Gynecol Surg (2016) 13:457–467
DOI 10.1007/s10397-016-0970-4

REVIEW ARTICLE

Epidemiology of subtle, typical, cystic, and deep endometriosis: a systematic review

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Received: 22 June 2016 / Accepted: 19 July 2016 / Published online: 13 August 2016

Abstract Endometriosis is known as a cause of pelvic pain and infertility. The epidemiology of endometriosis is important since the prevalence and severity of endometriosis might be linked to pollution and to our modern lifestyle, comprising food intake, chemical disruptors, postponement of the first pregnancy, and stress, as indicated by "a career women's disease." Epidemiological data based upon hospital discharge records should be viewed with caution. Indeed, that subtle lesions are considered pathology causes a major increase in prevalence, while the laparoscopic recognition and histological confirmation of subtle and typical lesions vary with the expertise and interest of the surgeon. The epidemiological data published by surgical groups on severe forms, as cystic and deep endometriosis, have a referral bias and lack the numbers required for meaningful statistics. Fundamental to understanding epidemiology of endometriosis is that it is unclear that all presentations of endometriosis constitute one disease. We therefore performed a systematic review of the incidences and severity of subtle, typical, cystic, and deep endometriosis lesions separately. The only data found were that severe endometriosis carries a greater hereditary risk and that the prevalence of subtle endometriosis decreases with age whereas the prevalences of typical, cystic, and deep endometriosis increase with age. Surgeons that witnessed over the last 20 years in over 1000 interventions each the evolution of deep endometriosis, however, had a strong impression that severity and prevalence of deep endometriosis are increasing. In conclusion, there are no solid epidemiologic data of each type of endometriosis separately. With all restrictions imposed by the referral bias and by a clinical impression, the consistency of the observation of deep endometriosis surgeons should be a reason for concern. The investigation of the epidemiology of deep endometriosis is suggested since it is relevant because it is clinically severe pathologic and feasible since it can be done from hospital-based records. Indeed, most women will ultimately have surgery with solid information on severity and an unbiased diagnosis if defined as "adenomyosis externa."

Precis
In the absence of data, the clinical impression of deep endometriosis surgeons that severity and prevalence of deep endometriosis are increasing is a reason for concern.

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Keywords Endometriosis · Epidemiology · Prevalence · Severity

Introduction

Understanding the epidemiology of endometriosis is important since the prevalence and severity of endometriosis are eventually linked to pollution such as dioxin [1], PCB [2], and radioactivity

[3]. It has been linked to our diet and our fat consumption and to our style of living [4–6] with postponement of the first pregnancy and stress, both summarized in a "career women's disease." Most important is that understanding if and why prevalence and severity are increasing would permit prevention.

Endometriosis is a cause of pain and infertility and considered progressive and recurrent. This generates fear and anxiousness as reflected by the 22.398 peer-reviewed articles on PubMed (February 1, 2016), with an exponential increase since 2000 (Fig. 1), in the number of specific congresses, in the patient support groups, and in discussion groups on social media. It moreover emphasizes the associated costs of suffering, absence from work and of associated medical treatments, infertility treatments, and often repetitive surgeries.

The excellent articles on the prevalence of endometriosis [4–6] and of the analysis of the relationship with potential causal factors and with other diseases [7–12] unfortunately are not conclusive. These epidemiological studies have methodological problems which are the definition of endometriosis which permits to include asymptomatic women, the selection bias induced by the need of a surgical diagnosis, and the specific difficulties to perform cohort or case-control studies [6, 13]. The literature on epidemiology of endometriosis becomes even more confusing when the biases in observations and definitions over time are considered. Until the introduction of laparoscopy, endometriosis was limited to severe lesions as described in the beginning of the century [14–20] and to lesions found accidentally during surgery in the pelvis [21, 22] or in the umbilicus [23]. With the introduction of endoscopy in the late 1960s, the apparent prevalence increased since black-puckered lesions or typical endometriosis became a frequent observation in women with pain and/or infertility [24]. In the mid-1980s, the prevalence almost doubled by the recognition of non-pigmented or subtle lesions [25–28]. From the 1990s onwards, the recognition of deep endometriosis increased the apparent prevalence even further.

