

Chapter 6

Role of Environmental Pollutants in Endometriosis

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6.1 Introduction

Both animals and humans are exposed to toxins in the environment that may influence the onset and progression of endometriosis. Human exposure occurs mainly through ingestion of contaminated foods. Dioxins encompass a group of environmental pollutants that act as endocrine disruptors through the aryl hydrocarbon receptor and disturb the body's physiologic homeostatic mechanisms. Some have even been labeled as carcinogens. Human exposure to toxins is often unavoidable, but measures including a detailed history taken by clinicians and lifestyle changes can help detect and limit exposure and assist in the body's detoxification processes. Growing evidence suggests a possible link between endometriosis and environmental pollutants. Environmental pollutants such as dioxins, organochlorine pesticides (OCPs), bisphenols and phthalates and their association with endometriosis are highlighted in this review along, with the steps patients can take to avoid them. Even though results from studies remain contradictory, we can't overlook the positive association between environmental toxicants and endometriosis as they are disruptors of endocrine and reproductive function. The literature reviewed in this section highlights the general pathogenesis of endometriosis and proposed theories regarding its etiology. The chapter also provides an updated discussion of the implications of environmental exposure to pollutants in the development of endometriosis.

6.2 Classification of Environmental Pollutants

1. Polyhalogenated aromatic hydrocarbons
2. Dioxin like compounds
3. Organochlorine pesticides
4. Phthalates
5. Bisphenols

6.3 Toxic Effects of Environmental Pollutants

6.3.1 Human Studies

Some studies have suggested that exposure to dioxin-like compounds is linked to the development of endometriosis in humans. Mayani et al. conducted a study in which 44 infertile women with endometriosis were evaluated. Eight tested positive for the environmental pollutant 2,3,7,8-tetrachlorodibenzo-p-dioxin (dioxin) in their blood compared to 1 of 35 infertile women without endometriosis [1].

6.3.2 Animal Studies

Rier et al. [2] conducted a long-term controlled study that included a group of Rhesus monkeys—the 24 monkeys exposed to dioxin had biopsy proven accumulation of dioxin in their adipose tissue. Ten years after the termination of dioxin exposure, they found 7 of the monkeys had died: 3 of them due to endometriosis and 4 of them due to other unrelated causes. The long-term effect of dioxin exposure and the development of endometriosis are known to be significant [1].

Wood DH et al., found that when female rhesus monkeys exposed to protons of varying energy levels for a minimum period of 7 years developed endometriosis when compared to non-radiated animals of the similar age group. They also correlated this finding to the level of radiation exposure that a female crew worker experienced while she was flying in a near earth orbit amidst a random solar flare event. Thus, radiation should be taken into consideration as an important factor potentially promoting the development of endometriosis [3].

6.4 Mechanism of Toxic Induction

Dioxins exert adverse effects through binding and activation of the aryl hydrocarbon receptor (AhR)—a transcription factor containing two heat shock protein (HSP) 90 molecules, one prostaglandin E synthase 3 (p23) molecule, and one X-associated

protein 2 (XAP2) molecule [4]. This binding prevents AhR from performing homeostatic functions such as tumor suppression regulation of the cell cycle [5] and cell death [6]. Upon activation by dioxin, AhR dissociates from one hsp molecule, p23, and XAP2. It then translocates from the cell's cytoplasm to the nucleus and forms a complex with aryl hydrocarbon nuclear translocator (ARNT), releasing the remaining attached hsp 90 molecule [7]. Finally, the new AhR-ARNT complex binds to dioxin-responsive enhancers (DREs) found within the promoter regions of many TCDD-responsive genes [8], particularly CYP1A1 and perhaps CYP1B1 [9]. Through persistent activation of AhR, dioxins can disrupt the normal expression of genes and enzymes. Dieldrin, endosulfan, and lindane (γ -HCH) are amongst the OCPs that have both estrogenic and anti-androgenic properties [10]. Endosulfan and Lindane are also known to block the enzyme aromatase, which mediates the production of E2 by catalyzing the peripheral conversion of testosterone to estrogen. Ingestion of dioxins can cause several adverse effects in animals and humans. As endocrine disruptors, they can impair development, hormone actions, and immune defenses in the body. The endocrine disruptors are also considered carcinogenic.

