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RISK FACTORS FOR THE DEVELOPMENT OF ENDOMETRIOSIS

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ABSTRACT

Endometriosis is a gynaecological disease that affects 6-10% of women of reproductive age. It has a high impact on the quality of life and has important economic repercussions.

This article collects all the information regarding the risk factors for endometriosis, namely epidemiological, constitutional, childhood and adolescence, genetic, environmental, lifestyle, reproductive and personal history factors.

It was found that the women affected are most commonly aged between 25 and 29, with higher social status. Regarding their constitutional factors, they are mostly tall and thin, with lower BMI. They may have been exposed *in utero* to diethylstilbestrol (DES), been preterm new-borns or had low birth weight. Childhood and adolescence exposures and experiences are also important factors. Genetic factors include differences in chromosomes 1, 2, 4, 6, 9, 11 and 12. Environmental factors like pollution exposure, lifestyle factors like diet and work schedule, reproductive variables that increase exposure to menstruation fluids, and personal history with previous pelvic surgery and caesarean section are also prone to contribute to endometriosis development.

Endometriosis is still a complex disease that requires multiple steps from onset to clinical manifestations. Keys factors like genetic susceptibility combined with life exposures and habits play an important role in the development of the disease.

KEYWORDS

Endometriosis | Risk factors | Prenatal and childhood | Constitutional | Lifestyle | Environment | Genetic

INTRODUCTION

Endometriosis is a benign proliferation of functioning endometrial glands and stroma, located outside the uterine cavity.[1] The most common site of implantation is the pelvic peritoneum. Distant lesions, as in pericardium, pleura and liver have also been reported.[2]

It affects about 6-10% of women of reproductive age and is found among 20-50% of infertile women.[3]

The pathogenic mechanism for this disease is still unknown, but it is recognized that it depends on the existence of factors that may promote endometrial cell migration or the development of endometrial implants outside the uterus, as well as factors that promote the growth of the implants.

Three main theories have been proposed to explain the development of ectopic endometrial implants:

1. Sampson[4] suggested that the implants were associated with retrograde menstruation, since endometriosis is more common in women with outflow. Some studies from 1994 on baboons,[5] showed that partial obstruction of the cervix leading to retrograde flow increased risk of endometriosis. However, the fact that 70-90% of women experience retrograde menstruation without developing endometriosis is yet to be explained.[6]
2. In 1924, Halban et al. explained the presence of implants in distant sites by using the Vascular and Lymphatic Dissemination theory, which suggested that the spread of tissue through the different organs would happen by metastization from the endometrium through blood and lymphatic vessels.
3. Meyer et al. described the Coelomic Metaplasia theory, which explains the early development of endometriosis in some adolescents before the onset of menstruation. The authors suggested that some of the peritoneal cavity's multipotent cells, under certain conditions, could develop into functional endometrial tissue.

Regarding the growth of the implants, it is presently considered that endometriosis is an inflammatory oestrogen-dependent disease. The inflammation is shown by the high levels of macrophages and the differences in the cytokines levels, like TNF alpha, IL-8 and IL-10, in the peritoneal fluid of women with endometriosis.[7] These inflammation factors create a microenvironment prone to high prostaglandin (PG) levels. The prostaglandin levels are due to high levels of cyclooxygenase-2 (COX-2) seen in the macrophages.

Besides inflammation, higher oestrogen levels can increase PG levels. Higher oestrogen levels are provided by increased aromatase P450 levels seen in implanted cells, but not in endometrial cells. This enzyme promotes testosterone conversion into oestrogens and acts by inducing prostaglandin E2 (PGE2).

