REVIEW

Organochlorines and endometriosis: a mini literature review

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ABSTRACT

Background: A possible association between endometriosis and exposure to organochlorines has been hypothesized. Dioxins can affect endometriosis via their weak estrogenic hormonal effect and via the induction of inappropriate estrogen production in the endometrium. Furthermore, dioxins can stimulate pro-inflammatory cytokines and induce the direct activation of genes involved in cell cycle and death.

The **purpose** of this review is to summarize and present the existing evidence regarding the relationship between PCBs and/or dioxins and endometriosis.

Material and Methods: The literature concerning the association between organochlorines and endometriosis was reviewed. Relevant studies were identified by searching the following databases: the Cochrane Library, Medline, Embase and PubMed.

Results: Thirteen epidemiological studies that have assessed the relationship between endometriosis and organochlorine exposure were included in this review. The majority of examined studies have not demonstrated an association between organochlorines and endometriosis but only trends or non significant odds ratios. The evidence to date concerning the association between the levels of organochlorines and endometriosis is not entirely consistent and there is accumulative evidence from the individual studies that high concentrations of organochlorine compounds are not important predictors of endometriosis.

Conclusion: In conclusion, the majority of studies dealing with endometriosis did not observe a significant association with organochlorines. However, there is not always possible to identify causal relationships between organochlorine exposure and deleterious health effects. The role of health care professionals, and specifically the role of midwives, should be focused on the education of the public in order to minimize their exposure to organochlorines and other harmful substances.

Keywords: Organochlorines, dioxins, hormones, endocrine disrupters, endometriosis.

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INTRODUCTION

Endometriosis is a benign condition in which endometrial glands and stroma are present outside the endometrial cavity, usually in the ovary or on the pelvic peritoneum. In the general population, endometriosis is thought to occur in 7-10% of women [1], but random biopsies at laparoscopic sterilizations have revealed endometriosis in approximately 25% of women [2].

Although endometriosis is a common gynecological problem, the etiology of this disease is unknown. It is however, widely accepted that endometriosis arises from the aberrant adhesion and growth of endometrial fragments deposited into the peritoneal cavity via retrograde menstruation through the fallopian tubes[3], metaplastic transformation of the peritoneal mesothelium into endometrium under the influence of certain, generally identified stimuli [4], or vascular transport of embolised endometrial fragments. In women, the major hypothesis for the origin of the endometrial tissue outside of the uterus is retrograde menstruation. Koninckx[5] postulated that either peritoneal leukocytes fail to remove these retrograde endometrial cells or peritoneal macrophages and retrograde endometrial cells produced increased levels of cytokines and growth factors that facilitate ectopic endometrial growth. Cytokines and growth factors may actively promote implantation, proliferation, and angiogenesis. Moreover certain cytokines are also implicated in the attachment of endometrial cells to the peritoneal surface and invasion of these cells into the mesothelium. Moreover, immune cells in peritoneal fluid from women with endometriosis exert decreased natural killer cytolytic activity, an immune process that may limit the growth of ectopic lesions. To explain some rare examples of endometriosis in distant sites, such as lung or axilla, it is necessary to postulate hematogenous spread. Quite probably, all of these postulated mechanisms play a role in the development of endometriosis, and no single mechanism explain all cases.

Endometriosis requires estrogen. Growth of the endometrial cells, whether in uterus or outside from it, depends on estrogen. Some of the most intriguing findings are that endometriosis can even be found in men who are highly exposed to antiandrogens and estrogens, such as in therapy for prostate cancer [6]. Since these men never had a uterus to produce

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endometrial cells, dedifferentiation and then redifferentiation of other tissues has occurred under the influence of antiandrogen or estrogen therapy.

Biological effects of organochlorines

Organochlorines are a various group of organic compounds that contain chlorine and include polychlorinated biphenyls (PCBs), dibenzo- *p*- dioxins/ polychlorinated dibenzofurans (PCDDs/ PCDFs or dioxins) and organochlorine pesticides, such as dichlorodiphenyl-trichloroethane (DDT), lindane, aldrin and dieldrin. Organochlorine compounds have several properties, such as [7]: a) stability against decomposition or degradation by normal physical or biochemical processes, b) very low solubility in water, c) high solubility in hydrocarbon-like environment (lipophilicity), such as the lipid and fatty tissue. Organochlorines can impact on human health by disturbing the balance of endocrine system and therefore are known as hormone disrupting chemicals or as endocrine disrupters [8]. More general names of these substances are environmental hormones, synthetic hormonally active agents (HAAs) and xenoestrogens. The hypothesis that many environmental pollutants have hormonal action is not new. In recent years, attention has focused on the potential of some chemical to act as endocrine disrupters [7]. According to the (U.S.) Environmental Protection Agency an endocrine disrupter is defined as "a chemical that interferes with the function of the endocrine system by mimicking a hormone, blocking the effects of a hormone, or by stimulating or inhibiting the production or transport of hormones" [9]. Chemicals that act as endocrine disrupters alter the levels of hormones and particularly the levels of steroid hormones. Hormone disrupters may disturb the endocrine system by various ways. These chemicals bind to specific hormone receptors and thereby 'mimic' or block the attachment of endogenous hormone to its receptor [10, 11]. Endogenous hormones (estradiol) and organochlorine chemicals with endocrine disrupting action (estrogenic action) contain the characteristic four-ring steroid structure. Many organochlorine compounds, such as DDT, PCBs and dioxins are considered as endocrine disrupters because they are weakly estrogenic or anti-estrogenic in experimental assays[10]. Organochlorines have been shown to affect not only steroids hormones but also thyroid hormones. Dioxins exert their biological effect via binding not only to steroid receptors but also to a specific receptor, the aryl hydrocarbon (Ah) receptor [12].

