Best Practice & Research Clinical Obstetrics and Gynaecology 71 (2021) 14–26

Contents lists available at ScienceDirect

Best Practice & Research Clinical Obstetrics and Gynaecology

journal homepage: www.elsevier.com/locate/bpobgyn

2

The epidemiology of endometriosis is poorly known as the pathophysiology and diagnosis are unclear

Philippe R. Koninckx, M.D., Ph.D [a, b, c, d, e, *], Anastasia Ussia, MD [d, e], Leila Adamyan, MD, PhD [f, g], Muna Tahlak, MD [a], Jörg Keckstein, MD, PhD [h, i], Arnaud wattiez, MD, PhD [a, j], Dan C. Martin, MD [k, l]

[a] *Latifa Hospital, Dubai, United Arab Emirates*
[b] *Professor Emeritus OBGYN, KULeuven Belgium*
[c] *University of Oxford-Hon Consultant, UK*
[d] *University Cattolica, Roma, Moscow State Univ. Italy*
[e] *Gruppo Italo Belga, Villa Del Rosario Rome Italy*
[f] *Department of Operative Gynecology, Federal State Budget Institution V. I. Kulakov Research Centre for Obstetrics, Gynecology, and Perinatology, Ministry of Health of the Russian Federation, Moscow, Russia*
[g] *Department of Reproductive Medicine and Surgery, Moscow State University of Medicine and Dentistry, Moscow, Russia*
[h] *Endometriosis Centre, Dres. Keckstein Villach, Austria*
[i] *University Ulm, Ulm, Germany*
[j] *University of Strassbourg, France*
[k] *Professor Emeritus School of Medicine, University of Tennessee Health Science Centre, Memphis, TN, USA*
[l] *Institutional Review Board, Virginia Commonwealth University, Richmond, VA, USA*

Keywords:
Endometriosis
Epidemiology
Genetics
Epigenetics
Pathogenesis
Histology

A B S T R A C T

As the diagnosis requires a laparoscopy, we only have data in women with pain and/or infertility. Endometriosis has been considered to be a single disease defined as 'endometrium like glands and stroma outside the uterus'. However, subtle, typical, cystic ovarian and deep endometriosis lesions should be considered to be different pathologies which occur in all combinations and with different severities.

All large datasets, especially those based on hospital discharge records, consider endometriosis to be a single disease without taking into account severity. In particular, the variable prevalence

* Corresponding author. Vuilenbos 2, 3360 Bierbeek, Belgium.
E-mail addresses: Pkoninckx@gmail.com (P.R. Koninckx), danmartin46@gmail.com (D.C. Martin).

https://doi.org/10.1016/j.bpobgyn.2020.08.005

and recognition of subtle lesions is problematic. Reliable surgical data are small series not permitting multivariate analysis.
Endometriosis is a hereditary disease. The oxidative stress of heavy menstrual bleeding with retrograde menstruation and an altered pelvic microbiome are probably associated with increasingly severe endometriosis. Whether the prevalence is increasing, or whether endometriosis is associated with fat intake or an increased risk of cardiovascular disease is unclear.

Introduction

Epidemiology is the study of the distribution and determinants of a disease in a population. Epidemiology requires a clear definition of the disease and its diagnosis. Understanding the pathophysiology and natural history of the disease is important to interpret the many factors that cause or that are associated with an increased or decreased prevalence or risk of endometriosis. In addition, it is important to consider the many difficulties of epidemiological studies such as reliability of data, definition of the disease, association versus causality, risk factors, confounding factors and their interaction and the pitfalls of statistical inference [1].

The study of the epidemiology of endometriosis is hampered by multiple definitions and a variable and uncertain laparoscopic diagnosis of endometriosis. The histologic diagnosis is more of a research tool and varies from the basic criteria of glands and stroma and haemorrhage outside the uterus to complex criteria including fibrosis, CD-10, Ber-EP4, pan-cytokeratin and others. The different definitions and the criteria used by different authors can make comparisons difficult. The laparoscopic diagnosis is a clinical impression with a histologic confirmation far less than 100%, especially for smaller lesions. Moreover, recognition varies with the expertise and interest of the surgeon.

Epidemiology of endometriosis [2] is important as endometriosis is a major cause of infertility and pelvic pain in many women. It is a significant problem in women's health because of the associated suffering, the many surgeries and the health care expenses, along with the suggested link with pollution and with many problems such as cardiovascular disease. Understanding the disease might help to improve treatment and develop prevention strategies.

In this chapter, we will update our 2016 systematic review [2] of the epidemiology of endometriosis with the recent understanding of the pathophysiology and natural history of endometriosis and of the accuracy of the diagnosis of endometriosis, in order to discuss the observations concerning the epidemiology of endometriosis.

The accuracy of the endometriosis data

Before discussing the epidemiology of endometriosis, it is important to understand the accuracy of the data regarding endometriosis.

Definition of endometriosis

Historically, endometriosis was defined by pathology as 'endometrial glands and stroma outside the uterus'. It started with the observations of Rokitansky [3] who described what we now call ovarian endometriosis and adenomyosis, of Cullen [4] who described adenomyosis and rectovaginal endometriosis, and of Sampson who described ovarian endometriosis [5] while developing the retrograde menstruation and implantation theory [6]. Over the following decades, many case reports or small series (Fig. 1) described nodular, cystic, superficial and extra-genital endometriosis in many different localisations found during surgery. After the introduction of diagnostic laparoscopy in the 70s, we realised that typical lesions were much more frequent in women with pelvic pain or infertility than thought before. In 1986, subtle lesions were recognised as endometriosis [7,8]. Thus, many women who were

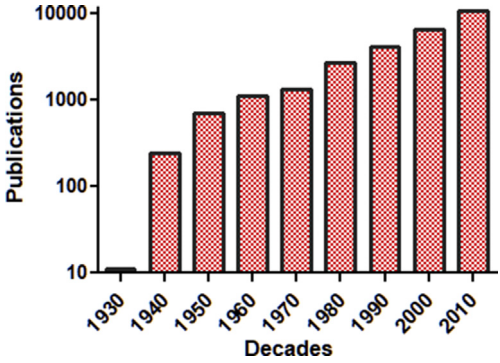

Fig. 1. Articles of endometriosis.

considered normal before 1986 were diagnosed with endometriosis later [9]. Smaller deep endometriosis lesions were described as a separate entity and as a cause of severe pain in 1990 [10], with an exponential increase of reports over the next decades mainly because it was surgically challenging.

