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Epidemiology of Endometriosis

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INTRODUCTION

Endometriosis is still a poorly understood condition. This is despite the high and still increasing publication of more than 500 articles per year. For example, there were 455, 426, 448, 504, and 534 articles in the past 5 years, respectively. Endometriosis is considered to be one of the most important causes of pelvic pain and infertility. The exact prevalence is unknown, as a laparoscopy is required to make the diagnosis and the recognition varies with the experience 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 concept of nonpigmented 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, it 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 are the reasons why there are still many controversies surrounding endometriosis.

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

DEFINITIONS AND BIASES IN THE LITERATURE

Endometriosis is defined as the presence of endometrial glands and stroma outside the uterus. It was described at the turn of the century as severe lesions such as ovarian "chocolate cysts" [1] and as adenomyosis externa [2–7]. In 1899, Russell [8] 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." In the following decades, endometriosis was described as a disorder causing pain and requiring surgery. During that period, other sites [9] were described, and endometriosis was reported as an "accidental" finding during surgery for other gynecological disorders [10–12].

Only after the introduction of endoscopy in the late 1960s, black-puckered endometriosis lesions were recognized as a frequent observation in women with pain or infertility. Following the description of nonpigmented endometriosis in the mid eighties [13–16], the prevalence of the disease increased [17–25]. In the 90s, the awareness of deep infiltrating endometriosis increased progressively, together with the recognition that this type of endometriosis was not always diagnosed during surgery.

Subtle Endometriosis

Following the recognition of nonpigmented endometriosis [26] in the mid-80s, the race to find smaller implants led to a series of articles describing polypoid lesions [14–16,27,28], white and red vesicles, flamelike lesions, and finally microscopic endometriosis [29–31]. The latter is visible only under the microscope or by scanning electron microscopy [32,33]. This led to the suggestion that microscopic endometriosis could be present in all women, which induced techniques such as peritoneal washings [34] or blood painting [35] to diagnose endometriosis.

The interest in nonpigmented endometriosis was further triggered by the observation that these lesions were morphologically very active, leading to the speculation that this activity is due to secretion of "active" substances in peritoneal fluid [36], which could explain infertility and pain. These lesions

can be stimulated to develop by substances in peritoneal fluid and suppressed by medical treatment [37–42]. It has been postulated that the severity of endometriosis is better assessed by its degree of activity, rather than by its extent [43]. We will use the term "subtle endometriosis" throughout the text to refer to these lesions. I prefer to define them as small, superficial, and active lesions without surrounding sclerosis and without the hemosiderin black spots.

Subtle lesions contain gland and stroma, and thus fit the definition of endometriosis. However, recognition and definition of these lesions remain controversial. Its recognition increases with the awareness and with experience of the surgeon. Morphologic confirmation of endometriosis rarely exceeds 60 (57%) [44]. This is generally attributed to technical problems of excision of these small lesions and detecting them after processing. Endometriosislike lesions are also well recognized. Their prevalence is unknown.

The concept of microscopic endometriosis makes the issue more complicated. According to this concept, all women would have endometriosis. The data to support it have been anecdotal, and a study in baboons showed that the incidence is low [45]. The newest concept is "nonimplanted endometriosis" in peritoneal fluid that has to be distinguished from retrograde menstruation.

Typical Endometriosis

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

We may assume that an experienced surgeon can readily recognize these lesions. Yet, at least two problems exist in their detection and reporting. The first is that the exact prevalence of endometriosislike lesions is unknown. The second is endometriosis on the diaphragm. This has been considered rare, but the number of surgeons who systematically inspect the diaphragm in steep Trendelenburg, with a 30-degree scope, is very low. Even for this lesion, the histological confirmation rarely exceeds 80% (76% [44], even 50% [46]).

Cystic Ovarian Endometriosis

Distinguishing cystic ovarian endometriosis from cystic corpus luteum can be difficult. Women with ultrasound findings of persistent endometriotic cyst of more than 4 months, including those who were treated with GnRHa or OCP, often were found to have only cystic corpus luteum at surgery. These clinical observations do not allow any conclusion about its prevalence, but are consistent with the report that ovarian cysts can develop during ovarian downregulation [47].

