

## Epidemiology of endometriosis

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*Book chapter written april 2003.*

### 1 INTRODUCTION

Endometriosis is still poorly understood despite a high and still increasing publication rate of over 500 articles a year, i.e. 455 426, 448, 504 and 534 in the last 5 years respectively. It is considered to be one of the most important causes of pelvic pain and of infertility. The exact prevalence is not known since a laparoscopy is required to make the diagnosis and since the recognition varies with the training and the interest of the laparoscopist. Moreover the pathophysiology is poorly understood, which makes it difficult to formulate and test simple hypotheses.

The definitions of endometriosis have changed over time, contributing to biases in the literature. In the mid eighties, the non pigmented or subtle endometriosis was introduced, and from the nineties onwards the recognition of deep endometriosis has progressively increased.

The revised American Fertility Society (rAFS) classification is widely used. Yet we have to recognize that this classification has never been validated as a classification for pain or infertility.

Taken together, the absence of an easy non-invasive diagnosis, the changing definitions, and the absence of a clear understanding of the pathophysiology and the absence of a validated classification system, is the cause that still today the endometriosis literature is full of confusion.

We therefore consider it a prerequisite to introduce definitions and biases, and the problems of pathophysiology and classification systems, before discussing epidemiology.

## 2 DEFINITIONS AND BIASES IN THE LITERATURE

Endometriosis, defined as endometrial glands and stroma outside the uterus, was described at the turn of the century, as severe lesions such as ovarian “chocolate cysts”<sup>1</sup>, and as adenomyosis externa<sup>2-7</sup>. Smaller lesions were already in 1899 described by Russell<sup>8</sup> who wrote, “*On the microscopic study of the ovary, we were astonished to find areas which were an exact prototype of the uterine glands and interglandular connective tissue.*”. For the next decades, endometriosis was described as a disorder causing pain and requiring surgery. During that period other localisations<sup>9</sup> were described and endometriosis was reported as an ‘accidental’ finding during surgery for other gynecological disorders<sup>10-12</sup>. Only after the introduction of endoscopy in the late 1960’s black-puckered endometriosis lesions were recognized to be a frequent observation in women with pain and/or infertility. When in the 1980’s non-pigmented endometriotic lesions were described<sup>13-16</sup>, the observed prevalence of the disease further increased<sup>17;1819-25</sup>. In the nineties, the awareness of deep infiltrating endometriosis increased progressively together with the recognition that this type of endometriosis was not always diagnosed during laparoscopy or surgery, especially not during the previous decades.

### 2.1 Subtle Endometriosis

Following the recognition of non-pigmented endometriosis<sup>26</sup> in the mid eighties, the race to find smaller and smaller implants led to a series of articles describing polypoid lesions<sup>14-16;27;28</sup>, white and red vesicles, flame like lesions, and finally microscopic endometriosis<sup>29-31</sup>, visible only under the microscope or by scanning electron microscopy<sup>32;33</sup>. This led to the suggestion that microscopic endometriosis could be present in all women, inducing techniques as peritoneal washings<sup>34</sup> or blood painting<sup>35</sup> to diagnose endometriosis. The interest in non-pigmented endometriosis was fueled, by the observation that these lesions were morphologically very active, leading to the speculation that this activity should be paralleled by secretion of ‘active’ substances in peritoneal fluid<sup>36</sup>, which could explain the infertility and pain. The activity of these lesions also made them prime candidates to be stimulated to grow and progress by substances in peritoneal fluid and to be inhibited by medical treatment<sup>37-42</sup>. This was indirectly expressed and emphasized when it was proposed to judge the severity of endometriosis by its degree of activity, rather than by its extend<sup>43</sup>. The word ‘subtle’ endometriosis will be used throughout the text to refer to these lesions, which I would prefer to define as small, superficial and active lesions, without surrounding sclerosis and without the hemosiderin black spots.

Subtle lesions are well recognized to containing gland and stoma, and thus fit the definition of endometriosis. Yet a major problem persist concerning recognition and definition. Its recognition increases with awareness and with training of the surgeon, whereas the morphological confirmation of endometriosis rarely exceeds 60 (57%<sup>44</sup>). This is generally attributed to technical problems to biopsy these small lesions and to detect them after processing. On the other hand, endometriosis like lesions are equally well recognized. These are presented at meetings as curiosities, or as occasional findings. It remains unclear, however, for each individual author, to judge exactly the prevalence of these endometriosis like lesions, in what is reported as endometriosis. Even when biopsies have been taken, it remains unclear how women with subtle lesions which have not been confirmed by biopsy, should be classified.

