Endometriosis and environmental factors: A critical review

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Review

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A B S T R A C T

This review provides an overview of current knowledge on the relationship between various environmental factors and endometriosis. We successively searched for a given exposure factor combined with the word "endometriosis." The literature was comprehensively analyzed and summarized by quoting only the most important and recent studies on each exposition factor. The data focused primarily on endocrine disruptors, such as dioxins and polychlorinated biphenyls, that appear to have the strongest effect. Intriguing data suggest a link with night work, sun exposure and red meat consumption. For the other risk factors studied, particularly those related to lifestyle (tobacco consumption, alcohol, coffee, soy, physical exercise), the data are not sufficient to draw conclusions. In summary, the epidemiological evidence does not support a strong, scientific link between exposure to environmental factors and endometriosis. The complexity of this disease requires advanced study designs and standardized methodology. Future studies should be carefully designed to address these issues to advance our understanding of the impact of the environment and its consequences on endometriosis.

Introduction

Endometriosis is an estrogen-dependent disease characterized by the ectopic growth of endometrial tissue. In industrialized countries, this benign disease affects approximately 10% of women of childbearing age [1]. Its incidence reaches 50% in infertile women [2]. Several circumstances may lead to the diagnosis: chronic pelvic pain, infertility workup, or incidental discovery during laparoscopy. Its pathophysiology currently remains debated but appears to be multifactorial, probably including genetic and environmental factors. Although retrograde menstruation of endometrial cells into the peritoneum is the most widely accepted theory, this phenomenon occurs in approximately 70–90% of women, whereas the prevalence of endometriosis is much lower [3]. Therefore, other factors may contribute to the pathogenesis of endometriosis, including environmental toxicants.

Recently, work has been done to examine the impact of environmental factors on the development of the disease. However, the results of these studies remain contradictory. Although the biological plausibility of the association between exposure to environmental chemicals and endometriosis is provided by several studies on primates and rodents [4,5], several methodological obstacles limit the generalization of the results to humans: lack of statistical power; difficulty in the precise diagnosis of endometriosis; and the selection of healthy controls [6].

The objective of this work is therefore to provide a critical review of current knowledge on the relationship between various environmental factors and endometriosis.

Methods

The literature search was performed using the PubMed database. Firstly, two of the authors established a list of factors to study by searching the environmental literature in general. This list was also expanded by exploring the results of the “endometriosis environment” and “endometriosis environmental factors” searches on PubMed and can be found in Supplementary Table 1. Secondly, we successively searched each exposure factor combined with the word “endometriosis.” Studies could be included if they presented data on the association between endometriosis and the environment. Only epidemiological studies involving human subjects were included. Articles published in languages other than English were not translated and were excluded. Medical treatments and hormone therapy were not considered as environmental factors and were also excluded from the review. This review does not present all the articles in an exhaustive manner; the literature was comprehensively analyzed and summarized. Depending on the factors studied, particularly when the number of studies found was important, only the most

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relevant and recent studies offering the best quality of evidence were retained and quoted. Conversely, for factors that had been very little studied, studies with a smaller impact or older studies could be retained to provide an understanding of the quality of the available data. Systematic reviews and meta-analyses were not excluded from our critical review. Articles could be included if they were published between January 1980 and June 2021, provided they were deemed relevant to the topic and were available on PubMed.

Results

The results of this critical review are summarized in Table 1.

Lifestyle factors

Caffeine

A 1994 case-control study of 180 infertile patients with endometriosis [7] showed that patients consuming 7 g of caffeine per month or more had an increased relative risk of presenting with endometriosis compared to low consumers (OR = 1.9 [95% CI = 1.2 - 2.9], $p = 0.005$). In contrast, in 2014, a meta-analysis based on eight studies, including 1407 women with endometriosis, found no evidence for this association [8]. However, in some selected studies, coffee consumption was reported without taking into account the caffeine content (variable based on the manufacturing process or the type of beverage consumed), and the estimated amounts were based on declarative data. The literature is therefore limited and does not allow any definite conclusions to be drawn regarding the relationship between coffee consumption and the risk of endometriosis.

