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Review

Organochlorines and endometriosis: A mini-review

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Abstract

Organochlorines (polychlorinated biphenyls and dioxin-like compounds) are suspected to play a role in the etiopathogenesis of endometriosis. This hypothesis, based on experimental data, has been circulating for years in the scientific community and several epidemiologic surveys have attempted to obtain confirmatory human data. The purpose of this mini-review is to provide an overview of the twelve epidemiological studies that have assessed the relationship between endometriosis and organochlorine exposure. Several studies did not observe a significant association between peritoneal endometriosis and organochlorines. The deep nodular form of endometriosis appears associated with a higher serum level of both dioxin-like compounds and polychlorobiphenyls. The type of control women, the nature of the chemicals measured, and the definition of the disease could modulate the ability to detect the possible relationship between endometriosis and organochlorine exposure.

Keywords: Endometriosis; Deep endometriotic nodules; Dioxins; Tetrachlorodibenzodioxin; Polychlorinated biphenyls; Epidemiology

Contents

Abbreviations: AhR, aryl hydrocarbon receptor; CALUX, chemically activated luciferase expression; OR, odds ratio; PCBs, polychlorinated biphenyls; PCDDs, polychlorinated dibenzo-*p*-dioxins; PCDFs, polychlorinated dibenzofurans; TCDD (2,3,7,8-TCDD), 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TEF, toxic equivalency factor; TEQ, toxic equivalent.

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1. Introduction

Endometriosis is a gynaecological disease characterised by the extra-uterine growth of endometrial tissue which causes internal bleeding, inflammation and scarring, and often leads to infertility (Donnez et al., 2002). Although the exact aetiology of the disease remains unknown, a role of both environmental (Birnbaum and Cummings, 2002; Gerhard and Runnebaum, 1992) and genetic factors (Treloar et al., 2005) has been suspected. Recently, some organochlorines (polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and polychlorinated biphenyls (PCBs)) previously suspected as risk factors (Rier et al., 2001), were found to be significantly associated with the disease (Heilier et al., 2004, 2005; Porpora et al., 2006).

2. Dioxins-like compounds and PCBs

Dioxins are made up of 210 chlorinated hydrocarbons divided into 75 PCDDs and 135 PCDFs. Dioxins are mainly by-products of industrial processes (e.g. waste incineration or iron and steel industries), formed when a thermal process (300–800 °C) occurs in the presence of chlorinated organic substances. Seventeen dioxin congeners which preferentially bio-accumulate in the food chain, bind to a specific receptor (aryl hydrocarbon receptor or AhR) that mediates most of their toxic effects and activates several genes, including cytochromes P450 (Hahn, 2003; Mimura and Fujii-Kuriyama, 2003).

Several PCBs were manufactured until the 1970s because of their physicochemical properties (stability, viscosity, . . .), and used mostly in closed applications such as heat transfer in capacitors and transformers. Among the 209 PCB congeners (for a full list see http://www.epa.gov/toxteam/pcbid/table.htm), 12 share with dioxins an activity on the AhR, and are refereed to as WHO-PCBs, dioxin-like PCBs, coplanar PCBs or non (mono)-*ortho*-PCBs because of the absence of chlorine substitution in *ortho* positions (1, 4, 6, 9) that gives the molecule a planar configuration.

All compounds able to bind the AhR (7 PCDD, 10 PCDF and 12 dioxin-like PCBs) have been classified relatively to 2,3,7,8-TCDD (the most toxic dioxin congener) and received a toxic equivalency factor (TEF) which reflects their respective biological potency. Concentrations of these compounds, often present as mixtures, are frequently expressed as pg TEQ/g lipids, which is the sum of the products of the concentration of each compound multiplied by its TEF. The biological concentration of organochlorines is expressed per g lipids because these compounds are essentially stored in the fatty compartments of the body (van den Berg et al., 1998).

3. Dioxins, PCBs and endometriosis

The role of PCBs and/or dioxin-like compounds in the aetiopathogenesis of endometriosis is controversial. This hypothesis has been initially based on experimental data reported by Rier et al. (1993) demonstrating, that rhesus monkeys chronically exposed to 2,3,7,8-TCDD (5 and 25 ppt per day during four years) exhibited, 10 years after termination of exposure, peritoneal endometriosis which incidence and severity directly correlated with exposure and dose. For a long time, this experiment appeared as the best evidence of a role for organochlorines in the onset or growth of endometriosis. Rier et al. (2001) reconsidered, some years later, blood samples from this experiment and detected significant amounts of dioxin-like PCBs that originated from a contamination of TCDD, indicating a possible role of dioxin-like compounds rather than TCDD in the endometriotic effect. Criticism on the statistical analysis of Rier's data has also been raised, after a reappraisal by Guo (2004) who concluded to the absence of relationship with endometriosis.

The hypothesis of a role of PCBs and/or dioxins in the onset or the growth of endometriosis has also been addressed in several epidemiologic studies. The purpose of this mini-review is to summarize the existing evidence of a relationship between endometriosis and PCDD/Fs and/or PCBs in humans, with a particular attention to factors that could modify this relation, if any. Factors that are particularly of concern are (i) the selection of control women, (ii) disease definition and (iii) the nature of the chemicals investigated.

The main results of 12 publications including 10 case-control, 1 cross-sectional and 1 cohort studies are summarized in Table 1. All reported on environmental exposures probably reflecting the fact that occupational exposures have essentially involved men (Zober et al., 1990). Eight studies reported odds ratio (OR), adjusted or not, for linear increment or cut-off in organochlorine blood content. In all studies but one (Fierens et al., 2003) patients and controls underwent gynaecological examination and were classified according to the presence of endometriosis or not. Fierens et al. (2003) classified participants according to self-reported information.

3.1. Type of controls

Most studies have included only women undergoing laparoscopic examination (for infertility, tubal ligation, pelvic pain, . . .) who were divided into cases or controls according to the presence of endometriosis or not. A large majority of studies are hospital-based and controls have been recruited in clinics for reproductive medicine or gynaecological