Imaging, such as ultrasound and CT scanning, has a sensitivity of 70% to 80% and a specificity of 90% to 95% [48–52]. This is a valuable method of preoperative diagnosis. Ovarian blood flow measurement does not seem to improve its specificity or sensitivity [48]. Measurement of CA125 in the endometrioma fluid increased the sensitivity and specificity to nearly 100% [53,54]. Unfortunately, a rapid test to assist an intraoperative diagnosis is not yet available.

In general, cystic ovarian endometriosis is associated with adhesions [25], whereas a "chocolate cyst" without adhesions is most likely a cystic corpus luteum. The presence of severe adhesions, especially in the fossa ovarica, should raise the suspicion of an endometriotic cyst. Diagnostic accuracy can be further increased by inspection of the inside of the cyst by ovarioscopy [55] or laparoscopy [56]. "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." [57].

A second problem is that the pathology report often reveals "compatible with endometriosis," without a positive identification of endometrial glands and stroma. This is not unusual, especially for larger cysts. However, it is rarely addressed in the literature, making it difficult to know how accurate the diagnosisis is.

Different treatments give different results and recurrence rates. During the microsurgery era, the procedure was done by excising the cyst wall and suturing the ovarian opening [58]. Today, there are several endoscopic techniques. Aspiration and rinsing of cystic ovarian endometriosis has been attempted, but the recurrence rate is high [59–61]. For cysts of less than 5 cm, the method of stripping the cyst from the ovary is rapid and relatively easy [62]. Closure of the ovary can be achieved by tissucol or sutures. The cyst wall can be vaporized [63] or destroyed with unipolar or bipolar coagulation. Another method is focal treatment [64]. To understand the rationale of focal treatment, the rediscovery of the work of Hughesdon [31, 65,66] is important. By serial sections of ovarian endometrioma, it was postulated that it developed from invagination of the ovarian cortex.

The difficulty in diagnosis, and the different techniques used for treatment should be taken into account when interpreting results and prevalence of endometriosis [67–70].

Deep Endometriosis

In the 90s it was realized that deep endometriosis was a frequent disease, either recognized during laparoscopic surgery [25,71] or by clinical examination during menstruation [72]. The endoscopic excision of endometriosis has

revealed that endometriosis deeper than 5 to 6 mm is associated with pai infertility. Three subtypes were described [73].

Type I is characterized by a large area of typical and sometimes s endometriotic lesions surrounded by white sclerotic tissue. Only during sion does it become obvious that the endometriosis infiltrates deeper 5 mm. Typically the endometriotic area becomes progressively smalle as it grows deeper, the lesion becomes cone shaped.

Type II lesions are characterized by retraction of the bowel. Clin they are recognized as a prominent bowel retraction around a small ty lesion. In some women, however, endometriosis might not be seen b laparoscope, and the bowel retraction is the only clinical sign. Diagnosis i difficult, because during the laparoscopy an induration under the bowe be felt. Otherwise, it is diagnosed only during excision.

Type III lesions are spherical endometriotic nodules above or i the rectovaginal septum. Typically, these lesions are felt as painful nodul some women, vaginal examination reveals some dark blue cysts (3–4 m the posterior fornix. Sclerosing endometriosis invading the sigmoid is si to the rectal endometriosis, but is situated 10 cm above the rectovagina tum. This is another rare form of deep endometriosis, which we propos classify as *type IV*.

The literature on deep endometriosis is confusing and controve The diagnosis of deep endometriosis cannot be established by clinical ex nation. Even during menstruation, high located deep endometriosis cann palpated. Large lesions can be diagnosed by contrast enema, transvagin transrectal ultrasound, or MRI. The sensitivity of these imaging techn for detecting smaller lesions is unknown. As my expertise and awarenes veloped, I realized that a substantial amount of these lesions, especiall smaller rectovaginal lesions or the type IV lesions, have been previ missed at surgery.

Biases and Shifts in the Literature

In the past 20 years, there has been a gradual evolution in the recogn of the different stages of endometriosis. Subtle endometriosis has been r nized since the mid-80s. This has increased the apparent prevalence of e metriosis. It has also change our perception of "normal women."

