and thus preventing it from further growth and infiltration.

In conclusion, our treatment of deep endometriosis is actually as follows. *Severe deep endometriosis* that is clinically obvious is pretreated with Decapeptyl (3.75 mg/month) or with danazol (400 mg daily) for 3 months. Clinically this makes the endometriotic nodule less vascularized while facilitating dissection. Shrinking of the nodule is anticipated but difficult to prove. *Mild forms of deep endometriosis* that are clinically only suspected are not medically pretreated. On the contrary, some have to undergo laparoscopy during menstruation, since in some women this is the only method of finding and excising deep endometriosis. In women refusing surgery, or with a recurrent disease, medical treatment is given for 6 months to 1 year. If necessary, the same treatment is continued intermittently for periods of 3 months.

DISCUSSION AND GENERAL CONSIDERATIONS

A Model of Endometriosis Which Suggests That Minimal and Mild Endometriosis Is a Natural Condition (FIG. 2)

Recent observations point to a very high incidence of endometriosis up to 80%—mostly subtle lesions—in women with pain and infertility.[8] Moreover, active remodeling of these lesions has become apparent in the baboon model,[21] whereas repeated laparoscopies suggest that subtle endometriosis is intermittently present in most animals. Since retrograde menstruation seems to be a normal condition occurring in most women we favor the hypothesis that implantation of some endometrial cells, giving rise to subtle lesions, could equally be a natural condition occurring intermittently in almost all women. This concept is consistent with the observation that endometriosis occurs in some 10% of normal fertile women and in some 10% to 20% of normal fertile baboons.[22] We suggest that a few months later, most of these lesions will have disappeared, whereas in some women new lesions at other localizations will be present; similarly some women with endometriosis would thus have become normal whereas others without endometriosis would have subtle lesions. This concept does not rule out that some conditions or influences would favor implantation and that some women would have a higher number and/or frequency of subtle lesions. Women with massive retrograde menstruation or with a LUF syndrome or with lower NK activity[23]

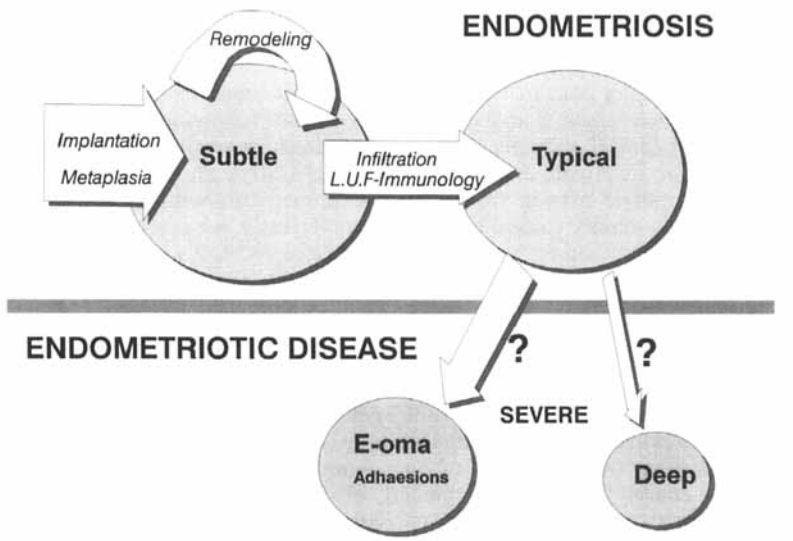

FIGURE 2. A model for endometriosis which emphasizes intermittent subtle endometriosis in (almost) all women and active remodeling. Superficial infiltration to burnt out typical lesions is rather frequent but in some women endometriosis develops into an endometriotic disease with severe lesions either cystic ovarian endometriosis or deep endometriosis, or both.

could thus have more implantation sites. Similarly, stress could be important as suggested in women, and since baboons have more and more frequently subtle lesions in captivity than in the wild.[24] Implantation of regurgitated endometrial cells would thus become a random process, which occurs rarely in some women and more frequently in others. At a cross sectional observation this would be reflected by a low or a high incidence of subtle lesions. Most important, however, is that in this concept subtle endometriosis would no longer be considered as a disease, but as a natural condition, only occurring more frequently in some women.

