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Environment and Endometriosis: a toxic relationship

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Abstract. – Endometriosis is a common, benign, estrogen-dependent gynecological disease that represents one of the main causes of hospitalization in industrialized countries. It is well established that a large amount of natural and man-made chemicals are present in the environment and both humans and animals are exposed to them. Dioxin and dioxin-like compounds have long biological half-life, can accumulate within the organism and could negatively affect several physiological processes. The purpose of this review is to provide an overview of the possible relationship between these chemicals and the pathogenesis of endometriosis.

Key Words:
Endometriosis, Environment, Dioxin, Dioxin-like compounds.

Introduction

It is well established that a large amount of natural and man-made chemicals are present in the environment and both humans and animals are exposed to them. Due to their long biological half-life, these toxicants accumulate within the organism and could negatively affect several physiological processes. In 2005 the Enviromental Working Group tested for chemicals and pollutants the umbilical cord blood, collected after the cut, of 10 babies born between August and September 2014. 287 different chemicals were detected: 217 of them are toxic to the brain and nervous system, 180 could play a significant role in cancer development and 208 negatively impact the developing fetus leading to birth defects. The astonishing result was that although not every child has been exposed to every toxicant detected, no child was exposed to no pollutants[1]. Several toxicants have individually been related to neoplasm development, reproductive dysfunctions, immunological and thyroid disorders[2]. It is difficult to determine the combinatorial effect of these agents because numerous chemicals act synergistically in disease processes, but an antagonistic effect it is also possible[3,4]. Timing of toxic compound exposure seems to be crucial in defining an individual's risk of disease. The knowledge of the mechanism of action of each chemical on organ systems at each stage of life is fundamental to assess the exact risk. Among numerous toxic agents identified in the human umbilical cord, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is the most studied because it is considered the most toxic compound ever produced. Nonetheless, some other chemicals such as polychlorinated biphenyls (PCBs) and polychlorinated dibenzofurans (PCDFs) showed a similar toxicity, due to their similar chemical structure[5]. The purpose of this review is to provide an overview of the possible relationship between these environmental toxicants and endometriosis.

Endometriosis

Endometriosis is a common, benign, estrogen-dependent gynecological disease that represents one of the main causes of hospitalization in industrialized countries[6]. It involves 5%-15% of reproductive age women and it estimated that almost 7 million women in the USA are affected[7]. Endometriosis has a huge economical burden, related to its debilitating nature that leads to high care costs and loss of productivity[8]. Endometriosis is described by pathologists as the presence of stromal and/or endometrial glandular epithelium implants outside the uterine cavity[9]. It commonly

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involves ovaries, uterosacral ligaments, peritoneum, rectocervical and rectovaginal area, appendix, bladder and ureters and sometimes could spread even beyond the pelvis[6,10,11].

At the present time major interest has been shown in the so called deep infiltrating endometriosis (DIE), which represent a severe form of the disease where ectopic endometrial glands end stroma penetrate > 5 mm under the peritoneal surface of different pelvic organs[12].

Regarding the symptoms some patients are completely asymptomatic, but most of them report pelvic pain, dysmenorrhea, dyspareunia, dyschezia and urinary symptoms during the menses.

Although endometriosis represents a leading cause of disability its exact etiopathogenenesis is still under debate and many aspects of the disease are under targets. Two main hypotheses have been taken into consideration in the last decades:

- the retrograde menstruation theory presupposes that menstrual blood containing endometrial cells flows back through the Fallopian tubes and into the pelvic cavity where for some reasons it would not be clear out by the immune system cells;
- the coelomic metaplasia theory postulates that endometriosis originates from the metaplasia of the mesothelium of the visceral and abdominal peritoneum.

Since the 90s, several studies have investigated possible immunological dysfuncions potentially related to endometriosis, with the main mechanism presumed to be additional to the retrograde menstruation theory[13]. The cells falling into the abdominal cavity should be identified as antigens and presented by macrophages to T cells through the major histocompatibility complex (MHC) class I or class II. Class I MHC activates cytotoxic T cells and class II MHC activates helper T cells, leading to target-cell death[14]. Any alteration of these processes could be involved in the pathogenesis of endometriosis.