Traditionally, women with minimal and mild endometriosis wer most exclusively those with typical lesions, whereas "normal women" subtle endometriosis only. This evolution alone explains why the associ between luteinized unruptured follicle (LUF) syndrome and minimal e metriosis systematically reported before 1985 disappeared from the litera Luteinized unruptured follicle syndrome has been associated with ty lesions, but not with subtle lesions.

The awareness of these changes is important in understanding and interpreting the data reported in the literature. This is essential when discussing prevalence, and when comparing older data with more recent observations.

The bias of confusing cystic ovarian endometriosis and cystic corpora lutea will have little effect on the reported prevalence, although in some series cystic corpora lutea could be as high as 30%.

As surgeons became more aware of deep endometriosis over the years, its reported prevalence increased. The recognition that the small lesions tend to go unnoticed even during laparoscopy, mainly 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.

CLASSIFICATION OF ENDOMETRIOSIS

Revised AFS classification is a point scoring system. We found that class I consisted of superficial lesions with a total area of less than 3 cm^2; class II, superficial lesions with a total area of more than 3 cm^2; classes III and IV comprised mainly cystic ovarian endometriosis. The contribution of adhesions to the rAFS classification and its association with cystic ovarian endometriosis easily explains this [25]. It should be stressed that the rAFS has never been validated as a tool to evaluate infertility or pain objectively.

As 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 four rAFS classes, but mainly in classes I and II. When we regrouped these lesions into a separate class, we found that cystic ovarian endometriosis and deep lesions are those that correlate with pain. Without regrouping, these associations disappear. This is because milder endometriosis groups are variably contaminated with deep endometriosis.

PATHOPHYSIOLOGY

Sampson and Metaplasia Theory

Sampson's retrograde menstruation, implantation, and the metaplasia theory focuses on the implantation/metaplasia of cells. It refers to subtle and small initial lesions that will subsequently grow and develop to more severe disease. It is an attractive theory because of the abundance of data demonstrating retrograde menstruation as a frequent phenomenon in all women and the presence of viable endometrial cells in the peritoneal fluid, which have the capacity to implant, grow, and infiltrate superficially. According to this hypothesis, the development into advanced condition may be influenced

by a decreased cellular immunity, a lower natural killer (NK) cell activ peritoneal fluid cytokines and growth factors, or low peritoneal fluid ster concentrations in the luteal phase. Each step in the pathophysiology has b documented.

This theory, however, cannot explain why progression occurs in so women only. It holds that progression of endometriosis, once establish is unavoidable, albeit at a different speed and to a different stage accord to modulating factors. This theory considers endometriosis as normal en metrial cells behaving abnormally in an abnormal environment, that is, peritoneal milieu. However, this theory is not supported by all [74]. The k event in the process is implantation or metaplasia, which has been the subj of many investigations. The early subtle lesions become very important.

The Endometriotic Disease Theory

The endometriotic disease theory (EDT) [75] considers retrograde menstr ation, viable endometrial cells in peritoneal fluid, and occasional implan tion of these cells as a normal physiological phenomenon. The non implant and implanted cells are normally removed by the defense mechanisms the body, such as macrophages. Attachment and implantation occur wh the mesothelial layer is damaged by trauma, infection, or low-grade inflar mation, for example, irritation caused by CO2 pneumoperitoneum, or abundant retrograde menstruation. It seems logical that attachment and i plantation must occur more frequently when more viable cells are present peritoneal fluid. These cells can temporarily grow and develop, depending the environment. When left alone, they can also disappear spontaneous This may result in some fibrotic or scar tissue as the remnant of local inflar mation. It contains some endometrial cells, shielded from the bloodstrea and immunocompetent cells similar to bacteria in an abscess.

Endometriosis is caused by cellular modification, such as genetic mut tion, as observed in many benign tumors. This cellular modification occu more frequently in genetically predisposed persons, and it is facilitated b other factors such as total body irradiation, or by chemical pollutants, suc as dioxins. The probability that such an event occurs is higher when more cel are present seems logical. The type of cellular modification, together wi local factors such as the peritoneal fluid microenvironment or the intr ovarian milieu, will determine whether they will develop into typical lesion deep endometriosis, or cystic ovarian endometriosis, and whether the mo phological characteristics will be chocolate cysts, endometrial glands an stroma, or adenomyosis externa.