When the normal pelvic clearance mechanisms fail these endometriotic lesions can infiltrate. Our defense mechanisms, however, generally stop and control infiltration which remains superficial and ends as a burnt-out typical lesion. So also for many of these lesions the questions could be asked whether this is a disease, or rather the scar remaining after a healing process. Some of these lesions, however, will further infiltrate and develop into deep lesions.

Considering subtle and some typical lesions, a normal condition would raise the question whether it is useful to treat these lesions as superfluous. Moreover, this concept is consistent with the prevailing clinical observation that these lesions do not cause pain, whereas fertility is not enhanced after medical or surgical treatment.[25,26]

The physiopathological question would thus change from "why do some women develop endometriosis?" into "why does endometriosis become aggressive in some women?" or "why does endometriosis become an endometriotic disease?"

Endometriotic Disease: Deep Endometriosis and Ovarian Cystic Endometriosis

In some women endometriosis becomes aggressive and forms cystic ovarian endometriosis and/or deep endometriosis. These forms will therefore be called endometriotic disease in order to contrast them with subtle lesions and some typical lesions which will be called endometriosis.

Deep endometriosis and cystic ovarian endometriosis are two separate entities of endometriotic disease. They generally do not occur in the same women.[12] Cystic ovarian endometriosis is strongly associated with pelvic adhesions, whereas deep endometriosis is not.[8] Consequently, cystic ovarian endometriosis is classified as stage III or IV of the rAFS classification, whereas deep endometriosis is classified mainly as stages I and II. Both manifestations of the endometriotic disease are statistically found to be independent variables which predict pelvic pain,[8] which predict infertility (paper in preparation), which predict decreased natural killer cell activity in plasma,[27] and which predict increased plasma concentrations of CA125 and PP14.

It is interesting to note that both deep endometriosis and cystic ovarian endometriosis have escaped from the predominant influence of peritoneal fluid (FIG. 1). The former is mainly influenced by plasma concentrations, whereas the latter will probably be influenced to a large extent by ovarian microenvironment with at least much higher steroid hormone concentrations. This model also reemphasizes peritoneal fluid which has a predominant inhibiting role upon the development of endometriotic disease from endometriosis. Future studies will be necessary to determine which factors of this microenvironment—macrophages and natural killer cells, cytokines, angiogenic[28] and growth factors, steroid hormones and specific proteins—are a consequence of the clearing activity of endometriosis, and which factors permit or promote the development of endometriotic disease.

SUMMARY

Deeply infiltrating endometriosis can be defined as endometriosis infiltrating deeper than 5 mm under the peritoneal surface. Type I is a conical lesion suggested to be caused by infiltration; type II is mainly caused by retraction of the bowel over the lesion; type III is the most severe lesion suggested to be caused by adenomyosis externa. Severe cases are clinically apparent by nodularities in the pouch of Douglas, whereas mild and subtle forms of deep endometriosis are easily missed. Clinical examination during menstruation and scrutiny at laparoscopy for indurations, followed, preferably, by CO_2-laser-excision are the key features for diagnosis and treatment. It is importnat to realize that depth of infiltration and lateral spread cannot be evaluated by laparoscopic inspection but only during excision, that CA125 concentration but not ultrasound or nuclear magnetic resonance can be helpful in the diagnosis, and that in the most severe cases medical pretreatment is advocated. Results of excision, as evaluated by disappearance of pain in some 80% of women, by a cumulative pregnancy of some 70% and a low recurrence rate, are excellent.

The peritoneal fluid is thought to play a key role in the physiopathology of deep endometriosis which is considered to be endometriosis which has escaped from the influence of the peritoneal fluid. This concept is clinically important for the medical treatment of endometriosis, which is suggested to shrink deep lesions and to bring them back under peritoneal fluid control.

A model of endometriosis is proposed and discussed. Subtle lesions are considered a natural condition occurring intermittently in all women, whereas we question whether mild endometriosis is a disease. In some women endometriosis has an aggressive behavior and develops into cystic ovarian endometriosis or into deeply infiltrating endometriosis. In this model subtle and mild forms would be called "endometriosis," whereas deep and cystic ovarian forms could be called "endometriotic disease." It is stressed that deep and cystic ovarian endometriosis are two distinct entities, which is important for our understanding of endometriosis, for classification and for treatment of endometriosis.

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