PGE2 stimulates aromatase activity, creating a positive feedback loop. The high levels of PGE2 stimulate adhesion, proliferation, apoptosis inhibition, angiogenesis, neuronal sprouting and inflammation, leading to the development of implants, as well as their growth. These can also explain the characteristic symptom, pain.[8]

The main symptoms of the disease include dysmenorrhea, which worsens over time and may not respond to medical therapy and dyspareunia, typical in deep endometriosis. Gastrointestinal symptoms may also occur. There is also a number of implications during women's life including infertility (50% of endometriosis patients), pregnancy, risk of coronary heart diseases[9] and of cancer later in life.[10]

The gold standard diagnostic procedure is still laparoscopic observation of lesions and tissue biopsy. The disease is usually staged using the classification from the American Society for Reproductive Medicine based on amount, severity, location, depth and size of growth of lesions. In this classification four stages are considered: I (minimal), II (mild), III (moderate) and IV (severe).[11]

Treatment includes expectant management, medical therapy and surgical therapy (conservative or radical).[12] Medical treatment is the first line option to control pain associated with endometriosis. The main pathway in which most of the medical therapies act is by down-regulating the ovarian production of oestrogen. This includes contraceptive methods such as combined oral contraceptives (COC), progestins and levonorgestrel-intrauterine system (LNG-IUS). COC act by decreasing the effect of ovarian hormones on the endometrium.[13] Isolated progesterone is also an option. LNG-IUS produces amenorrhea or hypomenorrhea by inducing endometrium atrophy and inactivation and, consequently, reducing the endometriosis-associated pain.

Other medical treatments include weak androgenic steroids, like danazol, and gonadotropin-releasing hormone (GnRH) agonists/analogues. Androgenic steroids create an environment

high in androgens and low in oestrogen – a pseudo menopause environment. These changes provide for the development of atrophy of the endometrium, decreasing the pain.[14] GnRH agonists and analogues bind to the pituitary receptors. This leads to the inhibition of pituitary hormone release, leading to the down-regulation of hormone production by the ovaries.

The use of GnRH antagonists, aromatase inhibitors, selective oestrogen receptor modulators and selective progesterone receptor modulators is not approved but may play an important role in the future.[15]

If medical therapy is not sufficient to decrease the symptoms, surgery may be necessary. Conservative surgery is preferred in younger patients, whose reproductive plan is not completed. Radical surgery is usually performed in older women with a complete reproductive plan.

In patients with infertility, the preferred treatment is surgery which aims to restore the pelvic anatomy and remove endometriomas.

As it is still an enigmatic disease with a number of questions to be answered, risk factors can play an important role by giving clues about the disease age of onset and pathophysiology, as well as helping to find new therapeutic targets. Risk factors can also play an important role in diagnosis, providing help in identifying patients likely to be affected even before the laparoscopic diagnosis. Moreover, knowing what puts a woman at risk of developing endometriosis can lead to preventive measures, perhaps decreasing the incidence of the disease.

The current paper aims to collect all the conclusions about risk factors for the development of endometriosis in several categories, namely epidemiologic factors, prenatal and childhood factors, constitutional factors, lifestyle factors and personal history.

METHODS

A narrative review based on the use of databases such as PubMed/Medline was carried out to identify studies involving risk of endometriosis. The papers included were case-control studies and reviews. The publications were restricted to the Portuguese, English, French and Spanish languages. The search included studies selected using different combinations of the following keywords: *epidemiology, body weight, diet, alcohol, tobacco, exercise, genetic, environment, exposure* or *in utero exposure* combined with *risk factors* and *endometriosis*. All

references of the studies were also reviewed to identify other relevant publications. A total of 100 papers were included in this review. The literature search was updated on November 30, 2018.

RESULTS

1. Epidemiologic factors

Age. Endometriosis is now a disease which is mostly diagnosed between the ages of 25 and 29, and is rare before menarche or after menopause. In the past, it was diagnosed later in life since the diagnostic methods and health care access were limited.[16]

Social class and race. Higher social status or higher levels of education are commonly found amongst the affected women.[16] In a traditional sense, this has been explained by a diagnostic bias, since people with higher socioeconomic status are usually more aware of their health issues.[17] However, recent reviews point to the possible correlation between higher social-economic status and other factors involved in this disease such has lower body mass[18] or higher alcohol consumption levels.[19]

Studies made in the USA report higher levels of endometriosis diagnosis among white women – about 20-40% more than other ethnicities. But, then again, this may be due to a diagnostic bias, since generally black and Latin women tend to be from lower social classes, have lower grades of education and less access to medical care.[16]

Physical traits. Some studies have found a higher incidence of endometriosis among red-haired women, women with a higher number of naevi and skin sensitivity to sun exposure.[20–22]

2. Constitutional factors

Generally, patients who suffer from endometriosis are taller, thinner and have lower BMI than the control groups.