Clinically, 'endometrial glands and stroma outside the uterus' in the pelvis can present as small and active 'subtle' lesions, that is, red and white vesicles, and polypoid- and flame-like lesions, as typical lesions presenting as burnt–out powder burn pigmented lesions in a sclerotic areas known, as cystic ovarian lesions containing 'chocolate' fluid, or as deep endometriosis which unfortunately is poorly defined. Deep endometriosis was initially described as scanty glands and stroma in large areas of fibromuscular tissue [10]. Soon thereafter, deep endometriosis was defined as endometriosis lesions deeper than 5 mm under the peritoneum because of a nadir in the frequency distribution of the depth of endometriosis lesions around 5 mm [11]. As the depth of typical and deep endometriosis lesions strongly overlap, this definition results in many typical lesions being classified as deep endometriosis. Still, today, deep endometriosis remains poorly defined with lesions varying from small to larger than 4 cm in diameter. Microscopically, they vary from glandular lesions to fibrotic lesions. 'Endometrial glands and stroma' outside the uterus present also as microscopically lesions [12] in the peritoneum [13–15], in the bowel as islets at distance from deep endometriosis nodules [16] and in lymph nodes [17].

In conclusion, endometriosis is a disease which is defined histologically as endometrial glands and stroma-like tissue outside the uterus and which presents clinically as microscopic, subtle, typical, cystic ovarian or deep endometriosis lesions. Other forms, such as Müllerianosis, are too rare to discuss the epidemiology.

Pathophysiology and natural history of endometriosis

Endometriosis, a name coined by Sampson [18], has been considered for a century as implants of endometrial tissue outside the uterus either following retrograde menstruation into the peritoneal cavity [5,19] or following haematological dissemination [6]. This implantation theory is attractive as endometriosis looks histologically like endometrium, as retrograde menstruation contains living cells which can implant [20] and as the fibroblasts from endometriosis or from the endometrium of women with endometriosis have an increased invasion capacity [21].

The implantation theory does not explain why endometriosis lesions develop in some women only, while retrograde menstruation seems to occur in most women [22,23]. Some observations are difficult to explain by the implantation of endometrial cells following retrograde menstruation. The clonality of each endometriosis lesion, as described for deep and cystic [24–27] and typical endometriosis [28], is more consistent with a G-E (genetic-epigenetic) incident related to intracellular aromatase activity resulting in intracellular oestrogen production than to newly implanted endometrium. The implantation theory does not explain the occurrence of endometriosis in women without a uterus, and in men. It is more likely that deep endometriosis lesions can become symptomatic more than 10 years after menopause in the absence of increased circulating oestrogens [29] as a result of a G-E cellular incident

than that implanted endometrium would suddenly start to develop. It should be realised that theories such as coelomic metaplasia, endometriosis originating from bone marrow/stem cells, Müllerian rests, tissue injury and repair, repeated tissue injury and repair, oestrogen toxicity and traumatic induction are compatible with and can be considered today to require epigenetic changes (for review [30]).

Recently, the G-E theory [31] of endometriosis was formulated as an update of the endometriotic disease theory [32]. Endometriosis starts in the G-E theory, irrespective of the original cell, when a cumulative combination of specific genetic and/or epigenetic cellular incidents exceed a certain threshold. The inherited genetic and epigenetic incidents at birth explain the hereditary character of endometriosis. It remains unclear whether and how epigenetic changes are transmitted *trans*-generationally in endometriosis [33]. The effects of minor G-E abnormalities remain clinically invisible because of the redundancy of molecular biological mechanisms in the cell, but they increase the risk of developing the disease when additional incidents occur. Additional incidents can occur during intrauterine development because of the maternal environment and external factors, and during live mainly as mistakes during mitosis. Most G-E mistakes result in apoptosis of the cell if they cannot be repaired. Some minor incidents, however, do not cause cell death and are transmitted to the next generation of cells. These incidents are favoured by mutagenic substances such as dioxins and other pollutants, radiation, or oxidative stress such as caused by retrograde menstruation or by infection or by the peritoneal microbiome [34]. The dynamic and gradual aspect of these mistakes and their inheritance is important. The crosstalk between genetic and epigenetic mechanisms [33] makes the cell vulnerable to new incidents, especially when the external circumstances are unfavourable. The cell thus becomes progressively more vulnerable to acquiring more mistakes, with some of them being cancer-associated mutations explaining the clonal expansion [35,36].

The G-E theory adds to the implantation and other theories that the onset of the disease requires a cumulative and triggering combination of G-E cellular incidents. With the G-E hypothesis, it seems logical to postulate that the specific set of G-E incidents will orient the development into clinically subtle, typical, cystic or deep lesions. A specific set of G-E incidents also explains that each type of lesion is heterogenous with variable [37] aromatase activity, progesterone resistance, oestrogen sensitivity and probably many other factors. Additional incidents occurring during further development result in endometriosis lesions which are probably also heterogeneous at the cellular level, as demonstrated for breast cancer.

The natural history of endometriosis lesions is poorly known as there is no animal model and because repetitive laparoscopies cannot be performed in women. After their triggered initiation [38], the lesions develop in an environment different from the uterus with different microbiota and different immunologic, endocrine and paracrine influences. The cyclic endocrine changes with eventual bleeding will moreover result in repetitive traumas which increase the risk of developing additional G-E incidents and ultimately fibrosis [39,40]. Therefore, all theories [30] emphasising trauma [41], immunology, the role of oestrogens [42] and peritoneal fluid retain their full importance for understanding the growth of endometriotic lesions.

Much of the many endometriosis-associated changes, such as changes in the endometrium and in the immunology can be viewed as a consequence of the inherited predisposition instead of being a consequence of endometriosis. As endometriosis cells can migrate to the endometrium, at least in animal models [43], both aspects are probably partly true. Thus, as an example, infertility becomes a consequence of endometriosis and a consequence of the inherited endometriosis susceptibility.

The potential reversibility of epigenetic changes and the relationship between epigenetic and genetic changes and histologic appearance of cells are important in this discussion [44]. Both aspects are unclear today. Epigenetic changes are theoretically reversible. They are reversible in plants and animal models [44,45] as well as the epithelial-mesenchyme transition in endometriosis [46], when the cellular environment changes. Although poorly understood, reversibility of epigenetic changes becomes more difficult when additional epigenetic incidents have occurred. When the associated genomic instability results in genetic errors, changes become irreversible. With regard to reversibility of epigenetic changes, it is important to understand the potential reversibility versus the risk of progression of precancerous lesions such as CIN lesions leading to cervical cancer [45]. Unfortunately, histology is unable to distinguish between reversible and irreversible changes. This is important for endometriosis. As endometriosis lesions can originate from endometrial cells, from coelomic fibroblasts or epithelium and even from bone

marrow cells, endometriosis cells might return to normal endometrium or even to normal coelomic epithelium/mesothelium when the driving forces inducing epigenetic changes disappear. This could explain why microscopical endometriosis has not yet been linked to any clinical pathology and why conservative excision of deep endometriosis which is obviously incomplete is not associated with a higher recurrence risk than a large bowel resection [47]. These observations suggest that some histologically endometrium-like cells with only reversible epigenetic changes can return to normal when the driving motor is removed such as following the excision of a deep endometriosis nodule.