Clinically, epidemiology of endometriosis is even limited since the laparoscopy required to make the diagnosis limits repetitive observations over time, since recognition varies with the training and the interest of the surgeon, and since confirmation by pathology is only 50 % [29] to 76 % [30] and even less for subtle lesions.

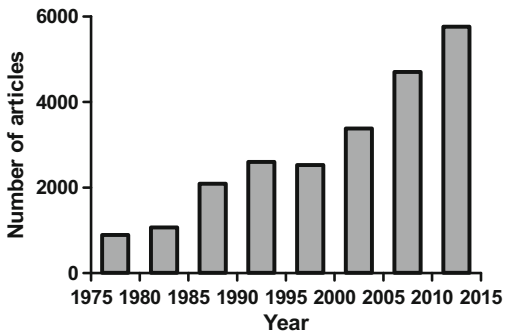

Fig. 1 Number of articles on endometriosis listed on PubMed. Indicated are blocks of 5 years since 1975

The pathophysiology and the natural history of the disease are unknown, and it remains unclear whether endometriosis is one or several different pathologies, whether all subtle and microscopical lesions are pathology, and whether it is a progressive and recurrent disease. Since clinically severe lesions as cystic ovarian and deep endometriosis are more important, we decided to review the data on epidemiology of subtle, typical, cystic, and deep endometriosis separately.

Materials and methods

Epidemiology

PubMed was screened for the keywords epidemiology OR prevalence OR incidence AND endometriosis generating 2656 articles. When instead of endometriosis "subtle endometriosis" OR "non-colored endometriosis" OR "microscopical endometriosis" was used, only 14 articles were found; "typical endometriosis" generated 5 articles, "endometrioma" OR "cystic endometriosis" OR "cystic ovarian endometriosis" 123, and "deep endometriosis" 37 articles. These articles for subtle, typical, cystic, and deep were subsequently searched manually. A distinction between subtle and typical lesions was made in two articles only. All other articles described the incidence of subtle and typical lesions together. Not a single article permitted to evaluate epidemiology over time for subtle/typical lesions, for cystic ovarian endometriosis, or for deep endometriosis. We therefore hand searched the 1409 articles found by "endometriosis" AND "epidemiology/incidence/prevalence" published between 2005 and 2016 without finding a single additional useful article.

Pathophysiology and definitions of endometriosis

In order to evaluate whether endometriosis should be considered one progressive disease with different degrees of severity or whether the different presentations of endometriosis should better be considered separately, we searched PubMed with the keywords endometriosis AND "pathophysiology" OR "natural history". The 400 articles over the last 14 years were hand searched. These articles described associated biochemical, immunological, inflammatory, endometrial, genetic, peritoneal fluid, or innervation changes or associations with waste products. Some were opinion papers. None of these articles nor any of the previous articles could explain the pathophysiology and natural history leading to the various clinical manifestations. How to interpret microscopical and on subtle or non-pigmented lesions caused most controversy.

Results

One or several diseases?

Endometriosis was defined more than 100 years ago as "endometrial glands and stroma outside the uterus" since microscopy was the only tool available at that moment [31, 32]. The clinical content of that definition changed over time. In the beginning of the twentieth century [14–18, 33], adenomyosis externa was described. The name endometriosis [19, 20] was introduced by Sampson when he described glands and stroma in ovarian "chocolate cysts." In 1940, he described the theory of retrograde menstruation and implantation [34], and in 1942, Gruenwald described the theory of metaplasia [35]. Only with the introduction of laparoscopy, we realized how frequent typical lesions were.

Following the observations that retrograde menstruation [36, 37] with viable cells [38] occurs in almost all women, it was logic to look for early lesions after implantation. In 1985, macroscopically visible non-pigmented lesions without surrounding sclerosis [25, 33] later called subtle lesions [26] were described. Somewhat later, minimal lesions by scanning electron microscopy [39, 40] and microscopical lesions in normal looking peritoneum were found in some 6 to 13 % of women without and with endometriosis, respectively [41–44]. In the early 1990s, some of these subtle lesions were described to disappear spontaneously called remodeling.

What is the significance of subtle lesions and of microscopical endometriosis?

