THE EFFECTS OF THE ENDOCRINE DISRUPTORS AND OF THE HALOGENS ON THE FEMALE REPRODUCTIVE SYSTEM AND ON EPIGENETICS: A BRIEF REVIEW

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ABSTRACT

Introduction: An endocrine-disrupting chemical (EDC) is defined as “an exogenous chemical or a mixture of chemicals that interfere with any aspect of the hormonal action”. Endocrine systems are a physiological interface with the environment and genetic-environmental interactions are disrupted by EDCs. Today, there are almost 1000 chemicals reported to have endocrine effects: the prevalence of EDC in our environment and in our bodies represents a major global health challenge. This review gathers the studies that have investigated the correlations between exposure to EDC and pathologies of the female reproductive system and fetal development.

Methods: A PubMed research was conducted using the keywords, their variants, and their combinations (BP A, DES, MXC, pesticides, phthalates, plasticizers, PCBs, dioxins, ovaries, oocytes, ovaries, fallopian tubes, follicles, vagina, uterus, fibroids, fertility, infertility, puberty, polycystic ovary syndrome, premature ovarian failure, birth, preterm birth, birth outcome, steroid, hormone, female, girl and menopause).

Results: The endocrine system plays a central role in all vertebrates and regulates critical biological functions such as metabolism, development, reproduction, and behavior. Epidemiological studies link EDCs with reproductive effects, neuro-behavioral and neurodevelopment alterations, metabolic syndrome, bone disorders, immune disorders, and cancers in humans. Human investigations confirm the results of the studies carried out on animal showing associations with many additional effects on health, including asthma, learning and behavior problems, premature puberty, infertility, breast and prostate cancer, Parkinson’s disease, obesity and other diseases.

Conclusions: It is important to undertake research with follow-up methodologies and/or longitudinal studies to detect the extent of exposure of pregnant women to EDCs and halogenated substances and the effects of such exposure on brain development. A future research hypothesis may consider the effect that these substances have on neuro-development and, more specifically, how EDCs are involved in pathogenic disorders such as autism spectrum disorders (ASD). In addition, a scientific study could be performed on the correlations between this type of substance and the inconveniences found in the field of executive frontal functions.

Keywords: Bisphenol A, embryonic development, endocrine disruptors, epigenetic, female reproductive system, halogens, Metal, Polybrominated Diphenyl Ethers, Phthalates, Pesticide.

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Introduction

The embryonic development process is complex and requires that the reproductive system be healthy and that here be the correct functional interaction of many organs and apparatus including the ovaries, uterus, vagina and the anterior pituitary. The substances are known as Chemical Endocrine Disruptors (EDCs) alter the embryo-fetal development, interfering with the structure and/or function of female reproductive organs. We analyzed the studies that examined the harmful effects of EDCs in...
the years from 2009 to 2015. These studies clearly show that plasticizers (M XC) and pesticides (TCDD) interfere with the formation of follicles, affect postnatal ovarian structure and function in animal models by decreasing ovarian weight, inhibiting follicle growth and accelerating atresia and apoptosis. On a wider scale, pesticides, phthalates, Bisphenol A (BPA) and environmental contaminants compromise ovarian steroidogenesis in animal specimens and in women (10-14). Although the data is not always consistent, mainly because there are a low number of human studies, experimental and epidemiological investigations suggest that EDCs may have adverse effect on the structure and/or function of the uterus, the vagina and the anterior pituitary and may be associated with abnormal puberty, irregular cyclicity, decreased fertility, Polycystic Ovary Syndrome (PCOS), endometriosis, fibroids, preterm birth, and teratogenesis. In addition, the mechanisms by which EDCs affect reproduction are clear. Finally, many potential EDCs have not been subjected to experimental or epidemiological studies and it is necessary that future studies concentrate, through experimental and epidemiological studies, on the effects and mechanisms by which EDCs affect reproduction (15-18).

Table 1 shows the main substances that interfere with endocrine systems: these findings refer to studies from 2009 to 2015.

