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DEBATE

Is mild endometriosis a disease?

Is mild endometriosis a condition occurring intermittently in all women?

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The actual concept

Endometriosis has been defined histologically as the presence of endometrial glands and stroma outside the uterine cavity. It was described in the beginning of this century as adenomyosis in the rectovaginal septum (Cullen, 1991) or as ovarian 'chocolate' cysts (Sampson, 1921), both severe diseases. During recent decades our awareness of the multiple appearances of endometriosis and simultaneously of the high incidence, especially of subtle and non-pigmented lesions, has steadily increased (Jansen and Russel, 1986; Redwine 1987a; Martin *et al.*, 1989). Besides black pigmented lesions, a whole variety of white and red vesicles, flame-like lesions and polypoid lesions have been described, and the reported incidence in women with infertility or pelvic pain has risen to >60% (Koninckx *et al.*, 1991). The observation of microscopical endometriotic implants in a macroscopically normal peritoneum (Murphy *et al.*, 1986) moreover has led to the suggestion that the real incidence could even be much higher.

This concept is based on the assumption that all forms of endometriosis, not only the severe forms, but also the mild and subtle lesions, are a disease, an abnormal condition. The pathogenesis of endometriosis has thus been addressed with the question asked for all diseases 'Why do some women develop this disease, called endometriosis?'. Since retrograde menstruation is an almost universal phenomenon with viable endometrial cells found in peritoneal fluid of >70% of women (Koninckx *et al.*, 1980; Badawy *et al.*, 1984; Bartosik *et al.*, 1986; Kruitwagen *et al.*, 1991), the question has been asked why these cells do not implant in all women, i.e. why don't all women develop endometriosis? Hence several mechanisms controlling the implantation of endometrial cells and/or the induction of metaplasia have been investigated. The amount of retrograde menstruation was suggested to be more important in women with endometriosis than in women without endometriosis, since women with endometriosis have a less competent uterotubal sphincter mechanism as evaluated by uterotubal pressure profiles (Ayers and Friedenstab, 1985) and by uterine flushings (Badawy *et al.*, 1984; Bartosik *et al.*, 1986). The luteinized unruptured follicle syndrome (LUF) was proposed to facilitate the development of endometriosis (Koninckx *et al.*, 1980). Since in these women the peritoneal fluid concentrations of 17β-oestradiol and of progesterone were much lower following ovulation (Koninckx *et al.*, 1980), the high progesterone concentrations found in peritoneal fluid of normal women could be delet
implantation/survival/proliferation of regurgitate
cells. If the peritoneal cavity is considered as a garb
and disposal system, endometriosis would become
of insufficient disposal by macrophages (Evers, 19
a decreased natural killer cell activity (Oosterlynck
Finally, in women with endometriosis, peritoneal
more and activated macrophages, which secrete lo
of products, such as growth factors and cytokine
have been investigated as controlling mechanisn
implantation and further growth (Badawy
Oosterlynck *et al.*, 1993; Haney *et al.*, 1981; Syrc
1987; Halme *et al.*, 1983; Olive *et al.*, 1985; Fakil
Eisermann *et al.*, 1988; Weinberg *et al.*, 1991; H

This concept of endometriosis also explains the
in subtle and non-pigmented lesions. They are c
early stages of endometriosis because of their
appearance, because of the absence of surrounding
they are morphologically active and since th
decreases with the age of the women (Redwine, 19
et al., 1991).

Is subtle endometriosis a disease?

