Endocrine Disruptors in Endometriosis

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Abstract- Endometriosis is an estrogen-dependent 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 prognosis. Toxicological studies indicate that many chemicals are able to interfere with endocrine homeostasis, called endocrine disrupting chemicals (EDC) like Bisphenol A, Phtalate, Polychlorinated Biphenyls and Dioxins. As well documented, endometriosis is an estrogen-dependent disease; therefore, environmental toxicants that either mimic estrogen or enhance estrogenic exposure in the endometrium are thought to increase the risk of endometriosis. The purpose of this mini-review is to provide an overview of epidemiological studies, which have evaluated the relationship between endometriosis and exposure to endocrine disruptors.

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Endocrine Disruptors in Endometriosis

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Abstract- Endometriosis is an estrogen-dependent 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 prognosis. Toxicological studies indicate that many chemicals are able to interfere with endocrine homeostasis, called endocrine disrupting chemicals (EDC) like Bisphenol A, Phtalate, Polychlorinated Biphenyls and Dioxins. As well documented, endometriosis is an estrogen-dependent disease; therefore, environmental toxicants that either mimic estrogen or enhance estrogenic exposure in the endometrium are thought to increase the risk of endometriosis. The purpose of this mini-review is to provide an overview of epidemiological studies, which have evaluated the relationship between endometriosis and exposure to endocrine disruptors.

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I. Endometriosis

Endometriosis is an estrogen-dependent disease defined as the growth of endometrial glands and stroma at extra-uterine sites. Reports on the incidence of endometriosis vary widely, from approximately 10% of reproductive-aged women (Barbieri 1990) up to 30% of women with chronic pelvic pain (Howard 1993). These reports may underestimate the true prevalence of this disease, which may approach 45% of women in their reproductive years(Rawson 1991). Although retrograde menstruation occurs in 70-80% of women of reproductive age, not all develop endometriosis (Halme et al. 1984). Therefore, other factors must play a role in the pathogenesis of endometriosis, like genetic background, malfunctioning inflammatory/immunological mechanisms and potentially environmental factors (Bischoff & Leigh 2004).

Endometriosis is intimately associated with steroid metabolism and associated pathways, corresponding to the dominant roles estrogen receptors (ESRs) and progesterone receptors (PGRs) play in uterine biology. Both human and animal model studies show endometriosis is estrogen (E2) dependent and is regulated through the ESRs alpha and beta (*ESR1* and *ESR2*) (Burns et al. 2012; Han et al. 2015; Zhao et al. 2015). Toxicological studies indicate that many chemicals are able to interfere with endocrine

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homeostasis, called endocrine disrupting chemicals (EDC), may directly or indirectly impair female reproduction (Mantovani 2006). The definition of endocrine disruptor by European Union is an exogenous substance able to mime the hormones that can interfere with the production, release, transportation, metabolism, link, action or elimination of natural hormones, which are responsible of maintenance of homeostasis and regulation on development processes (Caserta et al. 2008). The main targets EDC are bisphenol A (BPA), di-(2-ethylhexyl) phthalate (DEHP), mono-ethyl-hexyl phthalate (MEHP) and polyhalogenated aromatic hydrocarbons that consists of dioxins, mainly, 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) and poly-chlorinated biphenyls (PCB). Recently, they have gained special attention as emerged chemicals because of their persistence in the environment, potential for bioaccumulation and toxicity. Nuclear receptors pathways are the main cellular targets of the EDC under study, thus they are considered meaningful biomarkers of effective dose. The panel of nuclear receptors includes estrogen receptor alpha (ERα) and beta (ERβ), androgen receptor (AR) and aryl hydrocarbon receptor (AhR), it of these act in different pathways (Caserta et al. 2013).

As well documented, endometriosis is an estrogen-dependent disease; therefore, environmental toxicants that either mimic estrogen or enhance estrogenic exposure in the endometrium are thought to increase the risk of endometriosis. Therefore, this article aims to review the main endocrine disrupters that may be involved with endometriosis.