Confusion could be pushed further by the concept of microscopical endometriosis, according to which all women would have endometriosis. The data to support this concept have been rather anecdotal whereas in a systematic study in baboons the incidence is low<sup>45</sup>. Very recently even the concept of non implanted endometriosis in peritoneal fluid has been put forward, to be distinguished from retrograde menstruation.

### 2.2 Typical Endometriosis

Typical lesions are described as black puckered lesions generally surrounded by a sclerotic area and by a typical vascular pattern, suggesting, angiogenesis.

We may assume that these lesions are readily recognized by the dedicated surgeon. Yet at least 2 biases exist in their detection and reporting. The first was already mentioned, ie the endometriosis like lesions, of which the exact prevalence is unknown. The second is endometriosis on the diaphragm. This has been considered a rare localization, but we must admit that the number of surgeons who systematically inspect the diaphragm in steep anti-Trendelenburg, with a 30 degree scope is very low. Thirdly even for this lesion the histologic confirmation rarely exceeds 80% (76%<sup>44</sup>, even 50%<sup>46</sup>)

### 2.3 Cystic Ovarian Endometriosis

The most important bias in the literature on cystic ovarian endometriosis is that clinically it can be very difficult to distinguish this condition from a cystic corpus luteum. The persistence of a ‘chocolate’ cyst is unreliable to diagnose cystic ovarian endometriosis since over the years several women with a “chocolate cyst” on ultrasound, persisting for more than 4 months even during treatment with LH-RH agonist or on oral contraception, have been found to have a cystic corpus luteum. We are fully aware that these clinical observations do not allow any conclusion about frequency of this problem, but the observations are consistent with the report that ovarian cysts can develop during ovarian down regulation<sup>47</sup>. Imaging, such as ultrasound and CAT scanning, has a sensitivity of 70% to 80% and a specificity of 90% to 95%<sup>48;49;52</sup>. This is a valuable method of diagnosis helping in the clinical management. It will, however, not prevent errors of judgment during surgery. Ovarian flow measurement does not seem to improve substantially specificity or sensitivity<sup>48</sup>. CA125 in chocolate fluid has been reported to have a sensitivity and a specificity of nearly 100%<sup>53;54</sup>. Unfortunately a rapid test, e.g. a stick assay is not available to make the diagnosis during surgery. A clinical rule of thumb is that, since cystic ovarian endometriosis is so strongly associated with adhesions<sup>25</sup>, a “chocolate cyst” without adhesions has a high probability of being a cystic corpus luteum whereas the presence of severe adhesions especially in the fossa ovarica enhances the suspicion of an endometriotic cyst. This, together with the inspection of the inside of the cyst by ovarioscopy<sup>55</sup> or by inspection with the laparoscope<sup>56</sup>, will help to make a correct judgment in the majority of women. *Those with a flattened appearance and red or red and brown mottled ridges generally were endometriosis and those with a dark uniform base, an intracavitary clot, or a yellowish rim generally were corpus lutea or albicans*<sup>57</sup>.

A second bias is that the pathology report following surgery not infrequently concludes that the cyst is ‘compatible with endometriosis’, without a positive identification of endometrial glands and stroma. This problem is well known, especially for larger cysts, but rarely addressed specifically in the literature, making it often difficult to judge how strict the diagnosis of the reported endometriotic cysts was made.

Although probably not important to evaluate prevalence we should be aware that different treatments are important to interpret results and recurrence rates. The latter is rarely reported, ie whether women undergoing surgery for cystic ovarian endometriosis had been operated previously for endometriosis. During the microsurgery period the cyst wall was excised and the ovary was repaired with suturing<sup>58</sup>. After the introduction of endoscopic surgery several techniques were developed. Aspiration and rinsing of cystic ovarian endometriosis has been attempted but the recurrence rate is high<sup>59-61</sup>. For smaller cysts, i.e. less than 5 cm diameter, the method of stripping the cyst from the ovary, is rapid and technically relatively easy<sup>62</sup>. Closure of the ovary by tissucol or a suture is highly variable. The cyst wall can be vaporized<sup>63</sup> or destroyed by unipolar or semi bipolar coagulation. The third option besides wall excision and wall destruction is focal treatment<sup>64</sup>. To understand the rationale of focal treatment, the rediscovery of the work of Hughesdon<sup>31;65;66</sup> was important, since he described by serial sections that an ovarian cyst could develop from adherence of the ovary to the side wall with the subsequent invagination and the stretching of the ovarian capsule over a pseudocyst formed by the hemorrhagic/chocolate fluid.