Dioxin and Dioxin-Like Compounds

Dioxins and dioxin-like compounds are extremely resistant by-products of various industrial processes (e.g. waste incineration, iron/steel industries) and represent ubiquitous environmental pollutants, chemically stable and lipid soluble. Dioxins are polycyclic aromatic agents with chloral substituents. Based on the position of the chlorine atoms they are classified in different branches. Dioxins and dioxin-like compounds include:

- polychlorinated dibenzo-p-dioxins (PCDDs or dioxins): there are 75 PCDDs, 7 of them are highly toxic
- polychlorinated dibenzofurans (PCDFs): there are 135 PCDFs. They are not dioxins, but 10 of them have dioxin-like properties
- polychlorinated biphenyls (PCBs): there are 209 PCBs, 12 of them have dioxin-like properties (the so called coplanar PCBs because of the absence of chlorine substitution in ortho positions that gives the molecule a planar configuration). There have been widely used as dielectric and coolant fluids until they were banned worldwide in the 80s.

PCDDs, PCDFs and PCBs together form the group of polyhalogenated hydrocarbons and in recent studies were found to be significantly associated with endometriosis[15-17].

Dioxin generally enters the environment after accidents like the one in Seveso, Italy in 1976. Dioxins then get into soil sediments, being carried by weather patterns and become incorporated into the food chain[18,19]. They mainly enter the human body through food and, due to their lipophilic nature, accumulate in tissues with high fat content[20]. Because of this property, it does not surprise to find high levels of dioxin and dioxin-like compounds in older people and reduced levels after delivery or breastfeeding[21]. 10 PCDFs and 12 PCBs (those with dioxin-like properties) and 7 PCDDs bind to the aryl hydrocarbon receptor (AhR), an activated ligand transcription factor. AhR could be mostly found in the cytosol (sometimes in the nucleus) and represents the key component of the dioxin pathways[22]. In order to quantify their biological potency all dioxin-like compounds have received a toxic equivalency factor (TEF) in terms of the most toxic dioxin (TCDD), which has a TEF of 1. However, the toxicity of a mixture of these compound is often expressed in pg TEQ (toxic equivalent units)/g lipids, which represents the sum of the product of the concentration of each compound multiplied by its TEF. The concentration is expressed per g lipids because they are mainly stored in adipose tissue[23].

Mechanism of Action

Dioxin and dioxin-like molecules can pass the plasma membrane and when in cytoplasm can bind to the AhR. The AhR then reach the nucleus and bind to its AhR nuclear translocator (ARNT)

forming a heterodimer that activates genes with xenobiotic response elements (XREs)/dioxin response elements (DREs) at their regulatory site[23]. The major targets are elements of the detoxification system[24], but AhR could also activate factors normally involved in cell proliferation such as transforming growth factor-beta (TGFβ) and cytokines, leading to deregulated physiologic functions[25]. There is a high concentration of AhR in both endometrium and immune cells. Exposure to TCDD promotes the production of matrix metalloproteinases (MMPs) in endometrial tissue, even in the presence of normal concentration of progesterone, a hormone that typically abolishes their secretion[26]. In fact during the secretory phase of the menstrual cycle progesterone downregulates endometrial MMPs, making that the exfoliation of the endometrium does not occur before menstruation. In 2008, Bruner-Tran et al[27] found that these chemicals are able to activate an inflammatory-like pathway that reduces the ability of progesterone to suppress MMPs expression in both stromal and epithelial cells. In addition to that a direct crosstalk between dioxins/AHR complex and the estrogen receptor-α (ER-α) has been found[28]. Considered that upon ligand binding the receptor undergoes an affinity-dependent conformational change, it could result in an improper transcriptional process of ER targets, such as the progesterone receptor. Furthermore, is well known that reduced levels of natural killer (NK) cell cytotoxicity and alterations in peripheral blood monocytes and peritoneal macrophages characterize women affected by endometriosis[29,30]. Although more work needs to be done, it is plausible that inflammatory-like processes, caused by dioxin-like environmental chemicals, can alter normal endometrial and immune cell physiology allowing persistence and development of endometrial tissue within the peritoneal cavity, normally cleared by immune system cells.

Dioxins/Dioxin-like Compounds and Endometriosis

The first study to report a possible association between dioxins and endometriosis was the one published by Rier et al[31] in 1993, although it was not directly designed to investigate the disease. They found that Rhesus Monkeys previously exposed to TCDD (5 and 25 ppt per day during 4 years) developed a dose-related form of endometriosis. Some years later Rier et al[32] reevaluated their work and reported significant amounts of dioxin-like PCBs in the blood samples, indicating a possible co-exposure. After this study an increasing interest came up in regard to the role of dioxins and dioxin-like environmental chemicals in the pathogenesis of endometriosis. Although in the last decade several epidemiologic surveys have been published this relationship remains controversial (Table I).

In fact, the study conducted by Eskenazi et al[33] failed to demonstrate an increase incidence of endometriosis in women living in Seveso, Italy during a 1976 factory explosion. This was 20-year follow up study, which examined women who were 30 years old in 1976. A doubled but not significant risk of endometriosis was found in women who had ≥100 ppt TCDD in their serum. The authors concluded that a disease misclassification could have led to underestimate the risk.