In conclusion, in order to understand endometriosis, it is important to distinguish between the initiation and the subsequent growth of endometriosis lesions [38].

The diagnosis of endometriosis

Endometriosis is defined by pathology and recognised during surgery. However, neither pathology nor surgery have a gold standard. The recognition of subtle lesions varies with the interest and expertise of the surgeon, and the pathological confirmation varies with the method of biopsy and with the processing accuracy of these small lesions [48]. The identification of microscopical lesions in the peritoneum and in the bowel at distance from a deep endometriosis nodule varies with the scrutiny of pathological examination. Many lesions, including deep endometriosis lesions, can be missed during laparoscopy. Most importantly, laparoscopy is not performed without an indication and we therefore have no information in women without clinical symptoms except occasional data in women undergoing tubal ligation.

The value of imaging and biochemical tests in diagnosing endometriosis is also unclear [49]. First, we do not have a gold standard as endometriosis lesions can be missed during laparoscopy and because laparoscopy cannot be performed systematically in all women in the absence of symptoms. Second, accurate non-invasive biochemical tests to diagnose endometriosis are not available. Imaging, as ultrasound and MRI, is fairly accurate for the diagnosis of cystic ovarian endometriosis but cannot diagnose subtle and typical lesions. Although sensitivities and specificities of over 90% are reported for deep endometriosis, we do not know the lower detection limit. Therefore, the number of smaller or initial lesions is unknown.

Accuracy of hospital discharge records

The accuracy of the diagnosis of endometriosis in hospital discharge records is at least variable [50–52]. The diagnosis of cystic ovarian endometriosis will be fairly accurate with less than 10% being cystic corpora lutea. The diagnosis of deep endometriosis comprises both women with a deep endometriosis nodule and women with slightly deeper typical lesions. The major problems are the superficial peritoneal lesions with typical lesions and a variable inclusion of subtle lesions. Upon scrutiny, these can be found in almost all women with pain or infertility. Hospital discharge records therefore risk to contain the diagnosis of endometriosis in the large majority of women (if not all) undergoing a laparoscopy for pain or infertility and in whom no other obvious cause is found. The reported severity moreover is inaccurate because of the widely used rAFS classification, in which deep endometriosis are predominantly found in classes I and II.

Epidemiology

The prevalence of endometriosis

With regard to women with pain or infertility, prevalence of subtle, typical, cystic ovarian and deep endometriosis were reported in over 80%, 50%, 25% and 1–5% of cases, respectively.

Subtle endometriosis

Subtle endometriosis is found in 40% [53,54] of asymptomatic women. In women with pain or infertility, over 60% of women [55] had subtle lesions. Probably, almost all women would have subtle lesions if laparoscopy could be done repetitively; we only know that subtle lesions can disappear and reappear in other places when 2 laparoscopies were performed [56]. The incidence decreases with age

[55,57]. In adolescents, subtle lesions were found in 40% [58] and in 70% [59]. The epidemiology of subtle endometriosis over time does not allow the conclusion that the prevalence has been increasing in recent decades. The association of subtle lesions with variables such as early menarche, abundant or painful periods, subfertility, canalization defects of the cervix, race, dioxin, total body radiation, or any other factor is unknown.

Typical lesions

These data should be interpreted carefully because of the variable inclusion rate of subtle lesions. In asymptomatic women, typical lesions were reported in up to 5%; for example, in 4% of women undergoing tubal ligation [60], in 1.6% [61] and in 2.2% in Norway [62]. In the latter study, the risk was higher in women with early menarche, frequent menstruations, pelvic pain, infertility and without children. In women with infertility, endometriosis was more frequent when the partner was normal (5.7%) than when the partner had azoospermia (3.3%) [63]. In teenagers with severe dysmenorrhea, 50% had endometriosis [64]. In women with pain and infertility, 40–70%, with a mean of 33%, had typical lesions [65].

Data do not allow the conclusion that the prevalence of typical lesions is increasing in recent decades. It is unclear whether black women have lower rates and East Asians have higher rates than Caucasian women. It is also unclear that endometriosis increases with early menarche and abundant retrograde menstruation. Baboon data describing an increased prevalence of endometriosis following uterine outflow obstruction are not retained as retrograde menstruation was not confirmed in a recent study [66]. Dioxin pollution has been suggested to be causally related to endometriosis [67–69] but in humans, evidence is scarce [70,71]. Following the Seveso accident with severe dioxin pollution, the prevalence almost doubled (although not significantly) [72]. Breast-fed girls have been exposed to dioxins in mother milk, but they have a lower incidence of endometriosis in adult life [73]. Total body radiation increases endometriosis in primates [74], but we do not have data for humans. It is unclear whether changes in the immune system are causally related to the prevalence of endometriosis because it is not clearly affected by chronic immunosuppression, such as in transplant patients, smoking affecting NK activity, nor by caffeine or alcohol. The many associated changes in the immune system [75,76] and the decreased natural killer cell activity in plasma and in peritoneal fluid [77–79] can be interpreted both as a cause and as a consequence of endometriosis. The association of typical endometriosis with a higher trait anxiety could be due to the lower steroid hormone concentrations in peritoneal fluid of women with luteinised unruptured follicle syndrome [22]. Endometriosis is considered a career women's disease but without much evidence. This might suggest a relationship with stress, but also the delay of first pregnancy, to an increase of infertility with age, an increase in laparoscopies and a higher documented prevalence of endometriosis. This is consistent with a lower prevalence with increasing parity [80] and the use of oral contraception [81].

Cystic ovarian endometriosis

There is no evidence that the prevalence of cystic ovarian endometriosis is increasing in recent decades. There is no evidence of an association between cystic ovarian endometriosis and pollution or lifestyle. The relationship with ovarian cancer is unclear [82].

Deep lesions

Deep endometriosis was initially reported as case reports and small series. The recognition of smaller deep endometriosis lesions have increased only after 1990. Prevalence is difficult to ascertain because all reports have a referral bias. An indirect estimation of the prevalence can be derived from the rate of approximately 500 interventions/year in a population of 10 million (PK and J. Donnez) in Belgium. In the early 1990s, deep endometriosis surgery was almost systematically referred. Assuming a reproductive lifespan of 30 years and a diagnosis and surgery in around half of the women, its prevalence in the population ranges between 0.2 and 0.5%. In women with pain and infertility, the prevalence is estimated to be between 3 and 10% as 10–20% of women referred for pain to Leuven had deep endometriosis [55]. There are no valid data indicating that the prevalence of deep endometriosis is increasing or that deep endometriosis is caused by pollution or lifestyle. However, internationally recognised deep endometriosis surgeons AW, LA, JD, JK, AU, AS and PK who performed surgery over the last 20 years and who each performed between 1000 and 3000 interventions of deep endometriosis all

have the strong impression that the severity and probably the prevalence of deep endometriosis are increasing [2]. It is unclear whether this is a referral bias. It is interesting that in the 1990s, deep endometriosis in the South of Italy was rare and much lower than in Belgium. This contrasts with the high incidence of severe endometriosis today as observed by AU, AW and PK [2].