These considerations, describing the difficulty of diagnosis, and the different techniques used for treatment should be taken into account when interpreting results and prevalence<sup>67-70</sup>.

### 2.4 Deep Endometriosis

In the nineties it was realized that deep endometriosis was a frequent disease, either recognized during laparoscopic surgery<sup>25;71</sup>, or by clinical examination during menstruation<sup>72</sup>. The endoscopic excision of

endometriosis has revealed that endometriosis invading deeper than 5-6 mm is associated with pain and infertility. Three subtypes were described<sup>73</sup>. Type I is characterized by a large pelvic area of typical and sometimes some subtle endometriotic lesions surrounded by white sclerotic tissue. Only during excision does it become obvious that the endometriotic lesions infiltrate deeper than 5 mm. Typically the endometriotic area becomes progressively smaller as it grows deeper, the lesion is thus cone shaped. Type II lesions are characterized by retraction of the bowel. Clinically they are recognized by the obvious bowel retraction around a small typical lesion. In some women, however, no endometriosis can be seen through the laparoscope, and the bowel retraction is the only clinical sign. Diagnosis is generally not too difficult since during laparoscopy the retraction under which an induration is felt, is obvious. In some women however the retraction is hardly seen and the induration can be hardly felt. Only during excision the endometriotic nodule becomes apparent, emphasizing the need for a pre-operative diagnosis and training in recognizing these lesions. Type III lesions are spherical endometriotic nodules above or in the rectovaginal septum. In their most typical manifestation these lesions are felt as painful nodularities. At laparoscopy they generally present as a small typical lesion, and in some women a careful vaginal examination reveals some dark blue cysts (3-4 mm) in the fornix posterior. Sclerosing endometriosis, invading the sigmoid is similar to the rectal endometriosis, but is situated 10 cm above the rectovaginal septum. This is another form of deep endometriosis, which is fortunately a rare condition and which we proposed to classify as type IV.

The literature on deep endometriosis is confusing and biased. It is readily recognized that deep endometriosis cannot be diagnosed reliably by clinical examination. Even during menstruation higher situated deep endometriosis will not be felt. Although larger lesions can be diagnosed by contrast enema, or by transvaginal or trans rectal ultrasound, or MRI, for none of these imaging techniques the sensitivity of detecting smaller lesions have been reported. As expertise and awareness has grown, I have realized that I must have missed a substantial amount of these lesions, during surgery, especially the smaller rectovaginal lesions or the type IV lesions. About prevalence of other localizations, such as caecum, or bowel, we only can speculate. A second bias is the enthusiasm of reporting deep endometriosis surgery, including mainly endometriotic lesions, being rather small, but just fitting the definition of 5mm.

## 2.5 Biases and shifts in the literature

Over the last 20 years gradual shifts in the recognition of the different stages of endometriosis thus occurred. The most important is the recognition of subtle endometriosis since the mid eighties. This not only has increased the apparent prevalence of endometriosis, it has also caused major shifts in what are considered normal women. Before that period women with minimal and mild endometriosis comprised almost exclusively women with typical lesions, whereas so-called normal women comprised women with subtle endometriosis only. This shift alone explains why the association of the luteinized follicle syndrome (LUF) and minimal endometriosis which was systematically found before 1985 in all articles disappeared progressively after that period, the LUF syndrome being associated with typical lesions, but not with subtle lesions.

The awareness of these shifts is important to understand and interpret the data reported in the literature. This is extremely important when discussing prevalence, and also when older data are compared with more recent observations.

The bias of confusing cystic ovarian endometriosis and cystic corpora lutea, will have little effect upon the reported prevalence although in some series cystic corpora lutea can make up to 30% of the reported patients.

The increased awareness of deep endometriosis has increased the apparent prevalence over the years. The recognition that the small lesions tend to go unnoticed even during laparoscopy, because of lack of performing diagnostic methods, leads to the conclusion that the prevalence of deep endometriosis is underreported. This is especially important in studies concerning pelvic pain.