This theory also refers to subtle lesions as a normal physiological co dition, occurring intermittently in all women. Typical, cystic, and deep end

metriosis are considered as benign tumors, originating from a cellular modification transforming endometrial cells into endometriotic cells. Endometriotic disease is the presence of abnormal cells in an abnormal environment.

Pathophysiology and Prevalence

The theories of pathophysiology of endometriosis are essential in discussions of prevalence. Indeed, according to the EDT, subtle endometriosis is a physiological condition, occurring intermittently in all women, and these lesions should not be considered a disease [59]. According to Sampson/metaplasia theory, subtle lesions are the early stages of endometriosis and extremely important because they are very active. Accordingly, it is logical to examine the pelvis for these early and small endometriosis lesions and to treat them to prevent progression.

The epidemiology of the four major presentations of endometriosis will be discussed separately.

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* [76].

Subtle Endometriosis

Following the description of non pigmented endometriosis in the eighties [13–16], the prevalence of the disease increased from 5% to 20% to 60% to 80% in women with infertility or pelvic pain [17–25,77]. The prevalence clearly increases with the awareness and the experience 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 [25,78]. No studies have demonstrated an association with any of the variables considered important, such as early menarche, short cycles, abundant or painful periods, infertility, race, dioxin, or total body radiation.

Typical Endometriosis

Taking into account only typical endometriosis, the prevalence of asymptomatic endometriosis varies from 4% in women undergoing tubal ligation to 50% in teenagers with intractable dysmenorrhea. The prevalence in women

with pain or infertility ranges between 40% and 70% [25,46]. In general, incidence is estimated to be 1.3 per 1000 women aged 15 to 44 [79]. In a rec large study in Norway, the lifetime risk for endometriosis was 2.2% [80] this study, early menarche, frequent menstruations, pelvic pain, infertil and nulliparity were associated with endometriosis. In a controlled study women with infertility and a normal partner, compared with women w azoospermic partner, stage I endometriosis is not more common in infer women than in control women. However, stage II endometriosis was m frequent (3.3% vs 5.7%) in infertile women [81].

There is a non validated clinical impression that endometriosis co vary with race blacks having lower rates of endometriosis and Asians ha higher rates than Caucasians.

According to the Sampson's theory, abundant retrograde menstru tion is a predisposing factor for endometriosis. This seems to be clinica and experimentally supported by increased prevalence of endometriosis women and in primates with obstructed uterine outflow. Indeed, women w endometriosis have more abundant periods, and early menarche. Howev a recent review failed to demonstrate this association [82]. Endometriosis clearly associated with dysmenorrhea, but it is unknown whether this is cause or a consequence.

Dioxin has been suggested to be causally related to endometriosis. Th hypothesis was formulated in 1994 [83] based on indirect observations th the incidence and severity of endometriosis increased in primates treated wi dioxins [84,85]. In the human, final proof is still lacking [86]. The Seve accident, with massive pollution, suggests a nonsignificant doubling of prev lence [87]. Also, breast-fed infants, possibly exposed to dioxins in milk, have lower incidence of endometriosis in adult life [88].

Total body radiation is associated with increased prevalence of end metriosis in primates [89]. Little evidence is available to support this in th human.

Endometriosis is a hereditary disease [90–98]. The prevalence amor first-degree relatives is seven times higher than in control groups. In mono zygotic twins the prevalence is up to 15 times higher.

The lower natural killer cell activity in plasma and in peritoneal flui [71,99–106] has fueled speculation about the role of the immune system i endometriosis [107–110]. To date, however, no association has been foun between the prevalence of endometriosis and chronic immunosuppressio (e.g., in transplant patients), or smoking, caffeine, alcohol, or other lifestyl variable affecting NK activity.