The binding of organochlorines with Ah receptors seems to trigger the expression of gene CYP1A1 which encodes cytochrome P-450 1A1 enzyme, which is a key enzyme in phase I of bioactivation of xenobiotics [13]. Cytochrome P-450 1A1 is also involved in estrogen metabolism, catalyzing the hydroxylation of 17β estradiol [14].

Some PCBs have estrogenic effects, while some others have structural similarities with dioxins, bind with Ah receptor and consequently have anti-estrogenic effects [15]. According to Wolff and Toniolo [16], PCBs congeners can be classified into three groups, on the basis of their structural and biological properties. Group I includes congeners that are potentially estrogenic (*ortho*-congeners). Group II includes congeners (mono-*ortho* or non-*ortho*) that have structural similarities with dioxins and are potentially anti-estrogenic. Group III includes congeners that are phenobarbital-type. Up till now, more than 500 chemicals have found to be weakly estrogenic, including many common chemicals, such as pesticides and plastics [17, 18]. Some of these compounds are suspected to disrupt the endocrine system by mimicking estrogenic activities and thereby increase the risk of hormone dependent disorders such as endometriosis, early menarche and male and female infertility.

Potential mechanism(s) of organochlorines in endometriosis

Recent studies have suggested that endocrine disrupters and specially dioxins may be important in the development of endometriosis. Dioxins may exert effects on the pathophysiology of endometriosis through a number of pathways: 1) altered synthesis and metabolism of estrogen, 2) altered production of proinflammatory growth factors or cytokines, 3) activation of pro-carcinogens and 4) mis-expression of remodeling enzymes [19]. Dioxin is the prototypical endocrine disruptor, modulating essentially every hormone system: at the level of the receptor, by altering metabolism, or by affecting serum transport. One possible mechanism by which dioxins can affect endometriosis is via their weak estrogenic hormonal effect and via the induction of inappropriate estrogen production in the endometrium [19]. Endometriotic cells exhibit increased expression of P-450 aromatase, indicating that endometric lesions are capable of de novo estrogen production [20]. These findings lead us to speculate that dioxins may promote endometriosis

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via the induction of P-450 isoenzyme expression and increased formation of estrogens resulting in chronic exposure to growth-promoting estrogen [19].

Reproductive processes are regulated by sex hormones in concert with bioactive mediators (cytokines, growth factors) produced by immune and endocrine cells [21]. Leukocytes are primarily composed of T cells and granulocytes with fewer numbers of macrophages and B cells [21]. The phenotype and function of leukocytes change in numbers and orientation during the menstrual cycle in response to estrogen and progesterone. Suppression of immune responses in endometrium during the progesterone-dependent secretory phase likely offers protection for the fetus and for the establishment of pregnancy. The effect of dioxins to stimulate pro-inflammatory cytokines could lead to the establishment of endometriosis. Activation of this inflammatory cytokines network in the extrauterine environment may result in increased PGE synthesis in ectopic endometrium and consequently lead to inappropriate estrogen production and suppression of progesterone responses [20]. Among the host of growth-promoting cytokines produced during chronic inflammation, several lines of evidence suggest that tumor necrosis factor is a key factor in dioxin-induced toxicity and potentially the pathogenesis of endometriosis [19]. Importantly, dioxins induce the direct activation of genes involved in cell cycle and death via the direct response element in the promoter region [22]. A greater number of ectopic endometrial cells may survive, thrive, and disseminate because of inhibition of apoptosis and suppression of leukocyte cytolytic activity.

The purpose of this review is to summarize and present the existing evidence regarding the relationship between PCBs and/or dioxins and endometriosis.