II. Bisphenol a (BPA)

BPA is a compound used in the production of polycarbonate plastics and epoxy resins. Given its similarity to endogenous estrogen, BPA has the ability to interact with estrogen receptors and stimulate estrogen production and also alter gonadotrophin hormone secretion (Buck Louis et al. 2013). Cobellis and co-workers correlated BPA and endometriosis (Cobellis et al. 2009). In this study, they found detectable BPA serum levels in more than half of patients with endometriosis, whereas it was absent in women without the disease. This data is still controversial once other studies could not observe a relation between BPA and endometriosis (Buck Louis et al. 2013; Itoh et al. 2007). More studies should be performed once it was reported that BPA causes subfertility in male rats that neonatally exposed to 2.4 μg of the compound per day for five

days, by subcutaneous injection. This subfertility is manifested as embryo resorption, also known as post-implantation loss. In these resorbed embryos, the expression levels of three types of DNA methyl-transferases involved in CpG methylation were significantly decreased compared to viable embryos of neonatally BPA exposed males or control embryos. The authors suggested that BPA might have altered the epigenome. As suggested by Guo (2009), there is accumulating evidence supporting a concept that endometriosis is an epigenetic disease, therefore further studies should be performed to demonstrate the correlation between the epigenetics changes and BPA in endometriosis.

III. Phthalates

Phthalates are chemicals used in numerous industrial and consumer products and also exhibit endocrine disruptive properties or to mimic or alter endogenous hormone activity. Adult human exposure to phthalates is primarily through ingestion of contaminated food from food processing machines and packaging materials and dermal application of personal care and cosmetic products. Exposure is also possible through inhalation of indoor air contaminated from building materials, and parenteral exposure through medical equipment such as IV tubing and blood bags (Upson et al. 2013). Di-(2-ethylhexyl) phthalate (DEHP) is the most commonly used chemical additive to provide flexibility to polyvinylchloride and in humans, it is likely that the stomach acid lipases hydrolyze DEHP into mono-(2-ethylhexyl) phthalate (MEHP))(Albert & Jégou 2013). This compound is metabolized quickly and excreted in urine without evidence of accumulation within the body. Phthalates produce antiandrogenic effects largely through the reduction in testosterone production and, possibly, reduced estrogen production at high doses (Buck Louis et al. 2013). Results of investigations into the pathophysiology of endometriosis have suggested that disease onset and progression involve steroid-related mechanisms, including hormone-related changes of the endometrium and peritoneal cavity, excess estrogen production by ectopic endometriotic lesions, and alterations in ovarian steroidogenesis. Thus, it is plausible that endocrine-disrupting chemicals such as phthalates may affect endometriosis risk(Ulukus et al. 2006).

The in utero and neonatal exposure to low doses of bisphenol A (BPA) and/or phthalates (DEHP/MEHP and BBP/DBP/MBP) may cause DNA hypermethylation/hypomethylation at CpG islands near gene promoter regions, histone modifications (acetylation, methylation, phosphorylation, ubiquity-nation, sumoylation and ADP ribosylation), and expression of non-coding RNAs, including micro RNAs. These epigenetic marks can induce up/down alterations in gene expression that may persist throughout a lifetime (Singh & Li 2012).

IV. PCBS and TCDD

The main group of environmental pollutants that have been proposed to play a role in the pathogenesis of endometriosis includes polyhalogenated aromatic hydrocarbons, a class of widespread environmental contaminants consisting of polychlorinated dibenzo-p-dioxins (PCDD), dibenzofurans and 12 polychlorinated biphenyls (PCB) (Schecter et al. 2006).

Dioxins are byproducts of industrial processes such as bleaching of paper pulp and the manufacture of certain pesticides and incineration of plastic and medical waste (Foster et al. 2010). Dioxins are lipophilic substances that resist biological and environmental degradation, remaining in the environment. Studies in animals have shown that 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is considered the environmental contaminant, within dioxin group, with the greatest toxicity and thus is also significant to human health (Schecter et al. 2006).