6.5 AhR Modulation and Its Impact on Endometriosis Development

AhR exists in tissues throughout the body, including both eutopic and ectopic endometrium [11]. Dioxin-AhR complexes may encourage the development of endometriosis via a combination of growth factor activation, immunosuppression, gene dys-regulation, and altered estrogen-signaling pathways [12].

Rier et al. 1993 discovered endometriosis incidentally while conducting a study on reproduction and toxicants in Rhesus monkeys. The monkeys were treated with TCDD for 4 years. Six years later, the monkeys underwent laparoscopy and most of them had endometriosis. The amount of TCDD administered to the animals was found to be in direct proportion to the prevalence and severity of endometriosis [2]. In 2001, the group reported that elevated serum levels of PCBs are responsible for the greater prevalence and severity of endometriosis seen in the monkeys [13]. This experiment demonstrated the actions of PCB congeners through AhR in promoting endometriosis.

More recently, Willing C et al. demonstrated that the AhR-ARNT complex within endometrial cells caused alterations in hsp, leading to its amplification and ultimately invasion and implantation of ectopic tissue, causing endometriosis [14]. These results support the data reported from earlier studies [15–17].

6.6 Activation of Growth Factors

Dioxin has been shown to affect tumor growth factor (TGF) alpha and beta as well as the receptors for epidermal growth factor (EGF) and insulin growth factor (IGF). Induction of cytokines such as IL-1beta and IL-6 has also been demonstrated by dioxins [18, 19].

The effects of varied levels of TCDD exposure were measured 13 years later by Rier S et al. 2001. Exposure over a 4-year period was found to be associated with elevated TNF- α , which may influence the development of endometriosis [13]. Serum levels of IFN-gama and TNF- α are increased in women with endometriosis [20, 21]. Along with IL-6 and interferon- γ , TNF- α is important for the function, proliferation, and apoptosis of endometrial cells. Increased serum levels of dioxins and altered functions of leukocytes were also observed to disturb the regulation of growth factors, thus precipitating endometriosis in the animals [13].

Endometriosis is also associated with chronic inflammation, and several pro-inflammatory cytokines have been detected in the peritoneal fluid of affected women. Chronic ovarian inflammation was observed in rats in response to dioxins and PCB126. The study also linked uterine inflammation with dioxins and PCB153. It has been suggested that PCB153 may have estrogenic actions and thus could compete with estrogen for ER binding [22]. The combination of agonistic and antagonistic effects of DLCs on estrogen might account for the disrupted epithelial differentiation seen in endometriosis [23].

6.7 Gene Dys-Regulation

Interestingly, a study by Tsuchiya et al. [9] found that women with elevated serum dioxin TEQ levels had a statistically significant lower risk for. All 138 subjects were confirmed to have endometriosis by laparoscopy, and the role of cytochrome P450 (CYP) gene polymorphism was examined for its potential to protect against dioxin- and PCB-induced endometriosis. One particular gene polymorphism, *CYP1A1 462Val*, was found in association with a significantly decreased risk of endometriosis in women with higher serum TEQ. No association, however, was found between serum PCB TEQ, advanced endometriosis, and the *CYP1B1 Leu432Val* allele. Gene polymorphisms such as CYP1A1 and CYP1B1 were found to have a direct effect on how dioxins and DLCs affect the female body. It is the most recently published work relating specific CYP gene polymorphisms to dioxins and their effects on endometriosis [9]. Nevertheless, further studies must be conducted to validate this connection.