Stress could be related to endometriosis. This concept is derived fror the association of endometriosis and LUF syndrome, the relationship be tween a higher trait anxiety and LUF syndrome [111–114], and the hypothesi

that lower steroid hormone concentrations in peritoneal fluid might facilitate the implantation/development of endometriosis [115]. As there is no adequate animal model, this hypothesis cannot be tested. The best animal model is the baboon. It has been shown that baboons in captivity have more endometriosis than in the wild (probably through stress) [116]. Another argument to link endometriosis and stress is the widely held belief that endometriosis is a career women's disease. This, however, can 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 [117].

Oral contraception use has been reported to be associated with a decreased prevalence [17].

Endometriosis was recently suggested to be associated with an increased risk in ovarian cancer (OR = 1.73, 95% CI: 1.10, 2.71) [118], and of non-Hodgkin's lymphoma [119].

Cystic Ovarian Endometriosis

Cystic ovarian endometriosis increases with age [25]. Most reports confirmed that cystic ovarian endometriosis is clonal in origin [120–123].

Deep Endometriosis

Deep endometriosis increases with age [25]. Rectovaginal endometriosis was known since the beginning of the century, but the high prevalence of deep endometriosis remained unsuspected until recently. The observations from Leuven from 1988 to 1991 [25], a period during which endoscopic surgery has not yet developed, showed that the prevalence of deep endometriosis was 10% to 20%. Referrals were only for infertility and pain and not for deep endometriosis. Assuming that laparoscopies for infertility are performed in 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 1% to 3%.

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

Endometriosis and Cancer

Occasional reports describe cancer in cystic ovarian [124] or severe endometriosis [96,125]. We recently diagnosed an adenocarcinoma in a deep endometriotic lesion. The relationship between endometriosis and a possible increased risk of ovarian cancer, however, remains unclear.

CONCLUSIONS AND DISCUSSION

When evaluating reports on epidemiology of endometriosis, it is importa distinguish between subtle, typical, cystic, and deep endometriosis and t into account the evolution of subtle endometriosis and deep endometrio simple non invasive test of endometriosis is still not available.

The prevalence of endometriosis is high, particularly in women pain and infertility. Subtle endometriosis ranges from 5% to 50% in as tomatic women to 50% to 80% in women with symptoms. For typical le estimations are less than half of these figures, but the data came from re before 1985. For severe endometriosis either cystic or deep, the prevale between 1% and 10%.

A poorly addressed problem is the variability of prevalences by r and country. No systematic studies are available, but in my experier seems that the prevalence of very severe deep endometriosis is higher i gium than in the United Kingdom or south Italy. In Moscow, the preva of severe endometriosis is also high. In Middle Eastern countries, end triosis seems to be rare. Although the evidence is anecdotal, it could agreement with the hypothesis of pollution.

Endometriosis is a hereditary disease, particularly the typical and ovarian types. Increased retrograde menstruation, for example, by ou obstruction, will increase the prevalence of endometriosis.

The role of nutrition, lifestyle, personality traits, the immune sy the peritoneal fluid, and other variables in endometriosis is unclear. In evidence strongly suggests a modulating role. The question whether metriosis represents normal endometrial cells or abnormal-modified metrial cells remains unanswered. Until then, prevention of implant prevention of cellular damage, and the treatment of endometriosis w main empirical.

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2

Pathogenesis of Endometriosis: Peritoneal Endometriosis, Ovarian Endometriosis, and Rectovaginal Adenomyosis

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Pelvic endometriosis can be categorized into three different forms: peritoı endometriosis, ovarian endometriosis, and endometriosis of the rectovag septum [1].

PERITONEAL ENDOMETRIOSIS

Since its first detailed description by von Rokitansky in 1860 [2], sev theories relating to the pathogenesis of endometriosis have been propos The most widely accepted is the transplantation theory that was proposec 1927 by Sampson. He observed that endometrial cells regurgitated throı the Fallopian tubes during menstruation [3].

Three essential conditions must be met to consider retrograde menst ation as the explanation for the pathogenesis of pelvic endometriosis [4]. Fi endometrial cells must enter the peritoneal cavity through the Fallop tubes. Second, cells within the menstrual debris must be viable and capabl