The Impact of Endocrine-Disrupting Chemicals on Female Fertility

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Abstract. Nowadays, infertility is a prevalent problem among couples. Exposure to endocrine-disrupting chemicals (EDCs) may influence the female reproductive outcomes through multiple mechanisms, being one of the important causes of infertility. These compounds may interfere with some fertility and fecundity markers, leading to increased time to pregnancy, increased risk of spontaneous abortion, shorter menstrual cycles, early age at menopause, anovulation or delayed ovulation, smaller preovulatory follicles, increased serum FSH, decreased synthesis of estradiol and progesterone, low plasma levels of anti-Müllerian hormone and decreased antral follicle count. Endocrine-disrupting chemicals may also impair in vitro fertilization outcomes, being responsible for: a lower probability of implantation, reduced fertilization rates, diminished probability of clinical pregnancy, and near term pregnancies after in vitro fertilization. Another mechanism of altering the female reproductive function is through the disorders induced by EDCs, such as polycystic ovary syndrome, uterine fibroids, and endometriosis. Those conditions may finally lead to infertility.

Keywords: EDCs, phthalates, pesticides, BPA, perfluorinated chemicals, heavy metals, triclosan, fertilization rate, infertility

1.Introduction
The failure to obtain a clinical pregnancy after one year of regular and unprotected heterosexual intercourse defines infertility [1-3]. It is estimated to affect almost 8 to 12% of young couples worldwide [1].

Endocrine-disrupting chemicals (EDCs) are exogenous agents that interfere with the normal synthesis, secretion, transportation, binding, and metabolism of natural hormones [4-7]. Due to their capacity to disturb hormonal activity, endocrine-disrupting chemicals (EDCs) may lead to problems with pregnancy, fertility, and other aspects of reproduction [8, 9]. Thus, work-related factors, lifestyle behaviors, and environmental contaminants have an important role in impairing women’s reproductive health [10, 11].

EDCs interfere with female reproduction through their potential to alter the structure of female reproductive organs and also their capacity to disrupt steroid hormone levels and organ function [12]. There are findings regarding the impact of some endocrine disruptors in the occurrence of endometriosis, uterine fibroids, and polycystic ovary syndrome, disorders which can lead to infertility [13-16].

Many studies proved that these substances might impose adverse effects on the menstrual cycles [12], time to pregnancy [10], ovarian reserve [6], and reproductive senescence, being responsible for earlier age at menopause [7, 17]. Endocrine disruptors also impair in vitro fertilization outcomes [12, 18] and lead to pregnancy loss [3, 19-21].

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Phthalates

Phthalates are a group of chemicals currently used in medications, construction materials, cosmetics, and plastic toys, exposure to them occurring through dermal contact, inhalation, and ingestion [22].

Phthalates showed no negative effects as regards the time to pregnancy [18, 23, 24]. Moreover, some studies reported an association between some phthalates and a shorter time to pregnancy [24].

Exploring the effects of phthalates on female fecundity proved that urinary metabolites of di(2-Ethylhexyl) phthalate (DEHP) and diisodecyl phthalate (DiDP) are linked with reduced total and mature oocyte yield during in vitro fertilization, while metabolites of diisononyl phthalate (DiNP) and diisodecyl phthalate (DiDP) were associated with decreased fertilization rates [18, 25].

New evidence state that high urinary levels of DEHP metabolites are also related to a diminished probability of clinical pregnancy and live birth after in vitro fertilization, along with a decreased antral follicle count (AFC), especially among women younger than 37 years [18, 22, 26].

Urine phthalates also associate with the occurrence of endometriosis [3, 27]. Taking into account that the endometriosis-associated inflammatory response includes peritoneal oxidative stress as a major constituent, it is relevant to the positive association between phthalates exposure and inflammation markers, along with negative association with endogenous antioxidants, such as bilirubin [5, 28].

Besides endometriosis, DEHP is linked to other reproductive disorders, such as uterine fibroids and polycystic ovary syndrome, which is a leading cause of subfertility [22, 29]. Along with phthalates, diphenyldichloroethene is another endocrine disruptor responsible for the most common reproductive disorders in women, endometriosis, and fibroids [30].

Phthalates are also responsible for anovulation or delayed ovulation, longer estrous cycles, smaller preovulatory follicles, increased serum FSH and a decreased synthesis of estradiol and progesterone among women [4, 5]. In the case of DEHP, anovulation due to suppressed estradiol production may be a consequence of receptor-mediated signaling pathway, which is activated by his metabolite, monoethylhexyl phthalate (MEHP) [31].

Studies proved that high levels of phthalates around the time of conception lead to pregnancy loss [3, 32].

Bisphenol A (BPA)

Bisphenol A is widely used in the fabrication of epoxy resin can liners, polycarbonate plastics, medical equipment, dental sealants, and heat transfer papers [3, 5, 22, 33-35]. It has a dual mechanism of action, exerting both pro- and anti-estrogenic effects depending on tissue [35].

More studies found a relation between high serum or urinary BPA levels and anovulation and infertility [22, 36].