Even though it was thought that higher BMI would lead to higher oestrogen levels, thus leading to higher risk of endometriosis, this association does not exist and is exactly the opposite. This can be explained by arguing that higher BMI is associated with increased insulin resistance and hyperinsulinemia.[23,24] This endocrine deregulation leads to impaired oocyte maturation and to the stimulation of androgen production, causing anovulation.[25,26] Anovulation decreases exposure to menstrual fluids. Higher BMI may also be related to lower sex hormone-binding globulin, meaning lower levels of circulating sex hormones.[27] Some investigations even

suggest that a higher BMI can act as a protective factor, with a 12-14% decrease in the risk of being diagnosed with endometriosis for every unit of BMI increase.[28]

Lower BMI levels, although consistently demonstrated to have a relation to the disease, may be a cause or a consequence of the pathology. Conclusions have not been made about this question, but some authors hypothesize that genetic factors related to endometriosis may be also related to body type.[29,30]

The importance of body composition may start before adult life. Childhood and adolescence BMI may influence the development of the disease;[31,32] decreases in body-weight during childhood and adolescence were associated with an increased risk for the disease[32,33] and, even though the justification of this finding is still unknown, it is hypothesised that it may be related to the insulin-like growth factor (IGF).[32] IGF is a factor produced by the liver and it works together with insulin to maintain constant levels of blood glucose. It was found that it prevents apoptosis[34] and promotes mitogenesis[34] of endometrium cells. Higher IGF levels were found in women with lower body size at ages 5 and 10 and lower body mass index at age 18.[35]

3. Prenatal and childhood factors

Prenatal development. The evidence that supports the developmental origin for endometriosis comes from two findings: the theory for müllerianosis and the findings of endometriosis in human foetuses. Müllerianosis is a pathology that arises from embryonic müllerian tissue, misplaced during organogenesis, resulting in the formation of choristomas – tumour-like masses consisting of normal cells in an abnormal location. Different from endometriotic implants that appear to be on the organs, müllerianosis choristomas appear to be part of the organ's constitution. Despite these differences, there may be a common pathophysiology between both diseases, especially since they both represent ectopic localizations of endometrial tissue, suggesting an embryonic development of endometriosis.[36] Research has recently found evidence for endometriosis in human female foetuses at gestational ages as young as 16 weeks.[37,38] Authors suggest that the implants would develop during the foetal period but would remain inactive until puberty.

Prospective studies[33,39] show an association between diethylstilboestrol (DES) exposure during pregnancy, preterm birth, lower birth weight and increased endometriosis risk. DES is a potent oestrogen (E) used in the USA in the 70s to prevent miscarriage and pregnancy complications. However, it was found that it increased the risk of a rare vaginal cancer in

exposed daughters.[40] Many other abnormalities have been related to DES exposure, especially related to the female reproductive system, including infertility, pregnancy complications, uterine malformations and endometriosis.

Endometriosis was found to be higher among women who were preterm newborns. At the end of gestation, an outbreak is seen in the production of oestrogens by the placenta. High oestrogen levels stimulate organ maturation, including the uterus. Oestrogen can also inhibit hypothalamic-pituitary-gonadal (HPG) foetal axis, keeping a lower level of gonadotropins produced by the foetus at birth. In preterm, since the final weeks of gestation are not experienced, the maturation of the uterus is not complete and the HPG axis is not inhibited. Thus, premature infants have higher levels of gonadotropins, increasing exposure to oestrogens and risk of endometriosis.[41]

There may be an association between lower birth weight and endometriosis, but the mechanism is unknown. It may be due to multiple events (e.g., hormonal variations, changes in foetal blood flow) that may affect foetal growth and development.[33]

Studies about cigarette smoking during pregnancy have been inconsistent,[42] suggesting that, even though tobacco is related to an anti-oestrogenic effect,[43] smoking does not influence the probability of developing endometriosis.