The selection of the control group is a possible source of error in an epidemiological study. For example, Heiler et al[16] demonstrated that women with deep endometriotic nodules have significant higher levels of PCDDs/PCDFs/PCBs when compared to controls and a slight elevation was found in patients with peritoneal endometriosis when compared to controls. However, Tsukino et al[34] found no statistical differences between case and control group, including in the control group both infertile women and patients with stage I endometriosis while Heiler at al[15,16] considered only healthy women. These differences in population selection could explain the different results obtained. Furthermore, women living in the same area should be recruited as both cases as controls, so that both groups have been similarly exposed to toxicants. Another confounding source could be the development of endometriosis as comorbidity factor in infertile women. Dioxin-like compound could be associated to altered development of reproductive tract dysfunctions and could independently affect fertility. Thus, using infertile patients as controls can lead to a confusing interpretation of the results[34,35]. Another potential source of error is the method used to exclude the presence of endometriosis in the control group. Laparoscopy followed by histological confirmation remains the only reliable diagnostic tool for assessing the presence or absence of the disease.

In 2009 Porpora et al[36] found a significant association between selected PCB congeners and endometriosis, but the total TEQ was not increased, underlining that the different congeners examined could influence the results. In fact, most of the toxicants have limited activity and

Table I. Comparison of measured variables before and after intervention in BAL fluid.

Author	Country	Population		Diagnostic method	Chemicals	Significant association with endometriosis?
		Cases	Controls			
Mayani et al (1997)	Israel	Infertile women 44	35	Laparoscopy (blood)	2,3,7,8-TCDD	yes
Lebel et al (1998)	Canada	Women undergoing surgery (i.e pelvic pain, infertility, tubal fulguration)		PCBs Laparoscopy	(plasma)	no
Pauwels et al (2001)	Belgium	86 Infertile women 42	70 Laparoscopy 27	PCBs + PCDDs + PCDFs (serum)		no
Eskenazi et al (2002)	Seveso (Italy)	Women living in Seveso > 30 y in 1976 19	277	Laparoscopy; Laparotomy;	2,3,7,8-TCDD Ultrasound	no (serum)
Fierens et al (2003)	Belgium	Belgian women participating to a study to assess organochlorine concentration in general population 10	132	Self report of endometriosis	PCBs + PCDDs + PCDFs (fasted serum)	no
De Felip et al (2004)	Belgium Italy	Women suspected for endometriosis 23	17	Laparoscopy	PCBs + PCDDs + PCDFs (serum)	no
Heiler et al (2004)	Belgium	Women attending for endometriosis surgical intervention 10 DEN; 7 PE	Women attending for routine examination 10	Cases: Laparoscopy; laparotomy Controls: Pelvic examination, TV ultrasound, CA125 <35 U/ml)	PCBs (serum)	DEN patients have significant higher levels of PCBs when compared to PE or control patients
Heiler et al (2005)	Belgium	Women attending for endometriosis surgical intervention 25 DEN; 25 PE	Women attending for routine examination 21	Cases: Laparoscopy; laparotomy Controls: Pelvic examination, TV ultrasound, CA125 <35 U/ml)	PCBs + PCDDs + PCDFs (fasted serum)	DEN patients have significant higher levels of PCDDs/PCDFs/PCBs when compared to controls; slight elevation in PE patients when compared to controls

Table continued

Table I. Comparison of measured variables before and after intervention in BAL fluid.

Author	Country	Population		Diagnostic method	Chemicals	Significant association with endometriosis?
		Cases	Controls			
Tsukino et al (2005)	Japan	Infertile women with stage II-IV endometriosis 52	Infertile women with stage 0-I endometriosis 70	Laparoscopy	PCBs + PCDDs + PCDFs + pesticides (serum)	no
Louis et al (2005)	USA	32	Women undergoing laparoscopy (i.e. diagnostic, tubal sterilization) 52	Laparoscopy	PCBs (serum)	no
Reddy et al (2006)	India	Infertile women 85	Fertile women undergoing laparoscopy for tubal sterilization 88	Laparoscopy esters (plasma)	PCBs + phthalate with infertility	yes, possible relationship
Porpora et al (2006)	Italy	40	Nulliparous women 40	Laparoscopy	PCBs (blood)	yes
Hoffman et al (2007)		USA 79	Actively participating female members of the Michigan PBB cohort 864	Self report of endometriosis	PBBs + PCBs (serum)	no
Tsuchiya et al (2007)		Japan 79	Infertile women 59	Laparoscopy	2,3,7,8 –TCDD + PCBs (fasted serum)	No, but possible role of CYP1A1 and CYP1B1 polymorphisms
Niskar et al (2008)	USA	60	Infertile women 64	Cases: Laparoscopy Controls: Laparoscopy; ovulation problems, infertile partner	PCBs + PCDDs + PCDFs (serum)	no
Porpora et al (2009)	Italy	80	Women undergoing laparoscopy (i.e. endometriosis, benign gynecologic condition) 78	Laparoscopy	PCBs + PCDDs + PCDFs + p,p′-DDE + HCB (serum)	Significantly higher serum concentration of PCBs and p,p′-DDE