Subtle lesions are considered as the early lesions after implantation, and it was postulated but never proven that these lesions will progress to more severe lesions in some women. However, since subtle lesions were found in up to 90 % of women with pain and or infertility [45], since progression was never observed, and in the absence of evidence that subtle lesions are a cause of infertility or pain, it was suggested and it remains debated that "subtle lesions are a normal condition occurring at least intermittently in most women" [46–48]. An indirect argument to consider subtle and typical lesions differently is that the luteinized unruptured follicle syndrome, a cause of infertility, is associated with typical lesions and not with subtle lesions [49].

Also for peritoneal microscopical endometriosis, there is no evidence for progression or for causing pain or infertility. Recently, microscopical lesions were also found in the perirectal lymph nodes of 18 to 20 % of women with deep endometriosis [50]. Yet, a clinical pathology of this has not yet been described. Similarly, in bowel resections for deep endometriosis, microscopic nest of glands and stroma can be found at least up to 5 cm from the nodule [51, 52]. That recurrence rates following bowel resections and following a more conservative local resection for deep endometriosis are not manifestly different is another argument to postulate that these microscopical nests of glands and stroma are not always pathology [53, 54].

In the absence of evidence that all microscopical endometriosis and subtle lesions will progress or cause pain or infertility, these lesions should not be considered disease in all women. This does not exclude that some of these lesions might progress, but today, we cannot distinguish between the majority of these lesions that have no clinical importance and may disappear spontaneously and those that will develop into endometriosis lesions causing pain and infertility [53]. Therefore, subtle and microscopical lesions should at least be considered separately until we understand their significance.

Pathophysiology and natural history

None of the pathogenetic theories based upon retrograde menstruation [34], coelomic metaplasia [35], or Müllerian remnants can explain all the different types of endometriosis [55, 56]. With the observation of an increased prevalence of endometriosis in women with obstructed outflow [57–60], the never proven hypothesis is that after implantation or metaplasia, these "normal endometrial cells" will progress inevitably into more severe lesions as typical, cystic ovarian, or deep endometriosis. This theory, however, cannot explain why progression occurs in some women only and why typical, or cystic, or deep lesions develop [55]. In order to fill this gap, the endometriotic disease theory [61] postulated that progression started with a cellular incident and that the type of cellular incident or a mutation would determine progression into typical, cystic, or deep endometriosis, similar to what is seen in most benign tumors. This would explain that endometriosis is hereditary [62–69] and that cystic and deep lesions are clonal in origin [33, 70, 71]. It also explains that dioxin and total body radiation, both acting at the level of the genome, might be causally related to endometriosis [72]. Similarly, the many differences in the endometrium of women with or without endometriosis could thus be interpreted as a sign of susceptibility rather than as the consequence of endometriosis.

Whether these endometriotic cells are normal or not, they develop in the environment of the peritoneal cavity or of the ovary. Peritoneal fluid is a specific microenvironment with concentrations of steroid hormones, cytokines, immunology [73, 74], angiogenetic factors, and many others, that are much different from plasma [75]. In endometriosis patients, many of these are different, but it remains questionable whether this is the cause or the consequence of endometriosis. That the decreased natural killer cell activity in plasma [76] and in peritoneal fluid [77] remains decreased after surgical excision suggests that this might be causally related [78]. Also, the intra-ovarian hormone concentrations are much higher, and

also immunology is different, as evidenced by the preferential implantation of tumor cells as in the Krükenberg tumor. Lastly, especially considering also adenomyosis, pale cells [79] and the role of the junctional zone should be considered. The latter broadens the view to immunology of pregnancy, induction of the physiologic changes of the spiral arteries [80–85], and pre-eclampsia. The tumor-like development of endometrial cells on the chicken allantoic membrane [86] remains intriguing.

Subtle, typical, cystic, and deep endometriosis should be considered separately

In the absence of a clear model for pathophysiology and natural history of endometriosis and since not all glands and stroma outside the uterus constitute clinical pathology, and considering in addition adenomyosis and Müllerianosis and extra-pelvic localizations, it seems wise to consider subtle, typical, cystic ovarian, and deep lesions separately, at least until proven that it is one disease.