Childhood environment. Why and when endometriosis starts to develop is still unknown. Some authors accept the childhood and adolescence period as the probable time of the onset of the disease. Therefore, studying the influence of childhood and adolescence exposures may be the key to understanding the disease.

Only a few studies have been made on this subject. Some conclusions include a modestly higher risk of endometriosis with exposure to pets at home or by living on a farm for more than 3 consecutive months.[44] Also, an increased risk was found when women were exposed to passive smoking during childhood and food deprivation during World War II.[45]

There was also observed an association between soy milk consumption during childhood and the increased risk of endometriosis. This association was explained by the higher oestrogen levels found in soy milk consumers.[46]

New studies have started to study the role of a healthy psychological environment while growing up. There were reports of increased risk of endometriosis amongst emotionally abused women as well as neglected ones.[47] In another study, statistical analysis showed a 79% increased risk of laparoscopically confirmed endometriosis for women reporting severe chronic abuse of multiple types.[48]

4. Genetic factors

Genetic factors are thought to have a key role in the development of endometriosis.[49] The initial suspicion of this association was first made when the high incidence of familial cases was reported. Today, studies show an average of 50% inheritance.[50]

Over time, three gene mapping techniques have been applied to try to understand the genetic mechanism behind endometriosis, to identify specific risk factors and to create new therapeutic options – candidate gene, linkage and genome wide association (GWA) studies.

Candidate gene and linkage studies have failed to identify genetic variants strongly related to risk of endometriosis, as it is common in the complex disease area.[51,52] However, GWA studies have been playing a major role in the advance of knowledge related to endometriosis pathophysiology (Table I).

GWA were built to analyse the multiple single nucleotide polymorphism (SNP) in different study groups, comparing its frequency among them and trying to find an increased frequency of one or multiple SNPs. These studies, when applied to endometriosis, revealed an association between the disease and genes, for example:

- *LINC00339*[53], *WNT4*[54,55] and *CDC42*[53] in chromosome 1 – regions related to bone density, the development of female reproductive organs and coding of binding sites for ESR1 (oestrogen receptor 1), respectively;
- *GREB1*[54,56], *ETAA1*[54] and *IL1A*[54,57,58] in chromosome 2 – *GREB1* may play a role in oestrogen-stimulated cell proliferation. It acts as a regulator of hormone-dependent cancer growth in breast and prostate cancers; *ETAA1* is a replication stress response protein that accumulates at DNA damage sites and promotes replication fork progression and integrity. It acts by stimulating DNA repair and is associated with tumour growth; *IL1A* is related to primarily pro-inflammatory immune processes and haematopoiesis.
- *KDR*[54,59] in chromosome 4 – this codes a tyrosine-protein kinase that acts as a cell-surface receptor for vascular endothelial growth factors A, C and D. It plays an essential

role in the regulation of angiogenesis, vascular development, vascular permeability, and embryonic haematopoiesis.

- *ID4*[54,56] in chromosome 6 – implicated in regulating a variety of cellular processes, including cellular growth, senescence, differentiation, apoptosis, angiogenesis and neoplastic transformation.
- *CDKN2A-AS1*[55,60] and *CDKN2A-BAS*[54,61] in chromosome 9 – genes related to the regulation of tumour suppressor genes, mostly present in European and Asian ethnicities, respectively;
- *VEZT*[54,55] in chromosome 12 – this is a gene related to adherent junctions that showed a high correlation with endometriosis stages III/IV.

A recent meta-analysis[54] found five new loci that may be involved in endometriosis pathogenesis, including *FN1* (chromosome 2), involved in cell adhesion, cell motility, opsonisation, wound healing, and maintenance of cell shape; *CCDC170* (chr. 6), a gene related to breast cancer; *SYNE1* (chr. 6), a multi-isomeric modular protein which forms a linking network between organelles and the actin cytoskeleton to maintain the subcellular spatial organization; 7p12.3, of which the function is still unknown; and *FSHB* (chr. 11), which stimulates development of follicles and spermatogenesis in the reproductive organs.