Studying the liaison between the urinary levels of bisphenol A and the reproductive outcomes in women undergoing in vitro fertilization treatments, it is evident the protective effect of folate intake from food sources. Thus, BPA was associated with a 66% lower probability of implantation and with a similar pattern as regards the probability of clinical pregnancy and live birth among women who consumed no soy and less than 400 µg/day of food folate. However, the association between BPA and these outcomes isn’t noted in women who consumed soy and more than 400 µg/day of folate from food [18, 22, 37, 38]. Meanwhile, other studies showed no correlation of urinary BPA levels with implantation, clinical pregnancy, fertilization, and live birth rates [39].

Exploring the influence of female exposure to BPA concerning the ovarian reserve, an inverse association between urinary levels of BPA and antral follicle count (AFC) became evident among infertile women diagnosed with polycystic ovary syndrome [18, 40].

Another observation refers to the link between increased urinary levels of BPA and shorter luteal phases among women attempting pregnancy [18, 41]. High levels of bisphenol A also lead to pregnancy loss [3, 7, 42] and are related to the occurrence of polycystic ovary syndrome [3, 43].
The increased risk of miscarriage is explained by the negative effects of BPA on uterine receptivity, embryo transport, and development [33]. BPA has shown a negative impact on oocyte meiosis, leading to aneuploidy. The negative impact on the deciduae is related to the thinner endometrial lining [44, 45].

Other studies found that BPA may alter the estradiol response to gonadotropin stimulation, along with oocyte quality and ovarian steroidogenesis during in vitro fertilization (IVF) [5,46-49]. Moreover, blood BPA levels may have negative effects as regards the oocyte maturation and the number of oocytes obtained among women undergoing IVF treatment [22, 48].

More than half of patients with endometriosis included in a study had detectable BPA serum levels, while this substance was absent among women without endometriosis [5,50]. BPA was also associated with the occurrence of uterine fibroids; women diagnosed with this disorder having higher levels of BPA than those without fibroids [22].

Pesticides

It became clear that pesticides, which are widely used as herbicides, insecticides, rodenticides, and fungicides, interfere with female fertility. These agents include five major classes: organochlorines, organophosphates, carbamates, pyrethroids, and triazines [51].

Studies proved an association between pesticide exposure and reduced fertility in animal and women models [51, 52]. For example, a mixture of organophosphate pesticides was correlated to decreased live birth and pregnancy rates in rats [51,53]. Other studies linked the p,p′-dichlorodiphenyldichloroethylene (DDE) and 2,2′,4,4′,5,5′-hexachlorobiphenyl (CB-153) exposure to an increased risk of fetal loss in humans [51, 54]. The risk of spontaneous abortion has also been correlated with dichlordiphenyltrichloroethane (DDT) exposure [44].

Furthermore, the association between exposure to organochlorine pesticide and increased time to pregnancy in women is evident [8, 51, 55]. In plus, organochlorine pesticides are also linked to an increased risk of endometriosis, uterine fibroids, and polycystic ovary syndrome [22].

As regards the effect on the menstrual cycle, organochlorine pesticides are related to shorter menstrual cycles, whereas non-organochlorine pesticides led to longer menstrual cycles or absence of cycles [22,56]. Moreover, exposure to atrazine, a commonly used herbicide, was linked with longer follicular phases, and menstrual cycle irregularity [22].

Occupational exposure to methoxychlor (M XC), a well-studied organochlorine pesticide, was associated with spontaneous abortion and a two - to three-fold increase in the risk of prolonged time to pregnancy, increasing infertility in women [19, 21].

Other important pesticides affecting the reproductive outcomes in females are pyrethroids, which determined low plasma levels of anti-Müllerian hormone, a marker of ovarian reserve, among women living in rural South Africa [22, 57].

Regarding the effects of pesticide exposure on reproductive senescence, most of the studies showed that high levels of β-hexachlorocyclohexane, mirex, p,p′-dichlorodiphenyldichloroethylene (DDE) and dichlorodiphenyltrichloroethane (DDT) were correlated with early age at menopause [51]. In contrast with these results, studies found a later age at menopause in women exposed to pesticides than the control group [51, 58].

Heavy metals

Heavy metals are another type of endocrine-disrupting chemicals, exerting different effects on female reproduction. Several routes of exposure to heavy metals are described, such as contaminated food, water and air, dietary supplements, alcoholic drinks, and cigarettes [51, 59].

Interfering with the endocrine system, heavy metals may have adverse effects on reproductive health, including menstrual irregularities, delay in conception, infertility, subfertility, fetal death, early pregnancy loss, and an increased risk of spontaneous abortion [22, 60].
Some studies have reported high blood concentrations of lead in women with unexplained infertility, while other studies observed reduced fertility and an increased risk of spontaneous abortion in case of mercury exposure among dental health care workers [51,61].

Moreover, some studies reported a dose-response relationship between the serum lead level of the women and the risk of spontaneous abortion [21, 62, 63]. Occupational exposure to lead can also cause shorter menstrual cycles and prolonged time to pregnancy [10,64]. The negative reproductive effects appeared at relatively low doses of lead, as a contaminant of urban air [21].