Repetitive laparoscopies in the baboon, with a 2
of spontaneous, mostly subtle, endometriosis, have
an active remodelling of these lesions (D'Hooghe
After a few months some lesions had regressed s
whereas new lesions had developed in other
important was that some animals with endometric
laparoscopy had become free of endometriosis,
initially normal baboons had developed endome

This concept of active remodelling is consiste
observations in women (Hoshiai *et al.*, 1993; Wie
1993), which suggest that the early stages of endom
not be considered as stable, but as a very dynamic s
together with the fact that retrograde menstruatio
a normal condition occurring in most women, st
put forward the hypothesis that implantation o
endometrial cells and/or induction of metaplasi
intermittently in most if not all women. Minimal
could thus no longer be considered as a disease wl
or not, but rather as an event occurring intermit
if not all women. It is important to realise tha
contradiction between this concept and the repor
of endometriosis in women, i.e. between 5 and 2
women (Vercellini and Crosignani, 1993) and re
in women with infertility and/or pelvic pain (Kc
1991). Since these incidences describe the percent
having lesions at one moment, it is suggested that
months later the same incidence would be found in t
of women, these lesions could be present in
Moreover, if endometriosis is considered as a dyr
these numbers can be interpreted as the percenta

each individual woman has lesions. This concept does not rule out the possibility that some conditions or influences would favour implantation/metaplasia and that some women would thus have more lesions or that lesions would be present more frequently. Women with more abundant retrograde menstruation, or with an LUF syndrome (Badawy *et al.*, 1984), or with lower natural killer activity in their peritoneal fluid (Oosterlynck *et al.*, 1992), could thus have more, or more frequently, implantation/metaplasia sites. Implantation/metaplasia could thus be considered a random process which occurs rarely in some women and more frequently in others. In a cross-sectional observation this would, however, be reflected by a lower or higher incidence of lesions.

The high incidence of endometriosis in women with infertility could thus rather reflect the probability of implantation and/or the rapidity of clearance in this group of women, rather than a fundamental difference between women with and without subtle endometriosis. This could explain why fertility is not significantly enhanced following the destruction or medical treatment of minimal endometriosis (Schenken and Malinak, 1982). Most important, however, is that in this concept subtle endometriosis would no longer be considered a disease, but rather a natural condition, occurring only more frequently in some women. Subtle endometriosis would thus become a symptom rather than a disease. This concept questions the rationale of treating subtle lesions except to prevent progression; it would also explain why hardly any differences can be found between women with unexplained infertility and those with subtle endometriosis only.

Progression to endometriotic disease

When the normal pelvic clearance mechanisms ., subtle lesions can develop and infiltrate the peritoneu Our defence mechanisms will, however, generally stop thi ıfiltration, and these lesions will remain superficial as burnt-ou ıorphologically inactive typical lesions (Cornillie *et al.*, 1990). T ıs also for these lesions, the question could be asked as to w her they are a disease or a scar remaining after a healing p ɔess.

In some women endometriosis becomes agg sive and forms cystic ovarian endometriosis or infiltrates ɔeply to form rectovaginal endometriosis. In contrast with sul endometriosis, both of these forms of endometriosis are cl ly pathological conditions, causing pelvic pain and infertility oninckx *et al.*, 1991). Both induce massive pelvic adhesi ., rectovaginal scarring or rectum retraction. Deep endome ɔsis and cystic ovarian endometriosis are, however, two dist t entities. They mostly do not occur in the same women (Kon kx and Martin, 1992). Cystic ovarian endometriosis is strong associated with pelvic adhesions, whereas deep endometriosi not (Koninckx *et al.*, 1991). Consequently cystic ovarian ıdometriosis is generally classified as stage III or IV of the ised American Fertility Society classification, whereas deep ıdometriosis is often classified as stages I and II. Both mai stations of the endometriotic disease are statistically found ɔe independent variables to predict pelvic pain (Koninckx *et al.* 991), to predict infertility (Koninckx, 1992), to predict the decr ed natural killer

