Role of environmental organochlorinated pollutants in the development of endometriosis

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Summary

Endometriosis is a gynecological disease, which involves the growth of endometrial tissue outside the uterine cavity, commonly in the pelvic region. The etiology of the disease is unclear, but multiple factors may contribute to its pathogenesis. Environmental organochlorinated pollutants, particularly dioxins and polychlorinated biphenyls (PCBs), are thought to play a role in the development of this disease; however, the results of clinical trials are discordant, and it is not clear how the effect of exposure to these compounds is linked to endometriosis. Their effects on cytokines, immune system, hormones, and growth factors are thought to increase the risk of endometriosis. The purpose of this review is to provide an overview of epidemiological studies, which have evaluated the relationship between endometriosis and exposure to persistent organochlorinated pollutants.

Key words: Endometriosis, TCDD; PCB; Persistent organic pollutants; Organochlorinated pesticides; Dioxin-like compounds.

Introduction

Endometriosis, affecting about 10% of women of reproductive age, is often associated with pelvic pain and/or infertility. Pain symptoms can be severe particularly in the presence of deep invasive endometriosis and can affect the quality of life of these patients [1]. According to the literature, the number of cases and the severity of the disease are increasing and the actual incidence of the disease may be higher, owing to the requirement of surgical visualization for diagnosis [2, 3]. Moreover, the disease tends to recur even if the recurrence risk factors are not well clarify. Nevertheless, adhesions and previous surgery seem to have a role [4]. The etiology of endometriosis is unclear, but it is probably multifactorial involving hormonal, genetic, immunologic, and environmental factors [5]. The possibility that exposure to environmental chemicals is a contributing factor to the development of endometriosis has been a matter of scientific debate for 20 years.

Review

A compound, which has been of great concern, is 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), an undesired by-product of many combustion processes. It is the prototype of a group of substances which have similar chemical characteristics and spectrum of effects and are both persistent and bioaccumulative. Chemicals belonging to this group are polyhalogenated aromatic hydrocarbons (PHAHs) and they may contain multiple chlorine and/or bromine atoms at three or more lateral positions on the multiaromatic ring structure [6]. They include polyhalogenated dibenzo-p-dioxins (PCDDs and PBDDs), dibenzofurans (PCDFs and PBDFs), biphenyls (PCBs and PBBs), and naphthalenes (PCNs and PBNs). Polychlorobiphenyls (PCBs) include 209 different congeners which are divided into 'dioxin-like' (DL-PCBs) and 'non dioxin-like' according to their structure. Dioxin-like congeners have no or only one chlorine in the ortho position while non-dioxin-like PCBs are characterized by two or more chlorines in the ortho position. PCBs, polychlorodibenzodioxins and polychlorodibenzofuran**s** (PCDDs and PCDFs, commonly referred to as 'dioxins') are resistant to degradation and they bioaccumulate at higher levels in the food chain due to their lipophilicity. Food is thus the most important source of exposure to these pollutants [7]. Humans and animals are exposed to complex combinations of such chemicals; however, most studies focus only on single toxicants.

Some dioxin-like and non-dioxin-like PCBs and organochlorinated pesticides (such as *p,p'*-DDE, a metabolite of DDT) seem to interfere with the endocrine (as endocrine-disruptor) and the immune systems, causing reproductive disorders such as endometriosis. Endocrine disruptors (EDCs) are compounds that may interfere with the endocrine system and produce adverse developmental, reproductive, neurological, and immune effects in both humans and wildlife. They can mimic, reduce, and in some cases, completely block the effects of endogenous hormones.

The hypothesis that exposure to environmental pollutants could play a role in disease etiology was first suggested by Rier *et al.* [8]. The study conducted in monkeys, which were chronically exposed to TCDD, found a dose-dependent increase in the incidence and severity of spontaneous endometriosis. Although strongly criticized by some scientists [9, 10], this paper opened new ways for further research investigating the relationship between endometriosis and environmental pollutants.

The effects of TCDD, dioxins, and PCBs have been studied by numerous investigators and yielded contrasting results [3, 5, 11-14]. In 2002, Eskenazi *et al*. [15] evaluated the role of TCDD in the development of endometriosis in

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women exposed to a great amount of this toxicant. The study subjects were those who lived in Seveso, Italy, in July 1976, when a chemical explosion dispersed large quantities of TCDD into the atmosphere. The researchers did not find a significant association between endometriosis and TCDD concentrations in serum, but only a trend.

Many studies have investigated the relation between endometriosis and exposure to dioxins and DL-PCBs. All these compounds bind to the aryl hydrocarbon receptor (AhR), expressed in both the endometrium and immune cells, eliciting the same spectrum of toxicological activities. The binding affinity and the toxic potency of each congener is expressed in relation to the most toxic compound of the group (the TCDD), termed as the toxicity equivalency factor (TEF). The concentration of a mixture of congeners is therefore expressed in toxicity equivalents (TEQs), multiplying the analytical concentration of each congener by its TEF. TEQs for each single congener, are then summed to obtain the total TEQ, which characterizes the overall toxicity of the mixture [12].