Seventy-five dioxin congeners and 135 furan congeners comprise the complex mixture of dioxins, 7:10 congeners which are respectively capable of binding to and activating the aryl hydrocarbon receptor (AhR) (Van den Berg et al. 2006). This binding induces the proliferation, differentiation and apoptosis, although the mechanism for this stimulation is not completely understood (Kogevinas 2001). Of the 209 congeners of polychlorinated biphenyls (PCBs), twelve have the potential to activate the AhR (Van den Berg et al. 2006). In normal physiological conditions, AhR resides in an inactive state in the cytoplasm. After association with TCDD, the AhR is activated by a change in conformation and translocates to the nucleus where it forms a heterodimer with ARNT (Aryl hydrocarbon receptor nuclear translocator). The heterodimer binds to the XRE (Xenobiotic Response Element) and alters the expression of genes controlled by the enhancer XRES. XRES, with the conserved sequences " GCGTG " are found in the promoter regions of various genes involved in the metabolism of xenobiotics, including CYP1A1 (Cytochrome P450 Family, subfamily a polypeptide 1a -1), CYP1A2 (Cytochrome P450 Family, 1, subfamily a polypeptide -2) CYP1B1 (Cytochrome P450 family, subfamily B, polypeptide 1 -1) and NAD(P)H quinone Oxidoreductase (Mimura & Fujii-Kuriyama 2003). In addition to the expression of various genes to CYP connection with TCDD because several toxicological effects such as teratogenesis, tumor promotion and immunosuppression (Shimizu et al. 2000).

Furthermore, it is reported that, in somatic cells, the gene expression of DNA methyltransferase 1 (Dnmt1) is controlled by the transcription factor Sp1 (Bigey et al. 2000) and the promoter region Dnmt 3B

also contains an Sp1 binding site (Ishida et al. 2003). The Sp1 is important for a number of physiological processes, including angiogenesis, cell cycle progression, inflammation and senescence (Chang & Hung 2012). Taking into account the involvement of Sp1 with DNMTs, the change of the activity of Sp1 may affect the level of expression of DNA methyltransferases and their activity. Lee et al (Lee et al. 2011) showed that exposure to TCDD causes Sp1 phosphorylation. Based on this evidence, the phosphorylated Sp1 would bind to receptors of DNMTs, thereby increasing its activity. Thus, changes in methylation status in the promoter region of some genes can cause alterations in gene expression and consequently contribute to endometriosis development.

Dioxins have also been postulated to stimulate the development of endometriosis via their immune-suppressive effects and their interference with the estrogensignaling pathway. The immunosuppressive effect of high doses of dioxins is well documented(Oh et al. 2005). Firstly, dioxin exposure may lead to inhibition of leukocyte phagocytic function, which is possibly important in the prevention of endometriosis by the elimination of menstrual debris (Levin et al. 2005). Additionally, dioxins can decrease immunological memory induce apoptosis in both T cells and B cells), inhibit T-lymphocyte function and decrease natural killer cell activity in plasma and peritoneal fluid (Puebla-Osorio et al. 2004; Ahmed et al. 2005). Furthermore, dioxin may stimulate the activity of peritoneal fluid macrophages and their local production of pro-angiogenic factors, cytokines (e.g. interleukin-1) and growth factors. The combined effect of immune dysfunction and peritoneal inflammation could favor the development of endometriosis. Furthermore, cellular changes or genetic predisposition may predestine an individual to the immunological modulation caused by dioxin exposure (Simsa et al. 2010).

Local estrogen production can be increased following dioxin exposure and facilitate development of endometriotic lesions by elevating mRNA expression of aromatase, the key catalytic enzyme in estrogen synthesis (Attar & Bulun 2006). Dioxins and PCB are known to interfere with estrogen concentrations. Both agonistic and antagonistic effects have been ascribed to dioxins and PCB by direct interference with the estrogen receptor or by the interaction between the activated aryl hydrocarbon receptor (AHR)/aryl hydrocarbon receptor nuclear translocator heterodimer and the estrogen receptor a and b, leading to estrogen-dependent gene activation (Mimura & Fujii-Kuriyama 2003).

V. Conclusion

Developing a better understanding the basic mechanisms that may allow environmental toxicants to promote endometriosis, will enable us to develop better strategies to reduce the potential toxic impact of these compounds to the future generation.

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