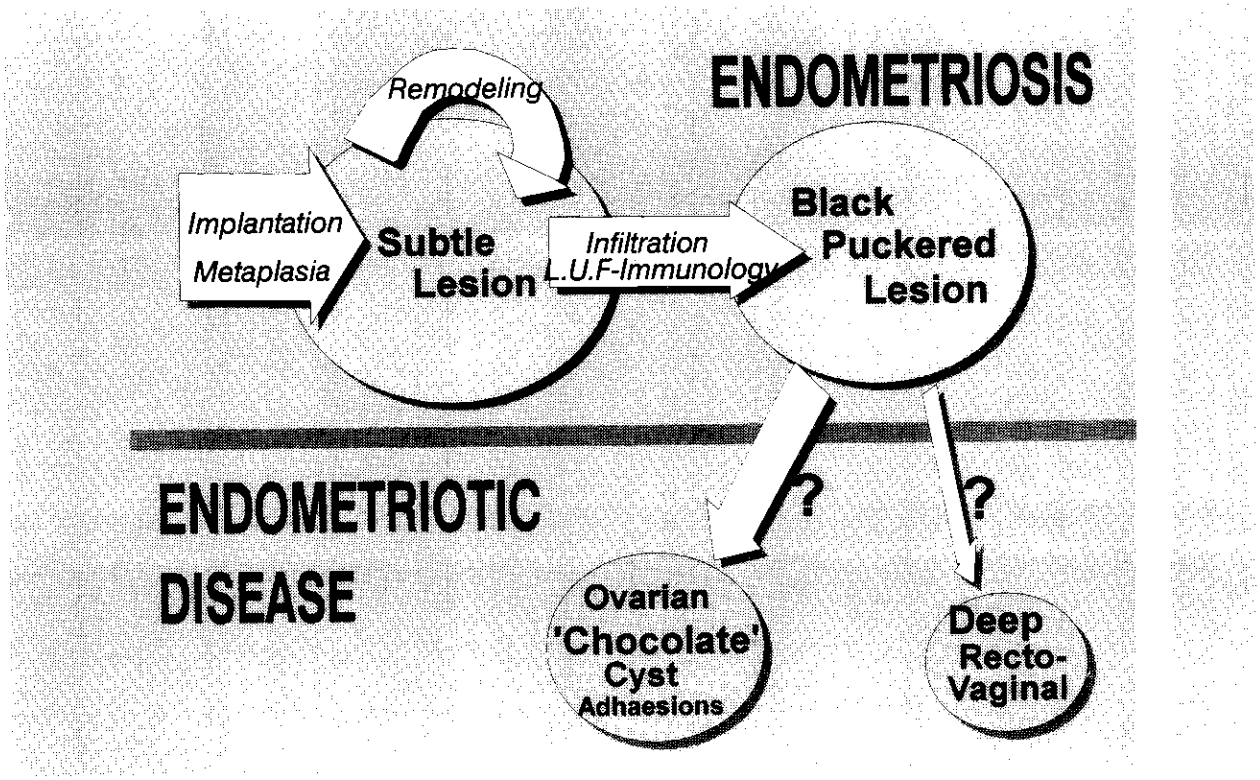

Fig. 1. A model for endometriosis. This model emphasizes the presence of subtle endometriosis in (almost) all women ai ictive remodelling. Superficial infiltration to burnt-out typical lesions, which are morphologically inactive, is rather frequent. In ne women endometriosis develops into endometriotic disease with severe lesions, either cystic ovarian endometriosis or deep endome ɔsis, or both.

cell activity in plasma (Oosterlynck *et al.*, 1991), and to predict the increased plasma concentrations of CA125 and PP14 (Koninckx *et al.*, 1992).

These considerations could lead to the following model (Figure 1). Subtle endometriosis would be a condition occurring intermittently in most women. The observed differences in incidence between normal women and women with infertility or pain would reflect the frequency of implantation or the activity of remodelling, rather than the presence or absence of a disease. Similarly, most black puckered lesions would become a manifestation of an infiltration, which has been arrested as burnt-out lesions. Subtle and black puckered lesions could be called 'endometriosis' to contrast them with pathological conditions for which the 'endometriotic disease' is proposed, i.e. when endometriosis becomes aggressive and forms cystic ovarian endometriosis, or deep endometriosis in the rectovaginal septum. In this model the question 'Why do some women develop endometriosis?' would become 'Why does endometriosis develop into an endometriotic disease in some women only?'.