Smoking

Tobacco exposure disrupts steroidogenesis, resulting in altered estrogen synthesis [9] and decreased progesterone synthesis [10]. In 2014, a recent meta-analysis combining data from 38 studies found no association between smoking and the risk of endometriosis [6]. The RR was 0.96 (95% CI 0.86 to 1.08) for ever smokers, 0.95 (95% CI 0.81 to 1.11) for former smokers, 0.92 (95% CI 0.82 to 1.04) for current smokers, 0.87 (95% CI 0.70 to 1.07) for moderate smokers and 0.93 (95% CI 0.69 to 1.26) for heavy smokers. However, various biases seem to affect the results of this meta-analysis: inconsistent diagnosis of the disease between studies, self-reported information, and selection of controls among asymptomatic patients. Additional studies would therefore be necessary to further evaluate this relationship.

Alcohol

The results regarding consumption are conflicting and were reported in a recent meta-analysis based on 15 articles [11]. The estimated risk for regular alcohol consumption was 1.2 (95% CI: 1.1−1.4). This relationship seems biologically plausible, as alcohol has been shown to interact with pituitary LH production and increase aromatase activity, leading to increased estrogen secretion [12]. However, some confounding factors were not always considered (socioeconomic status and BMI in particular). The few studies that adjusted for age, socioeconomic status, ethnicity, gravidity, and BMI [13] did not find an increased risk of endometriosis. In conclusion, although the present meta-analysis provides evidence of a positive association, it cannot be excluded that multiple mechanisms are also involved.

Dietary factors

Numerous forums, Internet blogs, and television shows address the issue of diet in endometriosis. In 2021, a review evaluated the influence of diet on endometriosis [14]. Nineteen studies were selected. The different food types were then analyzed separately. In summary, the authors report that high consumption of omega-3 and omega-6 was associated with a reduction in painful symptoms [15,16]. The consumption of red meat increased, and saturated fat was associated with a negative effect [17,18]. In the prospective cohort of Yamamoto et al., including 3800 laparoscopically confirmed cases of endometriosis, the authors showed a 56% increased risk of endometriosis in women consuming red meat more than twice a day compared with those consuming it less than once a week (95% CI=1.22−1.99; $p<0.0001$). The evidence for fruits and vegetables, dairy products, unsaturated fats, fiber, soy, and coffee is unclear. To make more concrete recommendations, additional studies are needed (consideration of overall lifestyle, composition of each food group, comparability of foods, etc.). Therefore, the data in the literature do not allow for a clear and scientific recommendation on a specific diet. Ideally, future studies could allow the formulation of individual nutritional action plans adapted to each type of patient.

Phytoestrogens

Phytoestrogens fall into three categories: isoflavones (soy, lentils), lignans (flax, millet), and coumestans (alfalfa, red clover). Phytoestrogens act by competitively binding to estrogen receptors [19]. In an Iranian case-control study based on 156 infertile women undergoing laparoscopy [20], the authors observed inverse associations between the risk of endometriosis and total phytoestrogen (OR: 0.68; 95% CI: 0.51−0.91, $p = 0.01$) and isoflavone (OR: 0.38; 95% CI: 0.33−0.83; $p = 0.002$) consumption. In a Japanese study, higher levels of urinary isoflavones were also associated with a reduced risk of advanced endometriosis [21]. Variety, harvest location, or type of cooking may also result in variations in phytoestrogen content and should be considered when interpreting the results. Given the inflammatory and hormone-dependent nature of endometriosis, phytoestrogens may have an impact, but the evidence for this association will need to be better evaluated in future studies.

Nightshift work

Intriguing data have revealed an association between night shift work and the risk of endometriosis [22,23]. A prospective cohort study of 116,608 U.S. nurses [22] found an increased risk only in infertile patients who had worked on a night rotation for more than 5 years (OR 1.71; 95% confidence interval, 1.18−2.49; $p = 0.005$). In a case-control study based on 235 women with surgically confirmed endometriosis [23], night shift work was associated with a 50% increase in the risk of endometriosis (odds ratio=1.48 [95% CI =0.96−2.29]). Although it should be confirmed by other studies, these results suggest that night work may influence the development of endometriosis.