Recent studies uncovered the possibility of the relation between some SNP variations in the FSH receptor gene and the *XRCC1* gene (related to DNA repair) in Asian populations.[62]

Despite recent advances, most GWA findings are located in non-coding regions of the genome, such as introns and intergenic regions, meaning there is still some research to be done regarding their function. To date, these associations only explain about 5% of inheritance.[54] Current GWA findings have no power to predict endometriosis risk for individual women.

5. Environmental factors

Humans and animals are daily exposed to chemical pollutants that can affect physiological processes and cause diseases. An analysis of chemical agents in the blood of the human umbilical cord made by the Environmental Working Group revealed that all the children studied have been exposed to some of the 287 pollutants detected,[63] suggesting that the influence of environmental exposure may start to develop even before birth.

Table I. Genes associated with endometriosis diagnosis.

Chr.	Gene	Function	Ref.
1	LINC00339	Increases bone density.	[53]
1	WNT4	Involved in the development of female reproductive organs.	[54,55]
1	*CDC42*	Coding of binding sites for ESR1 (oestrogen receptor 1).	[53]
2	*GREB1*	Oestrogen-stimulated cell proliferation. Acts as a regulator of hormone-dependent cancer growth in breast and prostate cancers.	[54,56]
2	*ETAA1*	Replication stress response protein that accumulates at DNA damage sites and promotes replication fork progression and integrity. Stimulates DNA repair and is associated with tumour growth.	[54]
2	*IL1A*	Primarily pro-inflammatory immune processes and haematopoiesis.	[54,57,58]
2	*FN1*	Involved in cell adhesion, cell motility, opsonisation, wound healing, and maintenance of cell shape.	[54]
4	*KDR*	Codes a tyrosine-protein kinase that acts as a cell-surface receptor for vascular endothelial growth factors A, C and D. Plays an essential role in the regulation of angiogenesis, vascular development, vascular permeability, and embryonic haematopoiesis.	[54,59]
6	*ID4*	Implicated in regulating cellular growth, senescence, differentiation, apoptosis, angiogenesis and neoplastic transformation.	[54,56]
6	*CCDC170*	Related to breast cancer.	[54]
6	*SYNE1*	Forms a linking network between organelles and the actin cytoskeleton to maintain the subcellular spatial organization.	[54]
7	7p12.3	Unknown.	[54]
9	*CDKN2A-AS1*	Related to the regulation of tumour suppressor genes.	[55,60]
9	*CDKN2A-BAS*	Related to the regulation of tumour suppressor genes.	[54,61]
11	*FSHB*	Stimulates development of follicles and spermatogenesis in the reproductive organs.	[54]
12	*VEZT*	Related to adherent junctions that showed high correlation with endometriosis stages III/IV.	[54,55]
19	*XRCC1*	FSH receptor gene related to DNA repair.	[62]

CDKN2A and XRCC1 are mostly found in Asian ethnicities.
Chr., Chromosome; Ref., References.

Dioxin and dioxin-like compounds. Amongst the pollutants detected, tetrachlorodibenzo-p-dioxin (TCDD) has been studied and is considered the most toxic environmental pollutant. Dioxins result from the combustion of materials and accumulate in the food chain, being stored in lipophilic tissue. Breastfeeding and fasting can reduce their body levels.[64] Overall, these toxins can be referred to as dioxins and dioxin-like compounds. Polychlorinated biphenyl (PCBs) and polychlorinated dibenzofurans **(**PCDFs) showed similar toxicity to TCDD due to their similar structure.[65]

Dioxins and dioxin-like compounds can pass the plasmatic membrane and bind to the aryl hydrocarbon receptor (AhR) in the cytoplasm. Then, the AhR binds to its nuclear translocator (ARNT) forming a heterodimer that activates genes with xenobiotic response elements, affecting the detoxification system and activating factors that promote cell proliferation (like TNF-β or cytokines)[64]. Cytokines increase COX-2 and PGE-2 activity, leading to higher P450 aromatase levels and thus oestrogenic production.[66]

It is also thought that TCDD can influence matrix metalloproteinase (MMP) - progesterone interaction during the menstrual cycle. MMP plays an important role in tissue remodelling, promoting the exfoliation of the endometrium that occurs in menstruation. Its action is inhibited by the high levels of progesterone seen in the secretory phase.[67] When TCDD is added to the process, MMP is activated even with high progesterone levels, promoting long-lasting menstruation.