### 3 CLASSIFICATION OF ENDOMETRIOSIS

The widely used rAFS classification, is a point scoring system. Reviewing its meaning we demonstrated that class I contained superficial lesions with a total area of less than 3 cm<sup>2</sup>, class II, superficial lesions with a total area of more than 3 cm<sup>2</sup>, whereas classes III and IV comprised mainly cystic ovarian endometriosis. The important contribution of adhesions to the rAFS classification, and the association of cystic ovarian endometriosis and adhesions, easily explains this.<sup>25</sup> It should be stressed that the rAFS has never been validated as a tool to score neither infertility, nor pain.

Since the clinical importance of subtle lesions is questionable, it might be preferable to regroup women with subtle lesions into a separate class.

Deep lesions are found in all 4 rAFS classes, but mainly in classes I and II. For pain it has been demonstrated, that if these lesions are regrouped in a separate class, both area, cystic ovarian and deep lesions correlate with pain. If this is not done, these associations disappear, since the milder endometriosis groups are variably contaminated with deep endometriosis, which is strongly associated with pain.

### 4 PATHOPHYSIOLOGY

#### 4.1 Sampson and metaplasia theory

Both Sampson retrograde menstruation, and implantation and the metaplasia theory focus upon the implantation/metaplasia of cells, and thus on subtle lesions, i.e. small initial lesions, which will subsequently grow and develop to more severe disease. These theories are attractive because of the abundance of data demonstrating retrograde menstruation as a frequent phenomenon occurring almost in all women, the presence in peritoneal fluid of viable endometrial cells, which have the capacity to implant, to grow and to infiltrate superficially. According to this view, the development into a more severe condition may be influenced by a decreased cellular immunity, a lower NK cell activity, peritoneal fluid cytokines and growth factors, or low peritoneal fluid steroid concentrations in the luteal phase. These theories are attractive since each step in the pathophysiology has been documented.

It is important to recognize that this theory, cannot explain why progression occurs in some women only. Fundamentally this theory holds that progression of endometriosis once established is unavoidable, albeit at a different speed and to a different stage according to modulating factors. Essentially, this theory considers endometriosis as normal endometrial cells which behave abnormally, because of the abnormal environment, i.e. the peritoneal milieu. This is however, not supported by all.<sup>74</sup> The key event in the process is implantation or metaplasia, which thus has been the subject of many investigations, and the early subtle lesions become very important.

#### 4.2 The endometriotic disease theory<sup>75</sup>

This theory considers retrograde menstruation, viable endometrial cells in peritoneal fluid, and occasional implantation of some of these cells a normal physiological phenomenon. These non-implanted and implanted cells are normally removed by the defense mechanisms of the body such as macrophages. Attachment and implantation is favoured when the mesothelial layer is damaged by trauma, infection or even by low grade inflammation, e.g. irritation caused by CO<sub>2</sub> pneumoperitoneum, or by abundant retrograde menstruation. It also seems logical that attachment and implantation must occur more frequently when more viable cells are present in peritoneal fluid. Although these cells can temporarily grow and develop depending upon the environment, their ultimate fate when left alone will be their spontaneous disappearance. This can result in some fibrotic or scar tissue as the remnant of local inflammation, containing eventually some endometrial cells, shielded from the blood stream and immunocompetent cells comparable to the bacteria in an abscess.

Endometriotic disease is caused by a cellular modification, e.g. genetic mutation as observed in many benign tumors. This cellular accident will happen more frequently in genetically predisposed persons, and will be favored by other factors such as total body irradiation, or chemical pollutants such as dioxins. It also seems logic that the probability that such a cellular accident occurs, is higher when more cells are present. The type of cellular modification together with local factors such as the peritoneal fluid micro-environment or the intra-ovarian milieu will determine whether they will develop into typical lesions, deep endometriosis or cystic ovarian endometriosis and whether the morphological characteristics will be chocolate cysts, endometrial glands and stroma or adenomyosis externa.

Key for the EDT, is that subtle lesions are considered a normal physiologic condition, occurring intermittently in all women. Typical, cystic and deep endometriosis are considered as benign tumor, originating from a cellular incident transforming an endometrial cell into an endometriotic cell. According to the EDT, endometriotic disease is an abnormal cell in an abnormal environment.

### 4.3 Pathophysiology and prevalence

The theories of pathophysiology of endometriosis are essential to discuss prevalence. Indeed, according to the EDT subtle endometriosis will be considered a physiological condition, occurring intermittently in all women, and that these lesions should not be considered a disease<sup>59</sup> According to Sampson/metaplasia theories, subtle lesions are the early stages as endometriosis and extremely important since very active. In this view, it is logical to scrutinize the pelvis for these early and small endometriosis lesions, which should be treated to prevent progression and to treat the disease.