Physical activity

Biological mechanisms suggest that exercise may reduce the risk of endometriosis [24]. In 2016, a meta-analysis based on 9 studies including a total of 7955 cases evaluated the potential link between physical activity and endometriosis [25]. The summary OR for any activity was 0.85 (95% CI: 0.67−1.07; $p = 0.08$) compared with women who were never physically active. However, in these studies, controls were extracted from hospital controls [26,27] or infertility centers [28]. Not all cases were surgically confirmed, and the level of physical activity was not defined consistently across studies. In a study of 473 women undergoing laparoscopy, regardless of indication [13], a decreased number of daily minutes spent sitting was modestly associated with a reduced risk of endometriosis. The authors interpret it as an effect, but the result remains not statistically significant ($p = 0.180$). Regarding this matter, it remains difficult to differentiate the cause and the consequence: women with the highest level of

Table 1
Summary of the critical review.

Exposure Factor	Number of patients with endometriosis (number of studies)(studies)	Quality of the evidence (grade)	Comments
Caffeine	2635(9 studies)	Very low	In 2014, a meta-analysis found no association between coffee consumption and the risk of endometriosis. However, various limitations affect these findings: estimation of caffeine content not reported in beverages, self-reported consumption, and heterogeneity in diagnosis and control selection between studies.
Smoking	13 179(38 studies)	Low	In 2014, a meta-analysis found no difference between heavy, former, current, and moderate smokers, and the risk of endometriosis. Various biases seem to affect the results: inconsistent diagnosis of the disease between studies, self-reported information, and selection of controls among asymptomatic patients.
Alcohol	5443(17 studies)	Very low	The estimated risk for regular alcohol consumption reported in a meta-analyses was 1.2 (95% CI: 1.1−1.4). Multiple mechanisms are also involved, and some confounding factors were not always considered in studies (socioeconomic status and BMI in particular).
Dietary factors	12 725(23 studies)	low	Current data in the literature do not allow for a scientific recommendation on a specific diet. However, the data seem to suggest an association with high red meat and trans fat consumption. The evidence for fruits and vegetables, dairy products, unsaturated fats, fiber, soy, and coffee remains conflicting. Ideally, future studies could allow for the formulation of individualized nutritional action plans tailored to each patient type.
Phytoestrogens	789(3 studies)	Very low	Studies observed inverse associations between the risk of endometriosis and consumption of phytoestrogen.Variety, harvest location, or type of cooking may also result in variations in phytoestrogen content and should be considered when interpreting the results.
Nightshift work	2297(2 studies)	Low	Intriguing data suggest that infertile women who work nights for more than 5 years may be at higher risk for endometriosis. The relationship between endometriosis and infertility is complex and must also be considered.
Physical activity	7294(10 studies)	Very low	Data suggest a protective role for physical activity in endometriosis. However, biases limit these data: non-surgical diagnosis, level of physical activity not homogeneously defined between studies. Regarding this matter, it remains difficult to differentiate cause and consequence: women with the highest level of pain generally practice less sport. The available data are therefore insufficient to draw a conclusion.
Pigmentary traits and sun exposure	10 674(8 studies)	Low	Recent studies with large numbers of patients reported a significant dose-response relationship with skin sensitivity to sun exposure, number of nevi, and number of freckles. Given these data, it would be tempting to argue for an association, by interaction with vitamin D. The relationship between endometriosis and the vitamin D endocrine system has not yet been clarified.
Psychological stress	4619(15 studies)	Very low	Only one meta-analysis evaluated this association. The psychological stress may be both a cause and a consequence of the disease and complex to measure. We cannot therefore conclude that a relationship exists between psychological stress and endometriosis.
Infection	305(9 studies)	Very low	The role of the microbiome has only recently been evaluated. Some authors found more pelvic infections and alterations in the microbiome in patients with endometriosis, by causing epigenetic changes. However, interpretation of these events must be taken with caution as it is unclear whether infections are a cause or consequence of endometriosis.
Dioxines and Polychlorobiphenyls	3519(24 studies)	Low	Among all environmental compounds, dioxins and PCBs are the most studied in endometriosis. These persistent organic pollutants act as endocrine disruptors. In summary, some studies suggest an association between chemical toxic and endometriosis, but epidemiological evidence remains insufficient. Many methodological barriers that may explain this weak association, precise diagnosis of the pathology, valid selection of controls and choice of sampling method. This subject is still under debate and future studies should be carefully designed to address these issues.
Parabènes	35(1 study)	Very low	Only one study has assessed this relationship, with a small number of patients. Several biases limit the validity of the results: single sample, unassessed co-exposures. There is insufficient evidence to conclude.
Bisphénol A	789(7 studies)	Very low	One study suggests that bisphenol A exposure may increase the risk of non-ovarian pelvic endometriosis, but the collection of a single urine sample makes the temporal relationship irrelevant. Other studies that have visualized endometriosis surgically have not found such an association. Although bisphenol A has estrogenic properties, the evidence therefore remains limited.
Phtalates	863(10 studies)	Very low	In infertile women with endometriosis, one study found an increase in several phthalate esters including DEHP (diethylhexyl phthalate). Other studies have not validated these results. A potential mechanism of action seems to involve oxidative stress, inflammatory enzymes and hormone receptors, but the pathophysiology remains unclear.
Heavy metals	409(3 studies)	Very low	Some studies have reported increased blood cadmium levels in patients with endometriosis. No association has been reported with lead or mercury. However, the heterogeneity of the results can be explained by the differences in the biological environments studied.
Diethylstilbestrol	33(4 studies)	Low	Two studies showed that in utero exposure to DES was significantly associated with the risk of endometriosis, with a greater than 80% endometriosis incidence rate in women exposed.