Impact of organochlorines on endometriosis

The hypothesis regarding the role of PCBs and/or dioxins in the aetiopathogenesis of endometriosis has been initially based on experimental data reported by Rier et al., [23] demonstrating, that rhesus monkeys chronically exposed to 2,3,7,8-TCDD exhibited, 10 years after termination of exposure, peritoneal endometriosis which incidence and severity directly correlated with exposure and dose. The hypothesis of a role of PCBs and/or dioxins in the endometriosis has also been addressed in several epidemiological studies.

Three studies [24, 25, 26] have considered only 2,3,7,8-TCDD only. Koninckx et al., in 1994 [24] suggested that the higher prevelance of endometriosis at infertility clinics in Belgium could be caused by the relatively high TCDD concentration in the Belgian population. In a cohort study in Israel the plasma concentration of TCDD compared in 44 women with surgically confirmed endometriosis to 35 women with no surgical confirm of this condition [25]. Mayani et al., [25] reported that more infertile women with endometriosis have a detectable serum TCDD concentration compared to infertile women without endometriosis. The study of Eskenazi et al., [26] included patients that were accidentally exposed to TCDD. They were living in Seveso, near to a plant that produced organochlorine herbicides, when in July 1976, an uncontrolled exothermic reaction lead to the release and creation of a chemical air cloud that deposited its content over several square kilometres of a population countryside. Eskenazi et al., [26] observed only a trend to endometriosis with TCDD concentrations in serum but not significant association. This study reported that more infertile women with endometriosis have a detectable serum TCDD concentration compared to infertile women without endometriosis.

All 17 PCDD/Fs and 12 dioxin-like PCBs able to bind AhR were measured in five studies [27, 28, 29, 30, 31]. Pauwels et al., [27] found a high relative risk for endometriosis in association with elevated total dioxin concentration, based on a bioassay for all of the dioxin-like activity. However, because of the small number of women, the increased risk was not statistically significant. Fierens et al., [28] didn't observe any difference in serum concentration of PCBs between women reporting endometriosis and controls. Studies by De Felip et al., [29] and by Tsukino et al., [30] reported non significant differences in concentration of organochlorines between women reporting endometriosis and controls. Study by Helier et al., [31] reported a significantly increased risk to develop endometriosis associated with higher serum concentrations of dioxin-like compounds.

Five studies measured only ortho-PCBs, which are not able to activate AhR [32-36]. Lebel et al.,[32] examined a cohort of women who were surgically diagnosed. The authors measured 14 of the most common PCBs, but they did not measure any of the dioxin-like PCBs, the PCDDS, or PCDFs. Given the animal data, as well as the other epidemiology studies, the lack of an association with total PCBs is

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not a surprise. Helier et al.,[33] reported a significant odds ratio for deep endometriosis but not for peritoneal endometriosis. Odds ration have been also calculated in studies by Luis et al.,[34], by Porpora et al.,[35] and by Reddy et al.,[36]. Only Porpora et al.,[35] reported significant odds ratio for PCBs.

The majority of examined studies have not demonstrated an association between organochlorines and endometriosis but only trends or non significant odds ratios. Only the study by Helier et al.,[31] reported a significant relationship with dioxin-like compounds and endometriosis and the studies by Helier et al.,[33] and by Porpora et al.,[35] reported a significant relationship with PCBs and endometriosis. Therefore, the studies that we have reviewed did not clearly support a role for organochlorines in the etiopathogenesis of endometriosis. The evidence to date concerning the association between the levels of organochlorines and endometriosis is not entirely consistent and there is accumulative evidence from the individual studies that high concentrations of organochlorine compounds are not important predictors of endometriosis.

Conclusions

In conclusion, endometriosis remains a common gynaecological problem of unknown cause. In conclusion, the majority of studies dealing with endometriosis did not observe a significant association with organochlorines. However, there is not always possible to identify causal relationships between organochlorine exposure and deleterious health effects. Limitations in the ability to identify or to quantify causal relationships are occasionally misinterpreted as evidence of safety. Therefore, when present activities entail potential, unknown adverse health effects, the need for more accurate evidence has often been used as a reason for inaction. The *precautionary principle* states that, in cases of serious or irreversible threats to the health of humans or ecosystems, acknowledged scientific uncertainty should not be used as a reason to postpone preventive measures. These preventive precautionary actions have the aim to reduce and if possible to remove exposures to potentially harmful substances, activities and other conditions.

The role of health care professionals, and specifically the role of midwives, should be focused on the education of the public in order to minimize their exposure to organochlorines and other

harmful substances. Health care professionals should inform women about risks, options for preventing risks, actions for reducing them and possible alternatives. Information can also discourage behaviours that lead to risks and make people to demand safer environmental conditions. Information and education will enable people to identify products that contain potentially hazardous substances, or that are environmentally friendly and have been produced by using organic methods.

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