Several genes have been suggested to be involved in endometriosis. Amongst these are CYP1A1, COX-2, CYP19, ER- α , ER- β , PR A and B, and *c-fos* [24, 25]. In a recent study, Van Ede KI et al. 2010 reported a dose-dependent elevation of uterine CYP1A1 mRNA secondary to activated AhR at day 3 and a significant 2.5-fold increase of COX-2 as well as an increase in ER- β mRNA. Of further significance is the sharp elevation of the *c-fos* proto oncogene at a dose of just 0.5 μg TCDD/kg body weight and subsequent dose-dependent *reduction* in levels at 25 μg TCDD/kg; this finding has also been documented by another group [26]. At day 14, PR A/B was significantly increased, but levels of COX-2 mRNA were unchanged. These

data indicate the possibility of TCDD-induced altered endometrial expression of genes linked to the development of endometriosis.

Estrogen metabolism involves conversion of estrone (E1) to estradiol (E2) by 17 β hydroxysteroid dehydrogenase (17 β -HSD) type I [27]; this process is catalyzed by CYP1A. By demonstrating the induction of CYP1A by dioxins and PCBs, the results of Tsuchiya et al. 2007 and Van Ede KI et al. 2010 suggest consequent post-exposure surges of estradiol production. Logically, this would promote the onset and maintenance of endometriotic lesions, which exclusively express activity of 17 β -HSD type I [28]. Also, Lai et al. noted that most genes induced by TCDD had three or more DREs (Dioxin-responsive element) [18]. Moreover, the CYP1A gene contains 14 DREs (Dioxin-responsive element) in the 5' \rightarrow 3' orientation and is very sensitive to TCDD induction [29]. It can be considered a prototype of the TCDD-inducible gene [18].

The glutathione S-transferase (GST) enzymes are essential in protecting cells against both toxin-induced and oxidative damage. GSTM1 may contain a particular deletion polymorphism, which may be altered by dioxins [30]. GSTM1 is one of the phase II detoxification enzymes that participate in a protective mechanism against toxic environmental pollutants. GSTM1 deletion polymorphism leads to the lack of detoxification and results in endometriosis.

Expression of the *GSTM1 null* mutation has been associated with endometriosis in some studies [30, 31], but others [32, 33] have failed to make the same link. To assess the role of PCBs on the *GSTM1 null* mutation and development of endometriosis, Roya R et al. 2009 studied a population of 199 infertile women. Their results confirmed a significant association between *GSTM1 null* mutation and endometriosis that had been reported in earlier studies [34]. Additionally, they observed that increased PCB levels were correlated with more severe disease [35]. Roya's group were amongst the first to demonstrate that in addition to expressing higher degrees of the GSTM1 polymorphism, women with histories of higher PCB exposures may also suffer from more severe disease.

6.8 Immunosuppression

Dioxin exposure decreases leukocyte phagocytic function, preventing the elimination of menstrual debris, and thus, may play a key role in establishing endometriotic implants from retrograde menstruation [8]. Another important dioxin-related immunosuppressive effect is inhibited—T-lymphocyte function and NK cell activity in the plasma and peritoneal fluid. Through the activation of AhR, endometriosis may be triggered by increasing interleukin levels, tissue remodeling, and activating cytochrome P-450 enzymes. TCDD-activated AhR can also disrupt normal cell function by stimulating NF- κ , resulting in altered immune responses and uncontrolled proliferation of cells [36] (Fig. 6.1).