Heilier *et al*. [13] provided epidemiological evidence linking endometriosis with increased concentrations of dioxin and dioxin-like compounds. This study conducted in women with peritoneal and/or deep infiltrating endometriosis found that they had higher serum TEQ levels than controls. Tsukino *et al*. [14] did not confirm this association, finding lower TEQ levels in patients with endometriosis than controls. However, Tsukino *et al*. included in the control group patients with Stage I endometriosis and infertile women, whereas in the study of Heilier *et al.*, the control group was constituted only by healthy women with no infertility or endometriosis [13]. These differences in the selection of control groups probably contributed to the differing results.

The mechanisms involved in the deleterious effects of such compounds on reproduction are still under evaluation. AhR mediates most of the toxic effects of "dioxins" on cell functions, and activates several genes including cytochrome P450. Exposure to AhR agonists may influence an inflammatory-like process, triggering endometrial menstruation [16]. Bruner-Tran *et al*. [12, 17] demonstrated that TCDD triggers an inflammatory-like pattern of cell-cell interaction in the human endometrium, which interferes with progesterone's ability to suppress matrix metalloproteinases (MMPs) expression in both epithelial and stromal cells. Progesterone exposure during the secretory phase of the menstrual cycle serves to down-regulate the endometrial MMP system, so that endometrial breakdown does not occur before menstruation. Under normal circumstances endometrial tissue, which has reached the peritoneum due to retrograde flow of menstruation, is eliminated by the innate immune system. Several studies show that inflammatory-like processes caused by dioxin-like toxicants can interfere with the normal physiology of the endometrium and the immune system. This condition may permit the persistence and the development of endometrial tissue within the peritoneal cavity [12, 17].

Exposure to PCBs may be linked to an altered endocrine status in humans, which may cause development of reproductive tract dysfunctions and diseases. Some studies suggest that endometriosis is linked to exposure to certain PCBs [3, 5, 13], while other studies do not confirm such a link [14, 18, 19].

In our studies we found a significant association between increased levels of some PCBs and endometriosis, but did not find any difference in blood concentrations of dioxin-like chemicals (PCDDs, PCDFs, and the 12 dioxin-like PCBs) in women with different stages of the disease [3, 5]. We also examined the immunological functions of patients with endometriosis and serum level of PCBs and p, p'-DDE to verify the impact of these environmental contaminants on the dysregulation of immune functions and they observed that increased concentrations of these compounds were associated with altered natural killer (NK) immune responses [20].

The different results obtained in the published studies may be influenced by differences in control groups, methods used for compound analysis, type of congeners investigated, and the statistical tests employed.

Selection of the control group is a possible source of error in an epidemiological study investigating the association between PCBs and endometriosis. Women living in the same area as the test subjects should be recruited as controls, so that both the groups are likely to have been similarly exposed to organochlorines. The development of endometriosis as a co-morbidity factor in infertile women may confound the interpretation of studies enrolling infertile subjects without the disease as controls [14].

Another potential bias is the method used to exclude the presence of endometriosis in controls, as laparoscopic examination remains the only reliable diagnostic tool to assess the presence or the absence of the disease.

In two studies that confirmed a link between exposure to PCBs and endometriosis, laparoscopy was performed in both cases and controls to confirm or exclude the presence of the disease [5, 21].

Lactation is an important PCB excretory route, which leads to a significant decrease in the body burden of organochlorine compounds. To avoid the confounding factor of breast-feeding, only nulliparous or non-nulliparous women, who have never breastfed should be enrolled [5, 22].

Furthermore, the type of endometriosis may also influence the results. Heilier *et al*. [13] found that concentrations of PCBs and dioxin-like compounds in the serum were associated with a significantly increased risk of developing deep endometriotic nodules of the recto-vaginal septum, although the risk of developing peritoneal endometriosis was not statistically significant. The authors also suggested that organochlorines might mainly cause development of deep endometriosis. Future studies should consider peritoneal endometriosis and deep endometriotic nodules as distinct entities, in order to assess the possible etiological contribution of organochlorines.

Genetic predisposition and environmental factors have been suggested to concur to the onset and progression of endometriosis. Genetic susceptibility was explored by studying mutations in genes responsible for detoxifica-

tion, such as glutathione transferase (GST), as a possible risk factor to endometriosis per se and in association with exposure to PCBs. Vichi S *et al*. [23] showed that the GSTs polymorphisms per se do not increase per se the risk of developing endometriosis. However, a gene-environment interaction was observed for GSTP1 and GSTM1 null genotypes, modulating the effect of total PCBs on disease risk.

Research should also focus on the risk of developing endometriosis by exposure to environmental chemicals in the womb, during early childhood, puberty, and adulthood.

In conclusion, accumulated evidence supports the hypothesis that exposure to organochlorine pollutants may induce endometriosis. The mechanisms involved are still unclear. They may act as immune toxicants and/or endocrine disruptors, enhancing estrogen synthesis and disruption of progesterone-dependent remodeling responses, which under normal circumstances prevent development of endometriosis. Additional standardizing studies in humans and animals are needed to better investigate the link between exposure to these toxicants and development of endometriosis and to identify the mechanisms involved.

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