Adenomyosis, müllerianosis, peritoneal pockets, and stromatosis

These diseases are often considered as endometriosis. They will not be discussed. Stromatosis does not contain endometrial cells, while with entities such as accessory cavitated uterine masses (ACUM), and Müllerianosis are too rare to discuss prevalence. Although the pathophysiology of adenomyosis is probably comparable to the pathophysiology endometriosis, adenomyosis will not be discussed.

Factors associated with endometriosis

In Leuven in the early 90s, a group of 900 women with pain and/or infertility, had subtle lesions (45%), typical lesions (29%), cystic ovarian endometriosis (31%) and deep endometriosis (18%). The total incidence of 710% remained constant with age, but subtle lesions significantly decreased, and typical, cystic and deep lesions increased with age [10] (Fig. 2).

Endometriosis is a hereditary disease (for references, see Ref. [31]) as evidenced by the seven times higher prevalence in first-degree relatives and the high associations in monozygotic twins. Genome-wide association studies could identify common genetic variants. Further, severity and early onset seem hereditary.

Endometriosis was reported to be increased by pollution such as dioxin [67] and PCB [83,84], and by radioactivity [85]. Endometriosis was reported to be linked to high fat consumption [86]; our lifestyle [50,87]; postponement of the first pregnancy, stress, lupus erythematosus and rheumatoid arthritis [88]; a family history of melanoma [89]; a higher risk of ovarian and breast cancers, cutaneous melanoma, asthma and some autoimmune, cardiovascular and atopic diseases [90]; reproductive medicine [91]; air pollution [92]; severe teenage acne [93]; adolescent endometriosis [94]; diminished ovarian reserve [95]; body size [96]; and cardiovascular disease [97].

Although statistically significant, these data do not permit final conclusions. As recognised before [50–52], they are hampered by the poor definition of endometriosis lesions, poor patient selection and unclear accuracy of the diagnosis because they are often based on hospital discharge records.

Many other associations have been described [31], such as a poor obstetrical outcome such as hypertension in pregnancy and small for date babies [98] and the association with adenomyosis.

Discussion

Understanding the epidemiology of endometriosis, its prevalence over time and at different ages, and the association with potentially causal factors is important as endometriosis can be linked to most gynaecological complaints such as infertility, pain, bleeding problems, fatigue, sexual problems and obstetrical complications. However, reliable epidemiological information today is limited. First, endometriosis has been studied as a single disease because it was considered to be implanted on the endometrium according to the implantation theory. With progressive understanding of oncogenic mutations, clonal development and epigenetics, the G-E pathogenesis was formulated. This hypothesis is compatible with all known aspects of endometriosis. Additionally, it can explain that endometriosis consists of more than four different pathologies, with each having a different set of G-E incidents at the start and a different natural history, since they acquire additional mistakes because of their G-E vulnerability. It makes it understandable that similar type of lesions are molecular biologically heterogenous and that each lesion is moreover heterogeneous at the cellular level. All theories concerning the growth and natural history of endometriosis lesions which are eventually self-limiting retain their full importance and will make the understanding of epidemiology only more complex.

The second major problem of endometriosis epidemiology is the diagnostic uncertainties. In the absence of a gold standard, and because a laparoscopy is needed to make the diagnosis, we only have information in women not undergoing surgery. Besides the surgical expertise, the diagnostic accuracy of laparoscopies should be evaluated as a test with verification bias [99]. As ‘the water of a river cannot raise

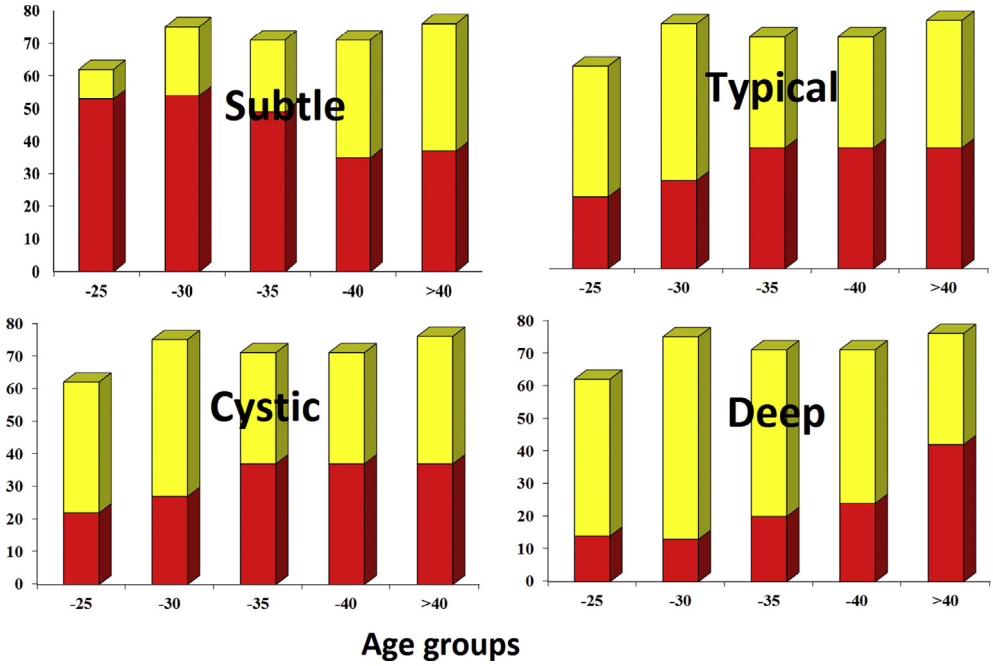

Fig. 2. Prevalence (red) of subtle, typical and deep endometriosis in women with infertility (n = 1297), pain (n = 918) and infertility and pain (n = 267). Subtle endometriosis decreases with age, whereas typical, cystic and deep endometrioses increase with age. The total prevalence (yellow) remains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

above its source', epidemiology of endometriosis requires accurate data with diagnostic accuracy of each type and severity of endometriosis, which we do not have today. To exploit the full power of statistical inference, we also need sufficiently large databases with adequately controlled and complete data. Probably, the most important bottleneck will be to find an agreement about which data to collect and the necessary collaboration of expert surgeons to collect and check the data for it to be exploited by statisticians.