pain generally practice less sport. Therefore, insufficient data are available to draw a conclusion.

Pigmentary traits and sun exposure

Intriguing data support an association between sun exposure, skin phenotype and endometriosis. In a prospective cohort of approximately 10,000 French women [29], the authors reported a significant dose-response relationship with skin sensitivity to sun exposure ($p < 0.0001$), number of nevi ($p < 0.0001$), and number of freckles ($p = 0.005$). A recent prospective study of 4791 laparoscopically confirmed cases of endometriosis also reported this association with sun exposure [30]. The risk of endometriosis increased with the use of tanning booths ($p = 0.04$), the number of sunburns in adolescence

(p = 0.03), and the percentage of time using sunscreen (p = 0.002). Given these two studies with large numbers of patients, it would be tempting to argue for an association. However, women who are highly sensitive to sun exposure or who have freckles tend to avoid sun exposure and thus have lower serum 25-dihydroxyvitamin D3 levels. Some authors have shown that vitamin D and UV independently stimulate interleukin (IL)−10 secretion, reduce the levels of the proinflammatory cytokine IL-17 and inhibit T-helper-1 immune function [31]. The relationship between endometriosis and the vitamin D endocrine system has not yet been clarified.

Psychological stress

Only one meta-analysis based on 15 studies evaluated the prevalence of psychological stress in 4619 women with endometriosis [32]. The mean stress level was 41.78%. Meta-regression showed a relationship with endometriosis staging. However, this is complex to measure and may be both a cause and a consequence of the disease. We cannot therefore conclude that a relationship exists between psychological stress and endometriosis.

Infection

The role of the microbiome has only recently been evaluated. In 2019, a review examined the association between endometriosis and upper genital tract infections and pelvic infections based on 31 articles. The authors found more pelvic infections in patients with endometriosis. Alterations in the microbiome of the upper genital tract and peritoneal cavity were also found as well as an increase in mollicutes and HPV in endometriosis lesions. These infections have the potential to initiate endometriosis by causing epigenetic changes and contributing to endometriosis growth [33]. However, interpretation of these events must be taken with caution as it is unclear whether infections are a cause or consequence of endometriosis due to various reasons. Further studies must be performed to understanding the interaction with the gut microbiota and confirm these findings.