Organochlorine pesticides. Organochlorine pesticides (OCPs) are artificial pesticides that were highly used during the 20th century. Despite their use being restricted in many countries, high serum concentrations of these compounds can still be found in the population. OCPs have an environmental persistence and bioaccumulation within organisms and the food chain. These chemicals have demonstrated oestrogenic properties in *in vitro* studies[68,69] and have exhibited adverse reproductive system effects in laboratory animal studies, altering uterine and ovarian function and endogenous hormone production[69,70], thus having the possibility of increasing risk of endometriosis.

Studies have shown an increased risk of endometriosis amongst people exposed to β-hexachlorocyclohexane (β-HCH), a technical-grade component of one of the OCPs – hexachlorocyclohexane – which was used as an agricultural insecticide. Mirex, used in the 1960s and 1970s as part of an insect control programme against fire ants, also revealed a positive association with the disease.[71,72]

Perfluoroalkyl and polyfluoroalkyl compounds. Two chemicals in this class (perfluorooctanoic acid and perfluorononanoic acid) were associated with approximately

twofold or higher odds of surgically visualized endometriosis in an operative cohort.[73] The mechanism underlying this association is yet to be explained.

Metals. It is thought that they may influence endometriosis development risk since they have an effect on the endocrine system: lead and mercury may have an anti-oestrogenic effect[74] and cadmium the opposite effect.[75] However, there are not conclusive findings of an association between metal exposure and endometriosis risk.[76]

Benzophenone-type ultraviolet filters (BP-type filters). 2,4-dihydroxybenzophenone was associated with increased odds (19% higher) of developing endometriosis.[77] BP-type filters are used in personal care to prevent skin damage by the sun. Part of the product applied enters the bloodstream. Some reports show a weak oestrogen-like activity by these compounds, including them in the endocrine-disrupting chemicals list.[78]

6. Lifestyle factors

Occupation. Women who work night shifts have an increased risk of endometriosis.[79,80] This can be explained by the deregulation that these workers may undergo in melatonin levels. Melatonin has the capacity of inhibiting the aromatase enzyme. When we have lower levels of this circadian cycle hormone, there are higher levels of aromatase. With higher aromatase activity, there is more testosterone being synthesized from oestrogen.[81,82]

Diet. Diet has been found to affect different diseases. The effect on endometriosis risk is still mostly unknown but researchers found a possible association between the disease and vegetable intake[83,84] as well as saturated.[83–85] polyunsaturated[84,85] and trans fat consumption.[83,86]

Vegetable intake was found to have a protective effect probably because of its antioxidant power. However, some results were not conclusive possibly due to the difficulty of excluding the environmental exposures related to vegetable production including dioxin and dioxin-like exposure.[83,84]

Saturated and trans fats may have a role in increasing the risk of endometriosis. Saturated fat comes mostly from red meat and butter and trans fat comes from processed food like French fries, doughnuts, cookies/biscuits, chocolate. They act by slightly increasing oestradiol and oestrogen sulphate concentrations[83–85] and are associated with higher inflammation markers,[83,86] respectively.

Polyunsaturated fat, found in nuts, fish, seeds, and algae, may be protective since it influences the synthesis and biological activity of cytokines such as IL1, 2, 6 and TNF. *In vitro* experiments have shown a significant suppression of endometriotic implants exposed to polyunsaturated fat.[84,85]

Coffee. The influence of caffeine on endometriosis was initially reported in the early 90s. However, recent studies have failed to find an association between coffee or caffeine intake and increased endometriosis risk.[87] It should be noted that most studies are based on the presence or absence of consumption rather than the type of caffeinated product consumed.