Epidemiology also causes risks and potential harm. The burden a statistical association implies for the patient is not always realised. The diagnosis of 'endometriosis' is associated by most women today with future infertility, with a risk of a future hysterectomy because endometriosis is progressive, with sexual problems and with an increased risk of cardiovascular disease and ovarian cancer. All this, especially in a period of social media, generates a climate of fear, the consequences of which are not yet understood [51]. This climate of fear is moreover fuelled by the widely believed ideas that endometriosis is driven by pollution, radioactivity, lifestyle and food. It is thus not surprising that this fear translates in many support and discussion groups.

New concepts and understandings also present new opportunities. Triggering genetic and/or epigenetic changes for initiation, and further incidents during development open the possibility of new treatments and preventions. If the cells are G-E abnormal, immunotherapy becomes conceivable. If the peritoneal or upper genital tract microbiota play a role in initiating endometriosis and in its growth, a stricter diagnosis and treatment of vaginal and uterine infections might be useful. If the onset of endometriosis is driven by oxidative stress, the amount and frequency of retrograde menstruation could be important as prevention. If nests of microscopical endometriosis at distance from a deep lesion in the bowel or if the outer layer of a deep nodule are epigenetically metaplastic cells [38] which would return to normal after excision of a deep endometriosis nodule, this would suggest that the concept of radical surgery and completeness of surgery should be reconsidered.

Our understanding of subtle and microscopical endometriosis remains unclear and controversial. Three observations seem important, although the last two were not confirmed in subsequent studies.

Most subtle lesions are histologically active. Subtle lesions can disappear spontaneously and reappear in other localisations, suggesting reversible epigenetic changes or spontaneous clearance of implanted endometrium. During conscious pain mapping, subtle lesions can be painful like typical lesions. We do not know whether the many observations on typical, cystic ovarian and deep endometriosis such as immunology, peritoneal fluid and inflammation and heredity also apply to women with subtle lesions only. With the observations that retrograde menstruation occurs in most women, that shed endometrium has implantation potential and that the increased invasiveness of endometrial stromal cells is enhanced by peritoneum, it seems logical to consider subtle lesions to be early lesions following implantation. Similarly, the extensive observation on EMT and MET open the door to postulate that retrograde menstruation together with peritoneal microbiota eventually induce a transformation of coelomic endothelium or mesothelium into endometrium-like tissue. Subtle lesions can thus be viewed as normal implanted endometrium or as normal coelomic endothelial/mesenchymal cells with epigenetic changes making them look like endometrium. However, subtle lesions can also be viewed as a symptom of an endometriotic constitution with predisposing G-E defects making them vulnerable to additional defects following which the development of endometriosis begins. Key in this discussion is reversibility. If the epigenetic reorganisation is reversible, the question becomes whether these lesions return to normal endometrium or whether they return to normal coelomic endothelium/mesothelium/stem cells. More important seems the probability of reversibility, which might decrease after additional G-E incidents because of the specific peritoneal environment. The same holds true for microscopical endometrium-like cells in the peritoneum, in the bowel at distance from an endometriotic nodule and in lymph nodes of women with deep endometriosis. Unfortunately, we do not have epidemiological data of women with subtle lesions only.

Summary

The epidemiology of endometriosis is poorly known, and the available data do not permit definite conclusions. First, the diagnosis requires a laparoscopy, and we thus have data in women with pain or infertility only. Therefore, most observations on endometriosis will also be significant for women with pain or infertility in comparison with normal women. Second, endometriosis has been considered to be a single disease due to its definition as 'endometrium like glands and stroma outside the uterus'. However, the significance of subtle lesions is still unclear and, in addition, typical, cystic ovarian and deep endometriosis lesions should be considered to be different pathologies with different degrees of severity. Thus, they should be studied separately, with the additional difficulty that these lesions all occur in different combinations.

Pathophysiology and natural history are poorly known. There is no valid animal model. Although attractive, the Sampson implantation theory does not permit an understanding of endometriosis. Further, it is important to distinguish between the initiation and the subsequent progression of endometriosis. Endometriosis starts when cumulative G-E changes reach a certain threshold. Variability in the set of G-E changes result in heterogeneous endometriosis lesions. In addition, epigenetic changes are reversible at least at the beginning. Therefore, the histologically defined word endometriosis, 'endometrium like tissue outside the uterus', is clinically and biologically a misnomer. Clinically, it comprises at least four different diseases. Biologically, it comprises normal implanted endometrium and mesothelial or bone marrow cells with reversible epigenetic changes making them look like endometrium, and endometrium-like tissue with irreversible G-E changes which will progress and form typical, cystic and deep endometriosis lesions. To understand growth, we must consider, in addition to the variable set of G-E changes, the specific characteristics of the endometrial stromal cell as EMT and the endocrine, paracrine, immunologic, microbiota and oxidative stress environment.

Data considering endometriosis as one disease are difficult to interpret because of the variable prevalence and recognition of subtle lesions, the unclear diagnostic accuracy and the variable prevalence, severity and combination of endometriosis lesions. This is a problem found with all large datasets based on hospital discharge records. More reliable surgical data on the other hand are small series which do not permit multivariate statistical analysis. A third problem is that women diagnosed with endometriosis often have pain and/or infertility and have had at least a diagnostic laparoscopy, while many of them had surgery and infertility treatments.

Endometriosis is a hereditary disease. We tend to believe that heavy menstrual bleeding with probably more retrograde menstruation and more pelvic oxidative stress, and pelvic infections and/or a different microbiome are associated with increasingly severe endometriosis. The latter moreover could explain the association with ovarian cancer. We think it is too early to conclude that endometriosis is associated with an increased risk of cardiovascular disease or fat intake. Insufficiently explored is the association of endometriosis with chronic pain and personality characteristics as suggested by concepts as 'a career women's disease' and by the association with depression. Today, these personality characteristics begin to be linked to epigenetic effects, eventually transgenerational, creating genomic instability.

As a conclusion, we suggest focusing epidemiology on severe deep endometriosis or cystic ovarian endometriosis as their diagnostic accuracy is much better, because these are the more severe forms with probably the most clear G-E incidents, and because of the clinical impression by surgeons, that the severity and prevalence of deep endometriosis is increasing over time.

Funding

No funding.

Authorship

Drafting and revision: all authors. Final approval: all authors.

Practice points

- We should pay attention to symptomatic adolescent women.
- Vaginal, uterine and pelvic infection deserve more attention.
- Continuous oral contraception might be a prevention by reducing oxidative stress.

Research agenda

- Identification of G-E incidents in the different endometriosis lesions.
- Histochemical differentiation between reversible and irreversible lesions.
- Histochemical differentiation of the different endometriosis pathologies.
- Enhancing the diagnostic accuracy of laparoscopy for each lesion.
- A database with the different lesions and their severity for epidemiology.
- Evaluation whether antioxidants are a prevention of endometriosis.
- Evaluation how diet and exercise influence intestinal and peritoneal microbiota.
- Evaluation how intestinal microbiota affect endometriosis prevalence and/or growth.