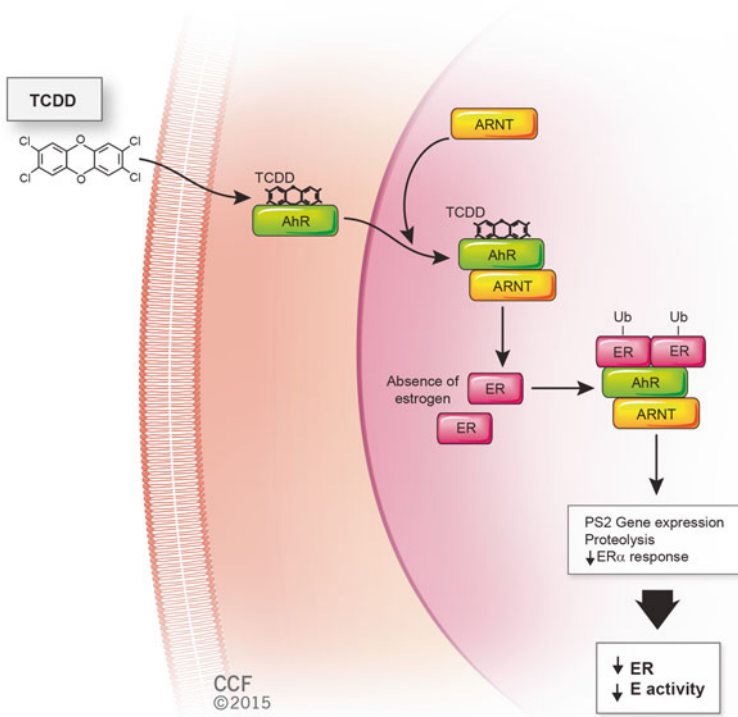


Fig. 6.1 TCDD induced AhR receptor modulation. *TCDD* tetrachlorodibenzo-p-dioxin, *ARNT* aryl hydrocarbon nuclear translocator, *ER* estrogen receptor, *AhR* aryl hydrocarbon receptor, *E* estrogen

6.9 Altered Hormone Signaling Pathways

TCDD has been shown to disturb the activities of both estrogen and progesterone [36]. As a known antagonist of estrogen, TCDD was determined to alter expression of CYP1A1 and CYP1B1 in human endometrial cells [37]. Because endometriosis is estrogen dependent, the disruption of normal estrogen function has the potential to influence the disease [8]. Therefore, the toxicity of dioxins and DLCs largely depends on the body's estrogen content. While estrogen-activation of ERs prevents AhR complex expression, failure of estrogen to ignite these receptors leaves them open for activation by the dioxin-activated AhR-ARNT complex [38] (Fig. 6.1).

Concentrations of estrogen and ERs decrease in response to dioxin exposure, and thus, dioxins are often believed to exhibit anti-estrogenic properties. On the contrary, an increase in the incidence and extent of endometriosis has been demonstrated in monkeys [2] and growth of ectopic lesions have been seen in mice and rats [39, 40] both in response to dioxin exposure. It can be clearly understood that TCDD disrupts the human reproductive system by acting as an estrogen antagonist and also

causing imbalances in progesterone distribution [36]. Other etiologic pathways of endometriosis may depend on TCDD exposure, other than the estrogen and progesterone disruption [36]. TCDD activates an inflammation-like pattern [41], which explains the development of endometriosis. Also, TCDD and dioxin-like PCBs affect gene expression by using AhR expressed in both endometrial and immune cells and disrupt endocrine signaling [36, 42].

In 2004, Kitajima M et al. conducted a study on mice after surgically inducing endometriosis. Four weeks of exposure to TCDD did not seem to enlarge lesion size but instead diminished the size of epithelial and stromal masses. Treatment with estrogen alone resulted in the enlargement of epithelial and stromal cells mass within the lesions, indicating that estrogen is an important factor for the growth of these lesions. When TCDD was administered short term, its anti-estrogenic effects reduced ectopic lesions and cell mass [43].

Increases in local estrogen production by heightened ER activity can promote estrogen-dependent diseases such as endometriosis. Elevated expression of mRNA of aromatase, an enzyme essential to estrogen synthesis, has been noted to increase estrogen levels and promote endometriosis. Heightened expression of aromatase may be propelled by environmental factors such as dioxins and results in reduced levels of 17 β HSD type II. This creates an environment of elevated local estrogen, making the local peritoneal environment a prime location for survival of ectopic endometrial stromal cells. Studies have reported that progesterone hinders endometrial growth and causes regression of endometriosis with treatment [12]. The endometrium of women with the disease, however, demonstrates a decreased response to progesterone. Because TCDD inhibits progesterone, it often exacerbates endometriosis, especially when combined with estrogen [44]. Endometrial dysfunction has been linked to progesterone resistance in endometriosis patients. Progesterone action through progesterone receptors (PR) is necessary for female reproductive functions in humans and other mammals [15]. During pregnancy, progesterone exposure has been shown to protect against endometriosis.