Environmental factors

Dioxins and PCBs

Polyhalogenated aromatic hydrocarbons (PHAHs) are a family of organic compounds containing a variable number of halogen atoms. This family includes dioxins and dioxin-like and nondioxin-like polychlorinated biphenyls (PCBs) [34]. These persistent organic pollutants act as endocrine disruptors. These substances originate from various industrial processes (waste incineration, metallurgy, iron and steel production) as well as from some natural phenomena (fires, volcanic eruptions) [35]. 2,3,7,8-Tetrachlorodibenzo (TCDD) is the most toxic dioxin (also known as "Seveso dioxin" in connection with the chemical accident at the plant in 1976). Among all environmental compounds, dioxins are the most studied in endometriosis. Recent reviews [34] have summarized studies on this matter. Overall, no significant correlation was observed in several case-control studies between dioxin-related and nondioxin-related PCB substances and endometriosis [36–39]. Conversely, in a case-control study conducted in Belgium, including 50 cases and 21 controls, the authors found a statistically significant increase in the risk of deep endometriosis with exposure to dioxins and DL-PCBs [40]. In an Italian case-control study of 80 women of reproductive age, higher levels of PCBs were found in the serum of patients with endometriosis [41]. The strength of this study was the inclusion of nulliparous women. Indeed, full-term pregnancy or breastfeeding can potentially reduce the body burden of lipophilic environmental toxins. Finally, in a more recent study of 30 patients with deep infiltrating endometriosis [42], dioxin and PCB levels were higher in adipose tissue compared with controls without endometriosis ($P < 0.05$). In summary, it seems that an association between chemical dioxins and endometriosis is emerging, but epidemiological evidence remains insufficient. However, there are many methodological barriers that may explain this weak association. At the present time, this subject is still under debate. Future studies should be carefully designed to address these issues, including more stringent subject selection strategies.

Parabens

Parabens are used as preservatives in cosmetics, drugs, or foods and as UV filters for sunscreens. A Spanish case-control study found higher urinary paraben levels in 35 patients with endometriosis compared with controls with no statistically significant difference [43]. Although this study used laparoscopic confirmation to identify cases and controls, several limitations are noted, including the small sample size, single urine sample collected for each patient (preventing variability in daily exposures related to the short half-lives of these substances), and no consideration of diet and smoking. The evidence for cosmetics is therefore limited.

Phtalates

Phthalates are chemical additives, endocrine disruptors, added to plastics to make them more flexible, thus having multiple applications: medical devices (intravenous tubing), children's toys, PVC objects [44]. Several studies found higher concentrations of various phthalate metabolites in human urine or plasma [45]. In a case-control study on 59 patients, plasma levels of DHEP (diethylhexyl phthalate) were significantly higher in cases [46]. Other authors used urine samples to compensate for potential contamination from intravenous tubing, finding an increase for two phthalates measured [47]. According to Kim et al., this association seems to involve oxidative stress, inflammatory enzymes and hormone receptors, but the pathophysiology remains unclear.

Heavy metals

The presence of heavy metals in the Earth's crust is advised by human activity (industrial, transportation, and waste management sectors) [48]. The role of cadmium (Cd) has been studied, particularly given its binding to hormone receptors [49]. In a case-control study based on self-reported data for the diagnosis of endometriosis [50], Cd blood levels were higher in 61 patients with endometriosis. No association was reported with exposure to lead or mercury. In two other studies, where endometriosis was surgically visualized, no such association was found [51,52]. The heterogeneity of these results may be explained by the difference in the biological media studied [53]. Blood Cd reflects recent exposures, whereas urinary Cd is representative of long-term exposure. Thus, the temporal relationship should be interpreted with caution.

Bisphenol A

Bisphenol A (BPA) is an endocrine disruptor and estrogen mimetic that binds to alpha and beta estrogen receptors. It is present in food and nonfood plastics and has the ability to migrate from its containers to the food or beverage in contact with it, thus being ingested by the body. In a case-control study with surgically confirmed endometriosis [54], urinary BPA levels were statistically associated with non-ovarian pelvic endometriosis but not with ovarian endometriosis. It should be noted, however, that BPA has a very short half-life on the order of 6 h, and the authors only assessed one sample that was collected after the case was diagnosed. Therefore, these measurements may not have accurately reflected exposure during the etiologically

relevant time window. In addition, controls did not undergo laparoscopy, so the possibility of asymptomatic endometriosis was not excluded. Two previous studies measuring urinary BPA levels in women with surgically visualized endometriosis reported no statistically significant association [47,55]. Through its estrogenic properties, BPA could influence the development of endometriosis, but further research is needed, particularly studies focused on the different endometriosis subtypes.