Typical, cystic, and deep endometriosis should not be considered a recurrent and progressive disease. Recurrence rates of each type of endometriosis are different. Following surgical excision, recurrence rates are estimated around 20 % for typical lesions, around 7 % after stripping and 20 % after superficial destruction of cystic ovarian endometriosis [87, 88], and very low (less than 5 % bowel recurrences) after excision of deep endometriosis. Progression from one type to another has not been observed. On the contrary, almost all three types can be considered clinically end stages, which at the moment of diagnosis are no longer progressive and which by pathology have a non-active burnt out aspect. Cystic ovarian endometriosis does not always increase in volume, and low rectovaginal deep lesions followed clinically over time remain mostly unchanged at least over a few years. Clinically, it seems that after a period of growth, progression will stop with surrounding fibrosis as the remnant of a previous inflammation. This is not in contradiction with the rare cases, in our experience some 10 in 3000 deep endometriosis nodules (PK, AU) that can be fast progressive. This highlights heterogeneity as supported by the fact that during pregnancy, some deep lesions behave differently and can cause spontaneous bowel or bladder ruptures [89].

Accuracy of the diagnosis of endometriosis lesions and epidemiology

The recognition and the confirmation by pathology of subtle lesions vary with the skill, interest, and expertise of the surgeon and the pathologist. Rarely considered is the bias caused by the surgeon, who scrutinizes women with pain or infertility in order to have a diagnosis. Even for typical lesions, the histologic confirmation is only 50 % [29] to 76 % [30]. Endometriosis of the diaphragm is underreported since not all surgeons will systematically inspect the diaphragm in steep anti-Trendelenburg with a 30° scope. Most important is that the recognition in the mid-1980s of non-pigmented lesions or subtle lesions [25, 26, 33] almost doubled the prevalence of endometriosis. Before that period, women with minimal and mild endometriosis were women with typical lesions, whereas thereafter, they became women with subtle lesions and/or typical lesions.

The prevalence of cystic ovarian endometriosis is biased by a variable inclusion of cystic corpora lutea, estimated up to 30 %. To distinguish between them can be difficult by ultrasound and also during surgery. CA125 in chocolate fluid could be used, but a rapid test during surgery is not available [90]. Cystic ovarian endometriosis is strongly associated with adhesions [45], and a chocolate cyst without adhesions has a high probability of being a cystic corpus luteum. The inspection of the inside of the cyst by ovarioscopy [91] was suggested as not conclusive. Moreover, it is often unclear whether diagnosis was confirmed by pathology or "compatible with endometriosis," without a positive identification of endometrial glands and stroma [92, 93]. The recent diagnosis of small cystic ovarian endometriosis by ultrasound [94, 95] increased the prevalence, as is evidenced by the actual discussion whether small cysts should be left alone or should be treated by laparoscopy or trans hydroculdoscopy [96], or whether it is preferable to proceed to IVF without surgery.

The clinical diagnosis of deep endometriosis is unreliable since in only 50 % of the larger nodules, the diagnosis is made by clinical exam [45, 97]. The diagnostic accuracy of MRI and of ultrasound hardly exceeds 90 % sensitivity and specificity, and it is unclear whether imaging is really helpful in the diagnosis of smaller lesions. Even the surgical diagnosis is biased by a variable indication for surgery, a variable recognition during surgery, a variable referral bias, and the absence of an unanimously accepted definition. Deep endometriosis is partially underreported, since smaller lesions are easily missed especially in the sigmoid. Deep endometriosis is suspected to be partially over-reported since deep endometriosis is considered the ultimate surgical challenge in gynecology; many centers interpret broadly the diagnosis of deep endometriosis in order to belong to the club of hospitals that perform this surgery. Underdiagnosed is deep endometriosis around the sciatic nerve and around the sacral nerve roots because of the surgical risk. It would be preferable to use as definition adenomyosis externa [98, 99], since with the definition of more than 5 mm under the peritoneal surface [99], many typical lesions can be classified as deep endometriosis.

Considering the prevalences of the lesions, women with the diagnosis of endometriosis in hospital discharge records mainly have typical endometriosis and/or subtle endometriosis, some cystic endometriosis, and a few deep endometriosis. Confirmation by pathology will be variable [100, 101].

Epidemiology of endometriosis lesions

Epidemiology and age and heredity

With all restrictions imposed by the inherent selection bias in Leuven in 1991, in a group of 900 women with pain and/or infertility, 49 % had subtle lesions, 29 % had typical lesions, 31 % had cystic ovarian endometriosis, and 18 % had deep endometriosis. Although the total incidence remained constant with age at some 71 %, subtle lesions significantly decreased with age whereas typical cystic and deep lesions increased with age [45] (Fig. 2).