Chemicals, interfering with endocrine systems, may be involved in the etiopathogenesis of the spectrum of autism disorders (ASD), but it is difficult to identify which chemical substances are involved. Braun et al. (2) investigated the exposure of pregnant women to EDCs and their correlation with child's autistic behaviors by measuring the concentration of 8 phthalate metabolites, bisphenol A, 25-biphenyl-polychlorinated (PCB) 6 organocloruric pesticides, 8 brominated flame retardants and 4 perfluoroalkyl compounds in blood or urine samples from 175 pregnant women. When the children reached the age of 4-5 years, the mothers compiled the Social Responsibility Scale (SRS), a set of autistic behaviors. The associations between the 52 EDCs and SRS scores were tested using two-step hierarchical analysis. Most EDCs have been associated with negligible differences in SRS scale scores. The increase of 2 standard deviations (SD) in serum diphenyl ether-28-polybrominated (PBDE-28) or trans-nonachlor serum was associated with more severe autistic behaviors. Conversely, autistic behaviors have been observed less frequently in children born of women with noticeable concentrations of PCB-178, β-hexachlorocyclohexane or PBDE-85-perfluorooctanoate (PFOA). The small sample size and the high number of EDCs detected in the urine of pregnant women do not allow for definitive definitions, especially for those chemicals that are not associated with autistic behaviors. PFOA, β-hexachlorocyclohexane, PCB-178, PBDE-28, PBDE-85 and trans-nonchlor deserve further control as factors that may be associated with autistic childhood behaviors (25-29).

**Bisphenol A (BPA)**

Numerous studies focused on the role of bisphenol A in relation to the origin of damage to the female reproductive system; comparative toxicological studies have confirmed that this substance is one of the highest cytotoxicity plasticizers (30-32), emphasizing the need to detect with increasing precision its concentration in the blood of neo-moms so that the degree of exposure to this toxic material can be monitored (33-35). Over the last ten years, the number of studies that have linked BPA to female infertility has gradually increased (36-40). According to recent studies, exposure to BPA during the embryonic development period could trigger reproductive system dysfunction, transmitted transgenerationally through epigenetic mechanisms involving the miRNA (41-44). Further studies have correlated BPA and Triclosan (TCL) to the endometrial impairment that can compromise fertility and possible outcomes of pregnancy (45-49).

The study conducted by Guida et al. (50) correlates the developmental exposure to BPA and the genesis of malformations in the fetus. The hypothesis is that the mother reducing the ability to metabolize the chemical substance can contribute to the occurrence of malformations in the child. More specifically, in the case of chromosomal malformations, the average free BPA value appears to be almost three times higher than that of the control group. Likewise, in the case of non-chromosomal malformations of the central and peripheral nervous system, the free BPA value is almost twice as high as that of the controls. Csaba (51) argues that “developmental abnormalities” are understood to mean all teratogenic phenomena relevant not only in the intrauterine period but also in the perinatal or subsequent periods that depend on hormonal dysfunctions that may occur at any time in life, which may be present in hidden forms and which can be triggered by internal or external environmental factors. Furthermore, through fetal testis assay (FeTA) studies, several studies have shown that 10 nmol/L of BPA reduce testosterone levels in testes in the fetus (52-57).
Giesbrecht et al.,(58), correlated prenatal exposure to BPA to the deficit of the neuroendocrine system of the offspring. High levels of BPA in mothers' urine were associated with increased cortisol in saliva and decreased stomach reactivity to stress in females and a reduction in cortisol and increased malformity reactivity in males. These data show that prenatal exposure to BPA is associated with gender-specific changes in the functions of the child’s Hypothalamic-pituitary-adrenal axis.

Polybrominated Diphenyl Ethers (PBDE)

The study carried out by Goodyer et al. (59) have investigated how the presence of polybrominated diphenyl ethers (PBDEs) (flame retardants) in mothers influences the development of the child's reproductive system. The aim of the study was to correlate the presence and concentration of eight BDE conjugates (BDE-28, -47, -99, -100, -153, -154, -183, -209), detected through a GC -MS (gas chromatography-mass spectrometry) in the mothers' hair and the presence of cryptorchidism in the child(60-61). Of the eight congeners, the BDE-99; -100 and -154, may be associated with the abnormal migration of gonads in the baby. An Italian study examined PBDE serum concentration in 31 girls with ICPP (Early Puberty) and related to eating habits and lifestyles. The average PBDE level was 59 ng/g of lipids, higher than of healthy girls in similar studies. It is interesting to note that older girls and girls with higher body mass index (BMI) showed higher serum levels of PBDE (62).