In endometriosis, the matrix metalloproteinases (MMP) are involved in degrading the extracellular matrix, a process important to the development and invasion of endometriotic lesions [44]. Suppression of MMP by progesterone is required to up-regulate TGF- β , resulting in diminished growth of ectopic endometrial tissue [45]. In their study on nude mice, Nayyar et al. 2007 demonstrated that significant decreases in progesterone-mediated expressions of TNF- β 2 and PR-B in response to TCDD exposure resulted in a more severe presentation of endometriosis [15]. The group concluded that TCDD can decrease progesterone levels via expression of TGF- β 2. This decrease in progesterone-propelled ectopic growth of surgically placed endometrial tissue leads to endometriosis. Exposure of mice to TCDD both in utero and during reproductive maturation decreased PR-A and PR-B, predisposing them to endometriosis [15].

Bruner-Tran et al. 2010 were unable to find a definite correlation between endometriosis and TCDD exposure in cynomolgus monkeys and rodents. However, since TCDD has both estrogenic and antiestrogenic properties, reduced lesion size and spontaneous abortion are plausible outcomes of exposure. As such, the group reported that rodents exhibited infertility and an inability to maintain pregnancy secondary to TCDD exposure in utero and pre-puberty [46].

6.10 Prevention and Management

Human exposure to environmental pollutants is often inevitable, however, strategies have been suggested in an effort to limit exposure, maximize elimination from the body, and implement lifestyle changes (Fig. 6.2). These strategies may prove useful to limit the toxic effects of environmental contaminants in human populations.

Persistent toxicants remain as residuals in human body long after the first exposure. This is probably the most important obstacle that can inhibit the progress of detoxification since many of the environmental toxicants have a long half-lives. Genis et al. [47] analyzed the sweat of 20 individuals and found some phthalates metabolites. Hence, induced perspiration may be a way to eliminate potentially toxic metabolites. Exercising may be another way to eliminate these toxins since it induces sweating. However, some studies emphasize that excretion rates do not change depending on how perspiration occurs (e.g., infrared sauna, dry or wet regular saunas or exercise) [48].