Endometriosis is a hereditary disease [62–68, 102] as evidenced by the seven times higher prevalences in first-degree relatives and the high associations in monozygotic. Genome-wide association studies could identify common genetic variants [103–107]. Also, severity and early onset seem hereditary.

Subtle lesions

Subtle endometriosis will be found in most women when scrutinized during laparoscopy. They are expected to be found in all women if laparoscopy could be done repetitively.

In women with pain and or infertility, the incidence of subtle lesions decreases with age [45, 108]. In adolescents with pain endometriosis (probably mainly subtle lesions), the incidence of subtle lesions was found in 40 % [109] and 70 % [110]. Also in women without symptoms, endometriosis was found in some 40 % [43, 109]. Not a single study permits to evaluate specifically the epidemiology of subtle endometriosis over time or to evaluate an association with early menarche, short cycles, abundant or painful periods, subfertility, canalization defects of the cervix, race, dioxin, total body radiation, or any other factor. There is no evidence that prevalence of subtle lesions is increasing over the last decades.

Typical lesions

Ignoring the bias of a variable inclusion of subtle lesions, typical endometriosis was reported in up to 5 % in asymptomatic women, e.g., in 4 % in tubal ligation [29], in 0.16 % in white females [111], and in 2.2 % in a large study from Norway [112]. In the latter study, the risk increased with early menarche, frequent menstruations, pelvic pain, infertility, and nulliparity. In women with infertility stage II, endometriosis (mainly typical lesions) was more frequent [113] when

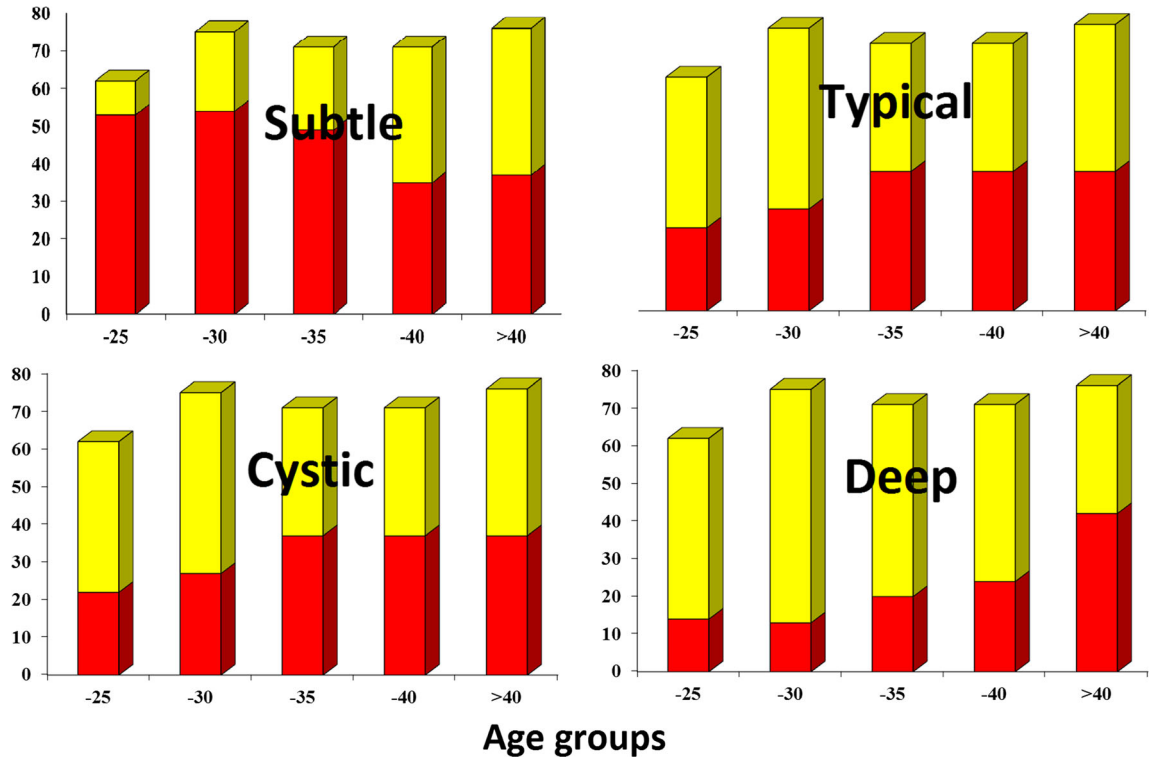

Fig. 2 Prevalence (*red*) of subtle, typical, and deep endometriosis in women with infertility (n = 1297), pain (n = 918), and infertility and pain (n = 267). Subtle endometriosis decreases with age, whereas typical, cystic, and deep endometrioses increase with age. The total prevalence (*yellow*) remains unchanged (from [45])