Declaration of competing interest

None of the authors have a conflict of interest to declare.

Acknowledgments

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

References

[1] Woodward M. Epidemiology: study design and data analysis. Boca Raton, USA: Taylor and Francis Group; 2014.
[2] Koninckx PR, Ussia A, Keckstein J, Wattiez A, Adamyan L. Epidemiology of subtle, typical, cystic, and deep endometriosis: a systematic review. Gynaecol Surg 2016;13:457–67.
[3] Rokitansky C. Über Uterusdrüsen-Neubildung in Uterus- und Ovarial-Sarcomen. (On the neoplasm of uterus glands on uterine and ovarian sarcomas). Zeitschr Ges Aerzte Wien 1860;16:577–81.
[4] Cullen TS. Adeno-myoma uteri diffusum benignum. Johns Hopkins Hosp Rep 1897;6:133–57. Plates I-III.
[5] Sampson JA. Heterotopic or misplaced endometrial tissue. Am J Obstet Gynecol 1925;10:649–64.
[6] Sampson JA. Metastatic or embolic endometriosis, due to the menstrual dissemination of endometrial tissue into the venous circulation. Am J Pathol 1927;3:93–110. 43.
[7] Jansen RP, Russell P. Nonpigmented endometriosis: clinical, laparoscopic, and pathologic definition. Am J Obstet Gynecol 1986;155:1154–9.
[8] Martin DC, Hubert GD, Vander ZR, el-Zeky FA. Laparoscopic appearances of peritoneal endometriosis. Fertil Steril 1989;51:63–7.
[9] Koninckx PR. Biases in the endometriosis literature. Illustrated by 20 years of endometriosis research in Leuven. Eur J Obstet Gynecol Reprod Biol 1998;81:259–71.
[10] Cornillie FJ, Oosterlynck D, Lauweryns JM, Koninckx PR. Deeply infiltrating pelvic endometriosis: histology and clinical significance. Fertil Steril 1990;53:978–83.
[11] Koninckx PR, Martin DC. Deep endometriosis: a consequence of infiltration or retraction or possibly adenomyosis externa? Fertil Steril 1992;58:924–8.
[12] Koninckx PR, Donnez J, Brosens I. Microscopic endometriosis: impact on our understanding of the disease and its surgery. Fertil Steril 2016;105:305–6.
[13] Murphy AA, Guzick DS, Rock JA. Microscopic peritoneal endometriosis. Fertil Steril 1989;51:1072–4.
[14] Nisolle M, Paindaveine B, Bourdon A, Berliere M, Casanas Roux F, Donnez J. Histologic study of peritoneal endometriosis in infertile women. Fertil Steril 1990;53:984–8.
[15] Khan KN, Fujishita A, Kitajima M, Hiraki K, Nakashima M, Masuzaki H. Occult microscopic endometriosis: undetectable by laparoscopy in normal peritoneum. Hum Reprod 2014;29:462–72.
[16] Badescu A, Roman H, Aziz M, Puscasiu L, Molnar C, Huet E, et al. Mapping of bowel occult microscopic endometriosis implants surrounding deep endometriosis nodules infiltrating the bowel. Fertil Steril 2016;105:430–4.
[17] Mechsner S, Weichbrodt M, Riedlinger WF, Kaufmann AM, Schneider A, Kohler C. Immunohistochemical evaluation of endometriotic lesions and disseminated endometriosis-like cells in incidental lymph nodes of patients with endometriosis. Fertil Steril 2010;94:457–63.
[18] Sampson JA. Peritoneal endometriosis due to the menstrual dissemination of endometrial tissue into the peritoneal cavity. Am J Obstet Gynecol 1927;14:422–69.
[19] Sampson JA. The development of the imlantation theory for the development of endometriosis. Am J Obstet Gynecol 1940;40:549–57.
[20] Kruitwagen RFPM, Poels LG, Willemsen WNP, De Ronde IJY, Jap PHK, Rolland R. Endometrial epithelial cells in peritoneal fluid during the early follicular phase. Fertil Steril 1991;55:297–303.
[21] Weimar CH, Macklon NS, Post Uiterweer ED, Brosens JJ, Gellersen B. The motile and invasive capacity of human endometrial stromal cells: implications for normal and impaired reproductive function. Hum Reprod Update 2013;19:542–57.
[22] Koninckx PR, Ide P, Vandenbroucke W, Brosens IA. New aspects of the pathophysiology of endometriosis and associated infertility. J Reprod Med 1980;24:257–60.
[23] Halme J, Hammond MG, Hulka JF, Raj SG, Talbert LM. Retrograde menstruation in healthy women and in patients with endometriosis. Obstet Gynecol 1984;64:151–4.
[24] Nilbert M, Pejovic T, Mandahl N, Iosif S, Willen H, Mitelman F. Monoclonal origin of endometriotic cysts. Int J Gynecol Cancer 1995;5:61–3.
[25] Jimbo H, Hitomi Y, Yoshikawa H, Yano T, Momoeda M, Sakamoto A, et al. Evidence for monoclonal expansion of epithelial cells in ovarian endometrial cysts. Am J Pathol 1997;150:1173–8.
[26] Tamura M, Fukaya T, Murakami T, Uehara S, Yajima A. Analysis of clonality in human endometriotic cysts based on evaluation of X chromosome inactivation in archival formalin-fixed, paraffin-embedded tissue. Lab Invest 1998;78:213–8.
[27] Yano T, Jimbo H, Yoshikawa H, Tsutsumi O, Taketani Y. Molecular analysis of clonality in ovarian endometrial cysts. Gynecol Obstet Invest 1999;47(Suppl 1):41–5.
[28] Wu Y, Basir Z, Kajdacsy-Balla A, Strawn E, Macias V, Montgomery K, et al. Resolution of clonal origins for endometriotic lesions using laser capture microdissection and the human androgen receptor (HUMARA) assay. Fertil Steril 2003;79(Suppl 1):710–7.
[29] de Almeida Asencio F, Ribeiro HA, Ribeiro PA, Malzoni M, Adamyan L, Ussia A, et al. Symptomatic endometriosis developing several years after menopause in the absence of increased circulating estrogen concentrations: a systematic review and seven case reports. Gynecol Surg 2019;16:3.
[30] Martin DC. Concepts and theories. http://www.danmartinmd.com/files/endotheory.pdf.
[31] Koninckx PR, Ussia A, Adamyan L, Wattiez A, Gomel V, Martin DC. Pathogenesis of endometriosis: the genetic/epigenetic theory. Fertil Steril 2019;111:327–39.
[32] Koninckx PR, Barlow D, Kennedy S. Implantation versus infiltration: the Sampson versus the endometriotic disease theory. Gynecol Obstet Invest 1999;47(Suppl 1):3–9.
[33] Schuebel K, Gitik M, Domschke K, Goldman D. Making sense of epigenetics. Int J Neuropsychopharmacol 2016;19:pyw058.
[34] Koninckx PR, Ussia A, Tahlak M, Adamyan L, Wattiez A, Gomel V, et al. Infection as a potential cofactor in the genetic-epigenetic pathophysiology of endometriosis: a systematic review. Facts Views Vis Obgyn 2019;11:209–16.
[35] Suda K, Nakaoka H, Yoshihara K, Ishiguro T, Tamura R, Mori Y, et al. Clonal expansion and diversification of cancer-associated mutations in endometriosis and normal endometrium. Cell Rep 2018;24:1777–89.