Diethylstilbestrol

Diethylstilbestrol (DES) is a synthetic estrogen that was prescribed in France until 1977 and initially used in the prevention of preterm birth and late recurrent abortion (DES-France). In 2020, a meta-analysis evaluating data from in utero exposures on the risk of endometriosis in adulthood showed that in utero exposure to DES was significantly associated with the risk of endometriosis [56]. Two studies supported these findings. In the prospective cohort of Missmer et al., the authors reported a greater than 80% endometriosis incidence rate in 21 women exposed to DES in utero with endometriosis confirmed by laparoscopy (95% CI −1.2 to 2.8) [57]. This risk was doubled in a second case-control study comparing 9 cases of endometriosis exposed to DES in utero with 11 controls (OR 2.0, 95% CI −0.8 to 4.9) [58]. Despite the very small number of patients exposed in these studies, the data suggest a potential role for DES in patients with endometriosis.

Discussion

This critical review provides an overview of current knowledge of the impact of the environment on endometriosis. To our knowledge, this is the most comprehensive review of literature on environmental factors in relation to endometriosis. Indeed, we have also taken into account lifestyle factors such as night work, exposure to sunlight, physical activity and stress."

Given the estrogen dependence of the disease, studies investigating the association between environmental pollution and endometriosis have mainly focused on endocrine disruptors, particularly PCBs, dioxins, and DES, and appear to be the strongest. Intriguing data also suggest a link with night work, red meat consumption and sun exposure. These data need to be confirmed in future studies. For most of the other risk factors studied, including lifestyle factors (coffee, soy, and alcohol consumption), smoking, physical activity, and exposure to phthalates and BPA, insufficient results are available to draw conclusions. Other exposures were studied in this analysis, including electronic cigarettes, cannabis, benzene, nanomaterials, radiation, acetaldehyde, and acrylamide, but no results were reported in the literature.

Although the biological plausibility of the association between exposure to toxic substances and endometriosis has been provided by several studies on primates and rodents [4,5], several methodological obstacles limit the generalization of the results to humans.

First, the difficulty lies in the accurate diagnosis of this disease. The enormous variability of reported symptoms, the complexity of interpreting imaging studies, and the varied surgical presentations often make case definitions complex. Laparoscopy remains the gold standard for diagnosis. However, not all patients with endometriosis undergo laparoscopy, thus excluding potentially affected but asymptomatic patients. The type of endometriosis chosen may also affect the results [40]. Furthermore, the literature reports an average delay of 7 years between the onset of symptoms and diagnosis, making it difficult to establish a causal link between a given self-reported exposure and the pathology [59]. To understand the results and the validity of published studies, the diagnosis of the disease, the temporal relationship, and the phenotypic variation among women with endometriosis must be clearly defined.

Second, one of the challenges of these studies is the correct and valid selection of controls. In some studies, controls also underwent laparoscopy but for other reasons (e.g., tubal ligation). However, these patients may have a different obstetrical profile from the cases (e.g., higher parity). The parity factor must be analyzed because full-term pregnancy or breastfeeding can potentially reduce the body burden of lipophilic environmental toxins.

Finally, the choice of sampling method (serum or urine measurements) and the consideration of coexposures (often multiple, particularly for endocrine disruptors or persistent organic pollutants) require vigilance in the interpretation of published results.

It is difficult to draw clear scientific recommendations on environmental exposures from this article. However, patients affected by this disease are generally young, often ask questions and are in constant demand for information about their disease. These results could therefore provide these patients with additional advice and data to improve their overall medical care.

Conclusion

In summary, the epidemiological evidence does not support a strong, scientific link between exposure to environmental factors and endometriosis. The complexity of this disease requires advanced study designs and standardized methodology. Future studies should be carefully designed to address these issues, including the development of more rigorous subject selection strategies and the incorporation of environmental and genetic factors, to advance our understanding of the impact of the environment and its consequences on endometriosis.

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