Alcohol. Alcohol has been found to increase the risk of several oestrogen-dependent diseases such as breast cancer. Considering that endometriosis is an oestrogen-dependent disease, its connection with alcohol intake is an important factor.

Alcohol was demonstrated to increase oestrogen levels by increasing aromatase activity, thus increasing the conversion of testosterone to oestrogen[88] and by acting on luteinizing hormone (LH) levels, increasing ovarian oestradiol production.[88]

Alcohol was also shown to have an effect on immune response, regulating the production of proinflammatory cytokines and having an important role in chronic inflammatory diseases like rheumatoid arthritis.[89]

Consequently, a positive association was found between any amount of alcohol consumption and a higher risk of endometriosis. There was no significant difference between light or heavy drinkers.[90]

Tobacco. Despite evidence showing that the antioestrogenic effect of smoking can work as a protective factor in some oestrogen-dependent diseases like endometrial cancer and fibroids, results have been misleading regarding endometriosis and a recent meta-analysis found no relation between the two variables.[91]

7. Personal history

Reproductive history. According to Sampson's theory, conditions or anatomical characteristics related to higher menstruation exposure are generally related to a higher risk of endometriosis. Conditions or anatomical characteristics associated with lower menstruation exposure are consequently associated with decreased risk of developing the disease.[92]

Accordingly, early age of menarche and shorter menstrual cycles (especially shorter or equal to 27 days) are related to higher positive diagnosis of endometriosis since both these menstrual

characteristics lead to higher menstruation exposure.[93] Since pregnancy is associated with reduced total lifetime exposure to menstrual fluids, not having a pregnancy – being nulliparous – is strongly associated with higher risk for development of the disease [94].

On the other hand, being multiparous and breastfeeding decreases the number of months exposed to menstrual fluids, acting as protective factors.[94]

Past surgeries. Caesarean section and general pelvic endometriosis were found to be associated with a higher risk of endometriosis, mainly because they generate an environment prone to inflammation. However, surgeries performed on the thorax and abdomen, extremities, and laparoscopy and gynaecology-related surgeries were not found to be associated with the risk of endometriosis.[95,96]

Concomitant diseases. Compared with women without asthma, women with asthma of reproductive age are at a higher risk of endometriosis. The underlying mechanism is still unidentified.[97]

Genital tract inflammation/infections may increase the risk of endometriosis, probably because of the increase of local inflammation.[98]

Some data suggest that endometriosis and melanoma may share some genetic or hormonal features:[20,99] in families with a positive history of melanoma the rates for endometriosis diagnosis are higher; oestrogen was found to be related to melanogenesis[100] and, as endometriosis is an equally oestrogen dependent disease, there may be a common hormonal pathway between the two pathologies.

CONCLUSION

Endometriosis is still a complex disease, that requires multiple steps from onset to clinical manifestations. Keys factors like genetic susceptibly, combined with life exposures and habits, play an important role in the disease's development.

The genetic factors can be a key point to the understanding of this disease. Genes involved in the development of the reproductive organs, like WNT4 and FSHB, point to a possible prenatal onset of the disease; genes involved in breast cancer development, as well as angiogenesis, cell growth, differentiation and adhesion are in favour of a tumour-like disease pathway. There is also an important association between genes that encode oestrogen receptors and endometriosis, reinforcing the oestrogen-dependency of the disease.

Regarding age of onset, it can be even before birth, influenced not only by genetics but also by *in utero* exposure. The environment in which a woman is brought up can also have a key role in this disease – from nutritional factors like drinking soy milk, to pet exposure, second-hand smoking and childhood emotional abuse.

Endometriosis is more common amongst women with white skin, of reproductive age, nulliparous, that had early menarche, that belong to a higher social stratus and with a higher education level. They are commonly tall and thin, as they were through their childhood and adolescence.

Lifelong contact with environmental pollutants have been indicated as one of the most accepted risk factors to this disease. Dioxins, OCPs, perfluoroalkyl and polyfluoroalkyl compounds and BP-type filters showed a positive association with incidence of the disease.

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