the partner was normal (5.7 %) than when azoospermic (3.3 %). In women with pain, higher incidences were found. In teenagers with intractable dysmenorrhea, 50 % had endometriosis [114], and in women with pain and infertility, prevalences of 40 to 70 % were reported, with a mean of 33 % after meta-analysis [115].

No studies permitted to judge the prevalence of typical lesions over the last decades.

In studies investigating the causes of endometriosis, typical and subtle endometrioses were the predominant lesions. Racial differences were repeatedly suggested, but it remains unclear whether black women have lower and Orientals higher rates than Caucasian. That endometriosis increases with earlier menarche and abundant retrograde menstruation is not substantiated. The baboon data describing an increased prevalence of endometriosis following uterine outflow obstruction are not retained since in recent studies, retrograde menstruation was not found [116]. Dioxin pollution has been suggested to be causally related to endometriosis [1, 117] but in the human evidence is scanty [72, 106, 118]. Following the Seveso accident with severe dioxin pollution, the prevalence doubled although not significantly [119]. Although breast-fed girls have been exposed to dioxins in mother milk, they have a lower incidence of endometriosis in adult life [120]. There are no data linking total body radiation to an increased prevalence of endometriosis in the human. It is unclear whether the immune system is causally related to the development of endometriosis notwithstanding the many changes in the immune system [73, 121, 122] and the decreased natural killer cell activity in plasma and in peritoneal fluid [76–78, 123–128]. Indeed, endometriosis prevalence seems not to be obviously affected by chronic immunosuppression, e.g., in transplant patients, nor by smoking affecting NK activity, nor by caffeine or alcohol. It is unclear whether stress is causally related to endometriosis. The only data are the associations between typical endometriosis and a higher trait anxiety [129–131]. The much lower steroid hormone concentrations in peritoneal fluid of women with the LUF syndrome moreover might affect the implantation and/or development of endometriosis [36]. That endometriosis is a career women's disease suggests a causal relationship with stress. It however also points to the delay of first pregnancy with the inevitable increase of infertility with age, an increase in laparoscopies, and thus a higher documented prevalence of endometriosis. This is consistent with a decreasing prevalence with increasing parity [132]. Oral contraception use has been reported to be associated with a slightly decreased prevalence [133].

Cystic lesions

There is no evidence that the prevalence of cystic ovarian endometriosis is increasing. There is no evidence in the human for an association between cystic ovarian endometriosis and pollution or lifestyle. The relationship with ovarian cancer is unclear and beyond the scope of this manuscript.

Deep lesions

The recognition of smaller deep endometriosis lesions only started in the 1990s, and all reports do have a referral bias. An indirect estimation of the prevalence in the Belgian population can be derived from a total of some 500 interventions/year in a population of 10 M (PK and J. Donnez) in the early 1990s, a period that deep endometriosis surgery was systematically referred. Assuming a reproductive life span of 30 years, and a diagnosis and surgery in some half of the women, prevalence in population ranges between 0.2 and 0.5 %. In women with pain and infertility, prevalence was estimated between 3 and 10 % in Belgium as derived from the 10 to 20 % incidence of deep endometriosis in Leuven from 1988 to 1991. Indeed, during that period, referrals were only for pain or infertility since deep endometriosis was not yet well known.

There are no valid data indicating that the prevalence of deep endometriosis is increasing or that deep endometriosis is caused by pollution or lifestyle. A clinical impression of epidemiology of deep endometriosis was asked to internationally recognize deep endometriosis surgeons who performed surgery over the last 20 years and who each performed between 1000 and 3000 interventions of deep endometriosis. With all restrictions imposed by the referral bias each was well aware of, AW, LA, JD, JK, AU, AS, and PK (authors and acknowledged) have the strong impression that severity and probably prevalence of deep endometriosis are increasing; for CK, it is unclear, whereas CN and his brothers consider it a referral bias. Of specific interest is that in the 1990s, surgery for deep endometriosis in the south of Italy was rare, anyway much lower than in Belgium, which contrasts with the high incidence of severe endometriosis we actually observe (AU, AW, PK).