[36] Guo SW. Cancer-associated mutations in endometriosis: shedding light on the pathogenesis and pathophysiology. Hum Reprod Update 2020;26:423–49.
[37] Zou Y, Zhou JY, Guo JB, Zhang ZY, Luo Y, Liu FY, et al. Mutation analysis of ZP1, ZP2, ZP3 and ZP4 genes in 152 Han Chinese samples with ovarian endometriosis. Mutat Res 2019;813:46–50.
[38] koninckx PR, Martin DC, Donnez J. Do we need to separate initiation and growth to understand endometriosis ? Fertil Steril 2020. in press.
[39] Guo SW. Cancer driver mutations in endometriosis: variations on the major theme of fibrogenesis. Reprod Med Biol 2018; 17:369–97.
[40] Zhang Q, Duan J, Liu X, Guo SW. Platelets drive smooth muscle metaplasia and fibrogenesis in endometriosis through epithelial-mesenchymal transition and fibroblast-to-myofibroblast transdifferentiation. Mol Cell Endocrinol 2016;428: 1–16.
[41] Canis M, Bourdel N, Houlle C, Gremeau AS, Botchorishvili R, Matsuzaki S. Trauma and endometriosis. A review. May we explain surgical phenotypes and natural history of the disease? J Gynecol Obstet Hum Reprod 2017;46:219–27.
[42] Liang Y, Yao S. Potential role of estrogen in maintaining the imbalanced sympathetic and sensory innervation in endometriosis. Mol Cell Endocrinol 2016;424:42–9.
[43] Santamaria X, Massasa EE, Taylor HS. Migration of cells from experimental endometriosis to the uterine endometrium. Endocrinology 2012;153:5566–74.
[44] Grimstad FW, Decherney A. A review of the epigenetic contributions to endometriosis. Clin Obstet Gynecol 2017;60: 467–76.
[45] Feng C, Dong J, Chang W, Cui M, Xu T. The progress of methylation regulation in gene expression of cervical cancer. Int J Genom 2018;2018:1–11.
[46] Konrad L, Dietze R, Riaz MA, Scheiner-Bobis G, Behnke J, Horné F, et al. Epithelial–mesenchymal transition in endometriosis—when does it happen? J Clin Med 2020;9:1915.
[47] Koninckx PR, Ussia A, Adamian L, Alsuwaidi S, Amro B, Gharbi H, et al. Conservative surgery of deep bowel endometriosis. In: Ferrero S, Ceccaroni M, editors. Clinical management of bowel endometriosis. Springer; 2020.
[48] Martin DC, Ahmic R, EL-Zeky FA, Zwaag RV, Pickens MT, Cherry K. Increased histologic confirmation of endometriosis. J Gynecol Surg 1990;6:275–9.
[49] Koninckx PR, Deslandes A, Ussia A, Gharbi H, Tahlak M, Adamian L, et al. Preoperative imaging of deep endometriosis: pitfalls of a diagnostic test before surgery. 2020. submitted.
[50] Missmer SA, Cramer DW. The epidemiology of endometriosis. Obstet Gynecol Clin N Am 2003;30:1–19. vii.
[51] Koninckx PR, Ussia A, Tahlak M, Wattiez A. Regarding: "link between endometriosis, atherosclerotic cardiovascular disease, and the health of women midlife. J Minim Invasive Gynecol 2020;27:237–8.
[52] Koninckx PR, Brosens IA. Dietary fat consumption and endometriosis risk. Hum Reprod 2011;26:731–2.
[53] Balasch J, Creus M, Fabregues F, Carmona F, Ordi J, Martinez-Roman S, et al. Visible and non-visible endometriosis at laparoscopy in fertile and infertile women and in patients with chronic pelvic pain: a prospective study. Hum Reprod 1996;11:387–91.
[54] Vercellini P, Parazzini F, Bolis G, Carinelli S, Dindelli M, Vendola N, et al. Endometriosis and ovarian cancer. Am J Obstet Gynecol 1993;169:181–2.
[55] Koninckx PR, Meuleman C, Demeyere S, Lesaffre E, Cornillie FJ. Suggestive evidence that pelvic endometriosis is a progressive disease, whereas deeply infiltrating endometriosis is associated with pelvic pain. Fertil Steril 1991;55:759–65.
[56] Wiegerinck MA, Van Dop PA, Brosens IA. The staging of peritoneal endometriosis by the type of active lesion in addition to the revised American Fertility Society classification. Fertil Steril 1993;60:461–4.
[57] Redwine DB. Age-related evolution in color appearance of endometriosis. Fertil Steril 1987;48:1062–3.
[58] Vercellini P, Crosignani PG. Epidemiology of endometriosis. In: Brosens IA, Donnez J, editors. New-York: Parthenon publishing group; 1993. p. 111–30.
[59] Laufer MR, Sanfilippo J, Rose G. Adolescent endometriosis: diagnosis and treatment approaches. J Pediatr Adolesc Gynecol 2003;16:S3–11.
[60] Walter AJ, Hentz JG, Magtibay PM, Cornella JL, Magrina JF. Endometriosis: correlation between histologic and visual findings at laparoscopy. Am J Obstet Gynecol 2001;184:1407–11.
[61] Cramer DW, Missmer SA. The epidemiology of endometriosis. Ann N Y Acad Sci 2002;955:11–22.
[62] Moen MH, Schei B. Epidemiology of endometriosis in a Norwegian county. Acta Obstet Gynecol Scand 1997;76:559–62.
[63] Matorras R, Rodriguez F, Pijoan JI, Etxanojauregui A, Neyro JL, Elorriaga MA, et al. Women who are not exposed to spermatozoa and infertile women have similar rates of stage I endometriosis. Fertil Steril 2001;76:923–8.
[64] Janssen EB, Rijkers AC, Hoppenbrouwers K, Meuleman C, D'Hooghe TM. Prevalence of endometriosis diagnosed by laparoscopy in adolescents with dysmenorrhea or chronic pelvic pain: a systematic review. Hum Reprod Update 2013;19: 570–82.
[65] Guo SW, Wang Y. The prevalence of endometriosis in women with chronic pelvic pain. Gynecol Obstet Invest 2006;62: 121–30.
[66] Donnez O, VL A, Defrere S, Colette S, VK O, Dehoux JP, et al. Induction of endometriotic nodules in an experimental baboon model mimicking human deep nodular lesions. Fertil Steril 2013;99:783–9.
[67] Rier SE, Martin DC, Bowman RE, Dmowski WP, Becker JL. Endometriosis in rhesus monkeys (Macaca mulatta) following chronic exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Fund Appl Toxicol 1993;21:433–41.
[68] Rier SE, Turner WE, Martin DC, Morris R, Lucier GW, Clark GC. Serum levels of TCDD and dioxin-like chemicals in Rhesus monkeys chronically exposed to dioxin: correlation of increased serum PCB levels with endometriosis. Toxicol Sci 2001; 59:147–59.
[69] Koninckx PR, Braet P, Kennedy SH, Barlow DH. Dioxin pollution and endometriosis in Belgium. Hum Reprod 1994;9: 1001–2.
[70] Terakawa N, Koninckx PR, Tsutsumi O, Ota Kanzaki, Taketani Y. The physiopathology of endometriosis: pollution and dioxin - Discussion. Gynecol Obstet Invest 1999;47(Suppl. 1):50.