Phthalates

Sheik et al. (63) identified the potential target of endocrine disruptor phthalates in SHBG (Sex Hormone binding globulin). SHBGs are glycoproteins that bind sex hormones, testosterone, and estradiol. All of the 9 flatati considered: DMP, DBP, DIBP, BBP, DNHP, DEHP, DNOP, DIMP, DIDP...
could interact with the SHBG molecules, replacing them in the binding site, producing an alteration of homeostasis between androgens and estrogens.

**Carbon Black Nanoparticles (CBNP)**

We have found only one study related to CBNP pollution. From the in vitro experiment, the way in which the steroidogenic activity of in vitro granulocyte ovary cells KGN was influenced by a progressive increase in CBNP concentration in tissues was analyzed. It has been shown that this substance significantly decreases the production of estrogen.

**Tributyltin (TBT)**

A research conducted by Macejova et al. is part of the range of studies on TBT endocrine disruptors affecting metabolites intervening in vitamin A functions. Macejova's work focuses on endocrine disruptors tributyltin chloride (TBTCl) and triphenyl tin chloride (TPTCl) to which have been associated genetic modifications of the reproductive organs. The human placenta plays a crucial role in steroid biosynthesis which is regulated by enzymes that can undergo the inhibitory effect of TBTs.

**Metals**

Data from a research conducted by Sen et al., suggest that exposure to metals such as Cadmium can reduce fertility and/or progressively lead to infertility. This phenomenon is related to the functions of the molecular clock genes contained in women's H-P-G axis.

**Pesticide**

There is significant evidence of correlations between pesticides and neurodevelopmental disorders and mental retardation, mainly due to the considerable consequence this type of disease has on public expenditure. Monteguado et al. analyzed the exposure to organochlorine pesticides (OCPs) and its relationship with the weight of newborns by measuring the anthropometric variables in both the mother and the infant. In serum extracted from the umbilical cord, a significant result was obtained: 95% of the 320 overweight babies had OCP in the blood. The study focused on the mother’s pregnancy diet and hence exposure to pesticides in the uterus. Basing the study on the Mediterranean Diet and the specific needs that are present in pregnant women, the authors have developed a Mediterranean Diet Score for Pregnancy (MDS-P) instrument, developing a predictive model of factors affecting the baby's overweight birth. This data is in line with previous studies, which showed that prenatal exposure to Chlordecone, an OCP used in the French West Indies, affects the TSH and the thyroid hormone levels at the age of three months differently in relation to the child’s sex.

**Conclusions**

This review collects studies that investigated the correlations between exposure to EDC and pathologies of the female reproductive system and fetal development. This collection highlights the scarcity of research carried out on humans and the need to deepen the pathogenic effect of this type of substance. Longitudinal studies are also required to detect the extent of exposure of pregnant women to EDCs and halogens and the effects of such exposure on brain development. A future research hypothesis may consider the effect that these substances have on neurodevelopment and, more specifically, how EDCs are involved in pathogenic disorders of ASD and DSA. In addition, a scientific study could be carried out on the correlations between this type of substance and the inconveniences found in the field of executive frontal functions.

It is possible to suppose that the increase of neurodevelopmental disorders recorded in the last 20 years could be explained by the effects of the EDC on the complex articulation of the stages of brain development in the embryo. The factors common to all neurodevelopmental pathologies are the presence of ectopic cells in various areas of the brain (the probable result of the proliferation, migration and differentiation phases) and the alteration of the brain maturation indexes, such as neuronal density, synaptic density, and myelination (following the compromise of synaptogenesis).

An analysis that intends to measure the impact of EDC on neurodevelopmental disorders must have the following characteristics:

1. It must repeatedly measure the presence of these toxic substances in the biological fluids of the mother and of the child after birth in order to be able to correlate their presence to the various stages of the embryonic development of the Central Nervous System;
2. It must detect the indexes of cerebral development and their possible alterations;
3. It must evaluate the course of synaptogenesis until the child is at least six years old.
At the same time, it is necessary that the parameters of the neuropsychological and psychopathological fine functioning of the child, of the parents and of the environmental contexts in which the family lives are recorded for a period not inferior to six years after birth.

In this way, it is possible to foresee all the possible interactive processes which occur between the psychopathological and the neurophysiological environment, and that are likely to underlie (cause) neurodevelopmental diseases.

References


109) Synergistic antiproliferative effect of arsenic trioxide combined with bortezomib in HL60 cell lineand prim-acy blasts from patients affected by myeloproliferative disorders. Canestraro M, Galimberti S, Savli H,


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