Adenomyosis, Müllerianosis, peritoneal pockets, and stromatosis

These diseases which are often considered as variants of endometriosis will not be discussed. Stromatosis does not contain endometrial cells, while Müllerianosis is a too rare condition to discuss prevalence. The pathophysiology of adenomyosis is even more enigmatic than endometriosis. Several forms exist, and prevalences vary with the diagnostic method.

Discussion

Epidemiology of endometriosis is important since endometriosis can be the cause of almost any gynecologic complaint such as infertility, pain, or bleeding problems up to fatigue and sexual problems. Therefore, women and physicians at least consider endometriosis for almost any gynecological complaint. In order to avoid surgery, many women with pain but without endometriosis are treated for endometriosis and live with the idea that they have endometriosis. They all are worried since they fear that endometriosis will cause infertility, that endometriosis is progressive with a high risk of hysterectomy later in life, that there is no effective treatment, and that surgery can be dangerous. After the millennium, awareness grew for pollution, radioactivity, and global warming, which all could be linked to endometriosis. In addition, over the last decades, we witnessed a progressive delay of the first pregnancy, while age, infertility, and endometriosis are correlated. All this, especially in a period of social media, generates a climate of fear of endometriosis. The questions are whether the prevalence of endometriosis and especially severe endometriosis is increasing in our western population and what causes an eventual increase. Asking the question is suggesting the answer as we spontaneously suspect pollution, radioactivity, our lifestyle, and food industry. Since in addition endometriosis has been linked to cancer, it is not surprising that this is fueling fear and concern as expressed by the many support and discussion groups and the explosion of the number of articles [134].

The epidemiology of endometriosis is not clear despite the many excellent articles. Besides the difficulties in collecting epidemiologic data for endometriosis [13, 100, 101] and the difficulties in recognition of endometriosis and in ascertaining the quality of the diagnoses of each form of endometriosis, a key problem is the definition of endometriosis and our prevailing concept of pathophysiology and natural history. With the definition "glands and stroma outside the uterus," the widespread belief is that all forms of endometriosis fitting that definition are one disease, progression after implantation is considered inevitable, and endometriosis is considered a progressive and recurrent disease.

As discussed, this concept can be challenged. Since glands and stroma outside the uterus do not mean pathology by definition, the word endometriosis is confusing since it is used for both normal and pathologic conditions. It indeed was never demonstrated that microscopic endometriosis, whether in the peritoneum or in lymph nodes (and maybe in the bowel), and also subtle lesions are a cause of pain or infertility. It is at least surprising that progression of these lesions still is postulated without being demonstrated except in vitro [56]. The traditional concepts of pathophysiology cannot explain all the different types of endometriosis [55] and do not explain heredity and the fact that cystic and deep endometriosis are clonal in origin. A genomic mutation of these cells [135] could explain why and when glands and stroma outside the uterus are normal or pathologic. It would facilitate understanding clonality and heredity. It could explain why lesions develop into typical, cystic, and deep lesions. It could explain that typical, cystic, and deep lesions are end stages—similar to a no longer growing myoma—without progression from one type to another as clinical observation suggests. It also could explain why in baboons and the rhesus monkeys induction of severe lesions has failed. It is consistent with primate date of the heredity of spontaneous typical lesions [136], with the fact that total body irradiation [3] induces typical endometriotic lesions and that dioxin induces cystic ovarian endometriosis, the severity of which was dose dependent [1]. These data are all consistent with the fact that it takes many years before a genomic incident becomes apparent [1, 137]. Recently, lesions similar to deep endometriosis were found by injecting slices of endometrium with myometrium [116] pointing to a relationship between functional endometrium, basal endometrium, and junctional zone. The role of the junctional zone only recently begins to receive attention.