Therefore the epidemiology of the 4 major presentations of endometriosis will be discussed separately.

## 5 EPIDEMIOLOGY

*“Although neither the ideal design nor the ideal case and control groups are likely to be achievable in epidemiologic studies of endometriosis, better subject-selection strategies may improve the validity of studies that are obliged to depart from the ideal”<sup>76</sup>*

### 5.1 Subtle Endometriosis

When, in the 1980's non-pigmented endometriotic lesions were described<sup>13-16</sup>, the prevalence of the disease increased from 5% to 20% to over 60% to 80% in women with infertility and/or pelvic pain<sup>17-25;77</sup> The prevalence clearly increases with the awareness and the training of the surgeon. In all series the underlying biases of no confirmation or at best limited confirmation by pathology should be recognized.

The prevalence of subtle lesions decreases with age for unknown reasons<sup>25;78</sup>. No studies are available demonstrating a clear association with any of the variables considered important such as early menarche, short cycles, abundant or painful periods, subfertility, canalization defects of the cervix, race, dioxin, total body radiation, or any other factor.

### 5.2 Typical Endometriosis

Assuming that typical endometriosis contributes predominantly, to the reported prevalences of endometriosis, the prevalences in a clinic populations vary from about a 4% occurrence of largely asymptomatic endometriosis found in women undergoing tubal ligation to 50% of teenagers with intractable dysmenorrhea. Prevalences in women with pain or infertility range between 40 to 70%.<sup>25;46</sup> General population incidence during the 1970s in the USA has been suggested to be 1.6 per 1000 white females aged 15-49, while a more current study based upon hospital discharges finds endometriosis as a first listed diagnosis in 1.3 per 1000 discharges in women aged 15-44.<sup>79</sup> In a recent large study comprising all women in an area in Norway the lifetime risk for endometriosis was 2.2%<sup>80</sup> In this study, early menarche, frequent menstruations, pelvic pain, infertility and nulliparity are associated with endometriosis. In a controlled study of women with infertility and a normal partner, compared with women with an azoospermic partner, stage I endometriosis is not more common in infertile women than

in an unselected women. However, stage II disease endometriosis was more frequent , (3.3% vs. 5.7%) in infertile women.<sup>81</sup>

There is a non validated clinical impression that endometriosis could vary with the race, blacks having a lower rates of endometriosis and Orientals have higher rates than whites.

According to the Sampson theory abundant retrograde menstruation should be a predisposing factor for endometriosis. This seems to be clinically and experimentally supported by increased prevalence of endometriosis in women and primates with obstructed uterine outflow. It has been reported that women with endometriosis might have more abundant periods, and early menarche. A recent review failed however, to demonstrate this association<sup>82</sup>. Endometriosis is clearly associated with dysmenorrhea, but it is unknown whether this is a cause or a consequence.

Dioxin pollution has been suggested to be causally related to endometriosis. This hypothesis, formulated in 1994<sup>83</sup> based upon indirect observations, became popular following the observation that the incidence and the severity of endometriosis increased in primates treated previously with dioxins<sup>84;85</sup>. In the human final proof is still lacking.<sup>86</sup> The Seveso accident, with massive pollution, suggest a non significant doubling of prevalence.<sup>87</sup> Breast-fed infants, possibly exposed to dioxins in milk, moreover have unexpectedly a lower incidence of endometriosis in adult life.<sup>88</sup>

Total body radiation is associated with increased prevalence of endometriosis in primates<sup>89</sup>. Little evidence is available to support this in the human.

Endometriosis clearly is an hereditary disease.<sup>90-98</sup> The prevalence of first degree relatives is some 7 times higher than in control groups. In monozygotic twins the prevalence is even up to 15 times higher.

The lower natural killer cell activity in plasma and in peritoneal fluid<sup>71;99-106</sup>, has fueled speculation about the role of the immune system and endometriosis.<sup>107-110</sup> Until today, however, no clear association is found between endometriosis prevalence and chronic immunosuppression, eg in transplant patients , nor with smoking affecting NK activity, nor with caffeine or alcohol, nor with any lifestyle variable.