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New clinical guidelines are needed for the treatment of endometriosis

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Dr Koninckx's clinical commentary is opportune after years of uncertainties. Together with recent publications by other experts (Editorial, 1992; Thomas, 1993), it suggests that the pelvis of women of reproductive age is not exactly as described in anatomy textbooks. Dr Koninckx summarizes the data that support the hypothesis of retrograde menstruation and implantation and proposes that mild endometriosis may be considered as a dynamic physiological state, occurring intermittently in virtually all premenopausal women. Only some cases have implants that do not regress spontaneously or are not eliminated by macrophages and lymphocytes, and develop into the progressive infiltrating or cystic lesions that characterize 'endometriotic disease'. The diagnostic variables, atypical aspects of the lesions, microscopic implants, genetic predisposition and possible immune deficiencies, are accurately reviewed by Dr Koninckx to support his proposal which, if confirmed, will generate more general questions.

For example, should the numerous 'menstrual insults' that the female pelvis has to tolerate nowadays be considered physiological from the phylogenetic point of view (Vercellini *et al.*, 1992)? Epidemiologic evidence has shown that one of the main risk factors for endometriosis is long periods of regular menstruations not interrupted by pregnancy (Vercellini and Crosignani, 1992a). In the course of the last few decades age at menarche has fallen, age at first pregnancy has risen, the number of children has decreased, and the frequency and duration of breast-feeding are limited. According to a recent editorial in the *Lancet*, the number of menstruations during reproductive age has risen from 30 to 50 in our grandmothers to 450 in the present generation (Editorial, 1992). Could endometriosis be considered a female disease typical of industrialized societies? If so, the immune deficiencies considered by some authors as fundamental fo ıe development of the disease, would not have a primary rc

If we accept Dr Koninckx's hypothesis, and re are excellent reasons for doing so, should we modify ou :urrent clinical guidelines which consider unexplained infer ty and chronic pelvic pain of unknown origin as indicators r laparoscopy? What will be the value of a laparoscopic gnosis of mild endometriosis, a very frequent condition in won of reproductive age including asymptomatic multiparas? How we distinguish a chance from a causal association? This m have practical consequences as the general consensus regar ıg laparoscopic investigation in cases of unexplained infertility l chronic pelvic pain was reached many years ago when e ɔmetriosis was believed to constitute a disease in all its forms. N d endometriosis is the single 'anomaly' most frequently observe these patients, but this finding may not always change the sub uent therapeutic programme to any great degree. Treatment sp fically directed at mild endometriotic implants has not been initively shown to improve the reproductive prognosis compa with expectant management (Candiani *et al.*, 1990; Arumug and Urquhart, 1991). Medical treatments offer temporary rel to women with pain but symptoms frequently recur after su nsion of drugs (Parazzini, 1994). Removal of limited lesions c ing laparoscopy does not always yield good results (Lim *et* ., 1989; Toma *et al.*, 1992).

As ~50% of lesions may regress spont ously, as it is *uncertain that medical treatments affect the na al history of the* disease, and above all considering that no diff nces have been observed in the antalgic effects of the variou drugs, would it not be reasonable to propose the preparati with the most acceptable side effects, the least metabolic i act and lowest costs, that is, progestins and oestrogen–proge combinations, as first line treatment for symptomatic v nen with mild endometriosis (Vercellini *et al.*, 1993)?

Dr Koninckx's hypothesis presents us wit arious possible choices for future studies. If in most cases r endometriosis is an intermittent condition that manifests in ma healthy women, is it correct to continue to include these fe is in biological research? If we do, do we risk 'diluting seful scientific information that may be obtained from patie who are really ill, that is, those with more advanced lesions' t present, there is no reliable screening test; is it sensible t ope to identify one, given the distribution characteristics endometriosis? Lastly, considering Dr Koninckx's hypoth probable, we believe that it is crucial to concentrate our eff s on identifying the factor(s) that stimulate limited and temp ury endometrial implants to progress to extensive and infiltrati lesions in some circumstances (Vercellini and Crosignani, 1 3b).

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