[71] Heilier JF, Nackers F, Verougstraete V, Tonglet R, Lison D, Donnez J. Increased dioxin-like compounds in the serum of women with peritoneal endometriosis and deep endometriotic (adenomyotic) nodules. Fertil Steril 2005;84:305–12.
[72] Eskenazi B, Mocarelli P, Warner M, Samuels S, Vercellini P, Olive D, et al. Seveso Women's Health Study: a study of the effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on reproductive health. Chemosphere 2000;40:1247–53.
[73] Tsutsumi O, Momoeda M, Takai Y, Ono M, Taketani Y. Breast-fed infants, possibly exposed to dioxins in milk, have unexpectedly lower incidence of endometriosis in adult life. Int J Gynaecol Obstet 2000;68:151–3.
[74] Wood DH, Yochmowitz MG, Hardy KA, Salmon YL. Animal studies of life shortening and cancer risk from space radiation. Adv Space Res 1986;6:275–83.
[75] Barrier BF. Immunology of endometriosis. Clin Obstet Gynecol 2010;53:397–402.
[76] Riccio L, Santulli P, Marcellin L, Abrao MS, Batteux F, Chapron C. Immunology of endometriosis. Best Pract Res Clin Obstet Gynaecol 2018;50:39–49.
[77] Oosterlynck DJ, Cornillie FJ, Waer M, Vandeputte M, Koninckx PR. Women with endometriosis show a defect in natural killer activity resulting in a decreased cytotoxicity to autologous endometrium. Fertil Steril 1991;56:45–51.
[78] Oosterlynck DJ, Meuleman C, Waer M, Vandeputte M, Koninckx PR. The natural killer activity of peritoneal fluid lymphocytes is decreased in women with endometriosis. Fertil Steril 1992;58:290–5.
[79] Vinatier D, Dufour P, Oosterlynck D. Immunological aspects of endometriosis. Hum Reprod Update 1996;2:371–84.
[80] Parazzini F, Luchini L, Vezzoli F, Mezzanotte C, Vercellini P, Romanini C, et al. Prevalence and anatomical distribution of endometriosis in women with selected gynaecological conditions: results from a multicentric Italian study. Hum Reprod 1994;9:1158–62.
[81] Mahmood TA, Templeton A. Prevalence and genesis of endometriosis. Hum Reprod 1991;6:544–9.
[82] Guo SW, Zilberberg MD, Hummelshoj L. Endometriosis and ovarian cancer. Lancet Oncol 2012;13:e189–90.
[83] Birnbaum LS, Cummings AM. Dioxins and endometriosis: a plausible hypothesis. Environ Health Perspect 2002;110:15–21.
[84] Quaranta MG, Porpora MG, Mattioli B, Giordani L, Libri I, Ingelido AM, et al. Impaired NK-cell-mediated cytotoxic activity and cytokine production in patients with endometriosis: a possible role for PCBs and DDE. Life Sci 2006;79:491–8.
[85] Fanton JW, Golden JG. Radiation-induced endometriosis in Macaca mulatta. Radiat Res 1991;126:141–6. PMID: 1850850.
[86] Missmer SA, Chavarro JE, Malspeis S, Bertone-Johnson ER, Hornstein MD, Spiegelman D, et al. A prospective study of dietary fat consumption and endometriosis risk. Hum Reprod 2010;25:1528–35.
[87] Vigano P, Parazzini F, Somigliana E, Vercellini P. Endometriosis: epidemiology and aetiological factors. Best Pract Res Clin Obstet Gynaecol 2004;18:177–200.
[88] Harris HR, Simard JF, Arkema EV. Endometriosis and systemic lupus erythematosus: a population-based case-control study. Lupus 2016;25:1045–9.
[89] Kvaskoff M, Han J, Qureshi AA, Missmer SA. Pigmentary traits, family history of melanoma and the risk of endometriosis: a cohort study of US women. Int J Epidemiol 2014;43:255–63.
[90] Kvaskoff M, Mu F, Terry KL, Harris HR, Poole EM, Farland L, et al. Endometriosis: a high-risk population for major chronic diseases? Hum Reprod Update 2015;21:500–16.
[91] Missmer SA. Safety in reproductive medicine: breadth, depth and discovery. Hum Reprod 2015;30:2252–3.
[92] Mahalingaiah S, Hart JE, Laden F, Aschengrau A, Missmer SA. Air pollution exposures during adulthood and risk of endometriosis in the Nurses' Health Study II. Environ Health Perspect 2014;122:58–64.
[93] Xie J, Kvaskoff M, Li Y, Zhang M, Qureshi AA, Missmer SA, et al. Severe teenage acne and risk of endometriosis. Hum Reprod 2014;29:2592–9.
[94] Shah DK, Missmer SA. Scientific investigation of endometriosis among adolescents. J Pediatr Adolesc Gynecol 2011;24:S18–9.
[95] Shah DK. Diminished ovarian reserve and endometriosis: insult upon injury. Semin Reprod Med 2013;31:144–9.
[96] Shah DK, Correia KF, Vitonis AF, Missmer SA. Body size and endometriosis: results from 20 years of follow-up within the Nurses' Health Study II prospective cohort. Hum Reprod 2013;28:1783–92.
[97] Taskin O, Rikhraj K, Tan J, Sedlak T, Rowe TC, Bedaiwy MA. Link between endometriosis, atherosclerotic cardiovascular disease, and the health of women midlife. J Minim Invasive Gynecol 2019;26:781–4.
[98] Koninckx PR, Zupi E, Martin DC. Endometriosis and pregnancy outcome. Fertil Steril 2018;110:406–7.
[99] Broemeling LD. Bayesian estimation of combined accuracy for tests with verification. Bias 2011;1:53–76.