A fundamental question is whether cells in subtle, typical, cystic, and deep lesions are genetically identical or different from endometrial cells. Similarly, it is important to understand whether the differences of endometrium in women with and without endometriosis are the consequence of endometriosis or are a sign of vulnerability and of predisposition to develop disease. In the absence of data, it seems prudent today to replace endometriosis by subtle endometriosis, typical endometriosis, cystic endometriosis, and deep endometriosis. This would highlight that they are potentially different. Typical, cystic, and deep endometriosis could be considered as a benign tumor similar to a myoma or a polyp generally having a genomic alteration, facilitated by the genetic background, and epigenetic modifications [138]. It would facilitate to understand that some deep endometriosis lesions are different and clinically fast progressive as suggested by clinical observation (personal observations) and evidenced by complications during pregnancy [89].

Considering subtle, typical, cystic, and deep endometriosis as separate entities changes our view on epidemiology. There is no hard evidence for an increase in the prevalence of typical, cystic, or deep endometriosis or for a specific causal factor. What remains is that the prevalences of typical, cystic, and deep endometriosis increase with age which is consistent with the observation that the prevalence of most benign tumors increases with age. Considering these lesions as benign tumors on the other hand risks to increase our concern of a relationship with dioxin, PCB [2], and

radiation, which all act at the level of the genome. Genetic predisposition moreover is easily connected with cancer development. Although weak as evidence, the impression by authors and other surgeons who all are pioneers of deep endometriosis surgery with a large personal experience that deep lesions become more severe and probably more frequent over the last 20 years should not be disregarded.

Considering subtle, typical, cystic, and deep endometriosis as separate entities could change the design of epidemiologic studies. Since deep endometriosis is associated with very severe pain in most women, the majority will undergo surgery. If considered as adenomyosis externa, diagnosis by pathology will carry little errors and the volume of the lesion, a measure of severity, will be available. Since recurrence rates of deep endometriosis are small, even women that undergo repetitive surgery can be identified and anyway should cause little bias. Even in women that undergo hysterectomy, the diagnosis of deep endometriosis can be made. This should permit hospital discharge record-based case-control studies, with as only bias that not all women undergo surgery, some 5 % being pain free. Epidemiology of deep endometriosis should permit to evaluate an eventual relationship with pollution, radioactivity, and our changing lifestyle with a delay in childbirth. Epidemiology of deep endometriosis will in addition permit to evaluate questions such as whether the use of oral contraception and the years of medical treatment for pelvic pain without a diagnosis might stimulate the development of some severe forms of endometriosis.

We should learn from the past, especially from the excellent available data of epidemiology [4–6] and associated diseases such as acne [7–12] or with food intake as fat consumption [100, 101] of endometriosis. Studies of the epidemiology of subtle, typical, cystic, and deep endometriosis would eliminate the question whether microscopical and subtle lesions should be considered pathology. The design would fully comply with the conclusion [13] that to be pathologic, endometrial glands and stroma should be progressive and invasive and that this "may increase the likelihood of observing true associations in etiologic studies" and avoid "threats to validity of substantial magnitude that exist in both clinic-based and population-based epidemiologic studies of endometriosis."

In conclusion, subtle, typical, cystic, and deep endometriosis lesions should be considered as separate entities, until pathophysiology and natural history are known. This would permit to answer whether subtle lesions are pathologic and whether and which lesions are recurrent and progressive. It could answer the question whether endometrial changes in endometriosis are the hallmark of pre-existing susceptibility. This would permit to run epidemiologic studies on deep endometriosis with little bias, which will permit to answer the question whether prevalence is increasing or not. This ultimately would permit to answer the questions whether pollution, radiation, and lifestyle would be etiologically involved.

Acknowledgments We thank Jacques Donnez, Brussels, Belgium; Antonio Setubal, Lisbon Portugal; Charles Koh, Milwaukee, USA; and Camran, Ceana, and Farr Nezhat, Atlanta, USA, for their clinical opinion on prevalence and severity of deep endometriosis over the last 20 years.

Compliance with ethical standards

Funding The authors did not have any funding.

Conflict of interest Neither Koninckx, nor Ussia, nor Keckstein, nor Wattiez, nor Adamyan report a conflict of interest for this study. Koninckx is shareholder of Endosat.

Ethical approval Not applicable.

Informed consent Not applicable.

Statement of authorship All authors are recognized deep endometriosis surgeons, active over the last 20 years with a large personal experience. The manuscript was initiated and conceived in many preparatory discussions, written by PK, and all other authors contributed in reviewing the data and the manuscript.

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