Table continued

Table I. Comparison of measured variables before and after intervention in BAL fluid.

Author	Country	Population		Diagnostic method	Chemicals	Significant association with endometriosis?
		Cases	Controls			
Simsa et al (2010)	Belgium	Infertile women 96	106	Laparoscopy	PCBs + PCDDs + PCDFs (plasma)	no
Cai et al (2011)	Japan	Infertile women 10	7	Laparoscopy	PCBs + PCDDs + PCDFs (serum + peritoneal fluid)	Higher levels of PCDDs and PCDFs in ascites are linked with endometriosis
Vichi et al (2012)	Italy	Women undergoing laparoscopy (i.e. endometriosis, benign gynecologic condition) 181	162	Laparoscopy	PCBs (serum)	Gene-environment interaction between PCBs and GSTP1and GSTM1 null genotypes
Martinez -Zamora et al (2015)	Spain	Women undergoing laparoscopy for DIE 30	Women undergoing laparoscopy for benign adnexal gynecological diseases 30	Laparoscopy	PCBs + PCDDs + PCDFs (fasted adipose tissue from omentum)	DIE patients have significant higher levels of PCDDs/PCDFs/PCBs in adipose tissue when compared to controls

PCBs = polychlorinated biphenyls; PCDDs = polychlorinated dibenzo-p-dioxins; PCDFs = polychlorinated dibenzofurans; PBBs = Polybrominated biphenyls; p,p′-DDE = 1,1-dichloro-2,2,-bis(4-chlorophenyl)-ethene; HCB = hexachlorobenzene; DEN = deep endometriotic nodules; PE = peritoneal endometriosis; DIE = deep infiltrating endometriosis

the total TEQ could not correlate with the disease, since they could restrict the activity of more potent chemicals. In most of the studies examined, the concentration of selected toxicants was measured in serum samples, not considering the effect of fasting. As a matter of fact, there is a significant difference in mean toxicant concentration between fasting and nonfasting samples[37]. In order to obtain a meaningful comparison between studies a standardized collection procedure or a correction for total serum fat is required. Additionally, breastfeeding is an important route of PCBs excretion, which leads to a significant reduction in the body burden of dioxin-like compounds. To avoid the confounding factor of breastfeeding, only nulliparous women or who have never breastfed should be enrolled. Also the type of endometriosis can affect the results. Heilier et al[15,16] found that concentrations of PCBs and dioxin-like compounds in serum were associated with a significantly increased risk of developing nodules of the rectovaginal septum, while the risk of developing peritoneal endometriosis was not statistically significant. Although, there is no clear agreement on the definition of endometriosis and deep infiltrating endometriosis seems to have a different disease process and including it in the same group of patients affected by peritoneal endometriosis may not be opportune. In a recent case-control study published by Martínez-Zamora et al[38] only patients with deep infiltrating endometriosis were enrolled and a significant higher TEQ and concentration of dioxins and PCBs were found in omental adipose tissue, suggesting a potential role of these chemicals in the development of the disease. Despite this, a main limitation of this study was the small sample size. Genetic and environmental factors may contribute to the onset and progression of endometriosis. The presence of mutations in genes responsible for the detoxification such as glutathione transferase (GST), alone or in combination with exposure to PCBs was analyzed. Vichi et al[39] demonstrated that GST polymorphisms per se do not increase the risk of developing endometriosis. However, a gene-environment interaction was observed for GSTP1 and GSTM1 null genotypes modulating the effect of PCBs. Given the increased sensibility of fetuses and infants, studies aimed to assess whether the exposure in utero, in childhood and during puberty may increase the risk of developing endometriosis in adulthood are underway.

Conclusions

The conflicting results obtained could be the consequence of small sample size, different selection of the controls, different methods of assessment for toxicants, different types of congeners tested and different statistical tests used, but a link between dioxins and dioxin-like chemicals seems to be plausible. However, the exact mechanism through which they operate is not clear, yet. They could interfere with both immune and endocrine systems. Further studies in this field are needed in order to promote prevention strategies.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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