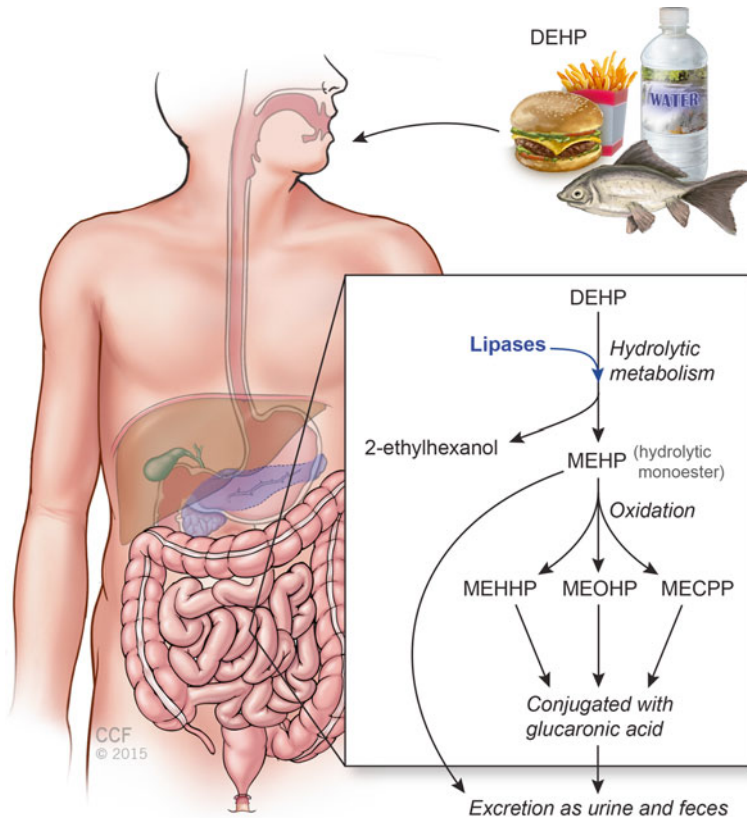


Fig. 6.2 Phthalate metabolism. *DEHP* di-(2-ethylhexyl)phthalate, *MEHP* mono-(2-ethylhexyl) phthalate, *MEOHP* mono-(2-ethyl-5-oxohexyl) phthalate, *MEHHP* mono (2-ethyl-5-hydroxyhexyl) phthalate, *MECPP* mono(2-ethyl-5-carboxypentyl) phthalate

There is also an effort to limit the exposure by restricting the use of these chemicals. Some nations, including the United States, have banned the use of some environmental toxicants like organochlorine pesticides, mostly DDT. Moreover, lifestyles changes like diet modification can be helpful. This include vitamin and mineral supplementation to replenish depleted body induces, increased fiber intake to limit body absorption of toxic compounds and promote elimination; and avoidance of certain types of foods known to have high accumulations of environmental toxins [49].

Conventional and novel treatment options for endometriosis are discussed elsewhere; this section will focus on disease prevention strategies and management options for endometriosis as they relate to human contamination with environmental toxins. Currently, no cure exists for the disease. As such, goals of management are mainly to provide relief from pain and restrict progression of the disease. When appropriate, efforts are also made to preserve or restore fertility through medical or surgical therapy. In general, combination oral contraceptives (COCPs), gonadotropin-releasing hormone (GnRH) agonists, progestational agents, danazol and aromatase inhibitors are commonly used in the medical treatment of endometriosis for patients who wish to conserve fertility.

As mentioned before, dioxins have been shown to up-regulate expression of P-450 aromatase, leading to increased estrogen synthesis within endometriotic tissue [50]. This is the rationale for the use of aromatase inhibitors to manage endometriosis. After administration, endometriotic lesions have been noted to regress, thus, signifying the need for aromatase in patients with persistent endometriotic lesions [51].

6.11 Key Points and Summary

The role of dioxins in the development of endometriosis remains controversial. Thus far, research has produced varying results, contributing to this uncertainty. Over time, experiments on animals have culminated in the development of correlations between environmental toxins and of endometriosis in mammals. These studies, including those on primates, have propelled current exploration of a possible similar association in humans.

Similarities between dioxin characteristics and risk factors for endometriosis have been noted. For example, dioxins are lipophilic with long half-lives and accumulate in high fat tissues. Obese females have large amounts of adipose tissue; thus, the more fatty tissue present in the body, the longer it will take dioxins to be eliminated from the body. Given that obesity is a risk factor for endometriosis, a potential link exists between lipophilic compounds such as dioxins and endometriosis. Due to their accumulation in lipids, dioxins can be largely excreted in breast milk and eliminated from the body through lactation, which is believed to be a protective factor against the onset of endometriosis.

Epidemiological studies on endometriosis in association with environmental pollutants have been quite inconsistent in both animal and human studies. Although copious studies investigating the involvement of environmental toxins in endometriosis

have produced promising results, no study has demonstrated a direct link nor confirmed a causal relationship between the two. Case-control studies can prove valuable under certain conditions. In addition to a large sample size, controls should be laparoscopically confirmed to be free of endometriosis. Since endometriosis tends to run in families, clinicians should aim to identify family members confirmed or suspected to have endometriosis when taking a family history.

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