Stress could be causally related to endometriosis. This concept is derived from the association of endometriosis and LUF syndrome, of an association between a higher trait anxiety and LUF syndrome<sup>111-114</sup>, and of the hypothesis that the lower steroid hormone concentrations in peritoneal fluid might favour the implantation/development of endometriosis<sup>115</sup>. This hypothesis can, however, not be tested since there is no adequate animal model. The best model is the baboon and it was shown that baboons in captivity have more endometriosis than in the wild (probably through stress).<sup>116</sup> Another argument to link endometriosis and stress is the widely held belief that endometriosis is a career womens disease. This, however, can equally well be explained by the delay of childbearing in this group of women, with the inevitable increase of infertility with age, and a higher prevalence of endometriosis at laparoscopy.

Nulliparity could be a consequence of the disease but in a large study in Italy the prevalence decreased with increasing parity.<sup>117</sup>

Oral contraception use has been reported to be associated with a decreased prevalence<sup>17</sup>.

Endometriosis was recently suggested to be associated with an increased risk in ovarian cancer (OR = 1.73, 95% CI: 1.10, 2.71)<sup>118</sup>, and of non hodgkin lymphoma<sup>119</sup>

### 5.3 Cystic Ovarian Endometriosis.

Cystic ovarian endometriosis increases with age<sup>25</sup>. Most reports confirmed that cystic ovarian endometriosis is clonal in origin.<sup>120-123</sup>

### 5.4 Deep Endometriosis

Deep endometriosis increases with age<sup>25</sup>. Rectovaginal endometriosis was known since the beginning of the century, but the high prevalence of deep endometriosis remained unsuspected until fairly recently. In the population these conditions, were considered relatively rare but actually estimates of prevalence of 3

to 10% seem appropriate. This estimation of some 10% to 20% deep endometriosis is derived from observations in Leuven from 1988 to 1991<sup>25</sup>, a period during which endoscopic surgery was not yet well developed, and in which deep endometriosis was not yet a well known entity. Referrals were thus only those for infertility and pain not for deep endometriosis. Assuming that laparoscopies for infertility are performed in some 10% to 15% of the population and taking into account that Leuven is a tertiary referral center, the prevalence of deep endometriosis can be estimated to be between 1% (the prevalence is 10% in younger age group with infertility which can be estimated at 15% of the population ; in a tertiary center the prevalence is probably slightly overestimated) and 3% (prevalence of 20% of the older age group with infertility). Taking into account the observation that by menstrual clinical examination deep endometriosis is more frequent, prevalences between 3% and 10% seem a fair estimate.

No data are available to link deep endometriosis specifically to a subgroup of women, or to a potential causal factor.

### 5.5 Endometriosis and cancer

Occasional reports describe cancer in cystic ovarian<sup>124</sup> or severe endometriosis<sup>96,125</sup>. We recently diagnosed an adenocarcinoma in a deep endometriotic lesions.

## 6 CONCLUSIONS AND DISCUSSION

To understand the reports concerning the epidemiology of endometriosis, it is important to clearly distinguish between subtle, typical, cystic and deep endometriosis, and to understand the shifts which have occurred mainly in the recognition of subtle endometriosis and of deep endometriosis. Moreover, a simple non invasive test of endometriosis is not available making unbiased studies almost impossible for ethical reasons.

The prevalence of endometriosis is undoubtedly high, certainly in women with pain and or infertility. Estimations of subtle endometriosis range from 5 to 50 and from 50 to 80% in asymptomatic or symptomatic women respectively. For typical lesions, estimations are less than half of these figures, but the data have been collected before 1985. For severe endometriosis either cystic or deep, estimations in the population range between 1 and 10%.

A poorly addressed problem is the variability of prevalences by region and country. No systematic studies are available, but in my experience, it is obvious that the prevalence of very severe deep endometriosis must be higher in Belgium than in eg the United Kingdom or south Italy, where I only occasionally encountered this type of lesion. In Moscow on the contrary, the prevalence of severe endometriosis is high. In arab countries endometriosis is rare. This unfortunately is anecdotic evidence, but in line with the hypothesis of pollution.

Endometriosis clearly is an hereditary disease, as demonstrated for typical and cystic ovarian endometriosis. Increased retrograde menstruation, eg by outflow obstruction, will increase the prevalence of endometriosis.

Poorly understood is the role of nutrition, of life style, of personality traits, of the immune system, of the peritoneal fluid and other variables. For most of these factors indirect evidence strongly suggest a modulating role. The key question, remains however, to find an answer to the question whether endometriosis is a normal endometrial cell or an abnormal-a modified endometrial cell. This is important to understand prevention which can be prevention of implantation, or prevention of cellular damage. Also for therapy this would constitute a fundamental difference, since a modified endometrial cell could have a specific point of attack, without damaging the endometrium.

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