An increased risk of spontaneous abortion is also noticed in case of exposure to high levels of arsenic through drinking water [51, 65].

Other studies showed that cadmium exposure to either a woman or a man could reduce the woman’s chances of pregnancy, this being one of the causes of unexplained infertility [60, 64, 66].

Exploring the effects of hexavalent chromium – Cr(VI), it is evident that prenatal and early postnatal exposure to this compound is related to the occurrence of premature ovarian failure in the next generation. In plus, occupational exposure to hexavalent chromium leads to dysmenorrhea and cycle abnormalities [64].

Diethylstilbestrol (DES)

Some studies reported that adulthood exposure to diethylstilbestrol, which is a non-steroidal estrogen, impairs the female reproductive outcomes, but the mechanism is still unclear [51]. Furthermore, daughters of women exposed to diethylstilboestrol had a decreased fertility [29].

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)

2,3,7,8-Tetrachlorodibenzo-p-dioxin is one of the most powerful polychlorinated dibenzodioxins, with a lasting biological half-life of 2–5 years [51, 67]. Exposure to high levels of TCDD was associated with infertility and with a prolonged time to pregnancy [51, 68]. Other studies found a connection between TCDD exposure and an increased risk of early menopause and endometriosis [51,52,69].

Polychlorinated biphenyls (PCB)

A major source of human exposure to PCB is the consumption of contaminated fish, cheese, butter, or fatty meats such as pork and beef [70,71].

PCB exposure was linked to subfertility in women and animals [51]. Several studies show that exposure to polychlorinated biphenyls reduces the couple fecundity, which is measured by time to pregnancy [51,72]. Studies performed on women consuming contaminated fish have reported a correlation between a moderate to high PCB exposure index and shortened menstrual cycles [51].

Other findings are related to an increased risk of endometriosis and uterine fibroids in case of exposure to several PCB congeners, while mono-orthoPCBs are tied to anovulation [12, 51].

Studies on assisted reproductive technologies reported an association between reduced fertilization rate and measurable levels of PCBs in ovarian tissue and human follicular fluid [12]. PCBs have also proven to reduce anti-Mullerian hormone concentrations, a marker of ovarian reserve [73].

Perfluorinated chemicals (PFC)

PFCs are another group of endocrine-disrupting chemicals, characterized by long, fully fluorinated carbon chains, having different functional head groups, which make them resistant to degradation. These substances are used in consumer goods, including paper wraps, textiles, food packaging, firefighting foams, industrial surfactants, and emulsifiers [4, 74].

Human studies have shown that perfluorinated chemicals are linked with infertility and adverse pregnancy outcomes [4].

Perfluorooctanesulfonate (PFOS) and perfluorooctanoic acid (PFOA) are widely used as surfactants in industry and consumer products, the exposure happening especially through
contaminated food, in particular, fish, but also through indoor dust [5]. Several studies reported an association between high levels of PFOS, PFOA, and perfluorohexanesulfonate (PFHxS) and increased time to pregnancy [74-76]. Increased concentrations of PFOA and PFHxS in maternal plasma lead to reduced fecundability and infertility [77].

A relation between reduced fertility and PFOS exposure is also described, infertile couples having higher PFOS serum levels than fertile couples [5].

**Triclosan**

Triclosan is an antibacterial agent found in consumer products and personal care products, including toothpaste, mouthwash, detergents, surgical scrubs, sutures, anti-bacterial soaps, and shampoos [51,78]. It seems that triclosan exposure leads to an increased time to pregnancy [24,51,78].

Moreover, urinary triclosan concentrations were inversely related to antral follicle count (AFC), which is a marker of ovarian reserve in women seeking infertility treatments. In plus, the association was stronger among younger women (<35 years) and lean women (<25 kg/m²) [78].

**Benzophenones**

Benzophenones are commonly used as chemical UV filters in cosmetics and sunscreens, absorbed through the human dermis. In vitro and in vivo anti-androgenic, estrogenic, and anti-estrogenic properties of benzophenones were described [3].

Animal studies reported some negative effects of these compounds regarding the reproductive outcomes in females. Thus, it was shown that benzophenone 2 reduced egg production and inhibited oocyte development and spawning in fish [3, 79].

Human studies proved that exposure to benzophenone 1 is associated with the occurrence of endometriosis, which is an estrogen-dependent disease [80].

**Parabens**

Parabens are widely used in different foods and personal care products, but they are also found in indoor dust [51]. It has been demonstrated that urinary concentrations of ethylparaben and methylparaben are related to decreased fecundity in women [51]. Moreover, propylparaben was associated with decreased antral follicle count (AFC), which implies a diminished ovarian reserve [18, 81]. The sum of ethyl, methyl, propyl, and butyl parabens, but also butylparaben itself, are associated with shorter menstrual cycles [18].

**Cigarette smoking**

Smoking has a negative impact on female fertility, the risk increasing with the daily number of cigarettes [51, 82, 83]. The main chemicals contained in the smoke are polycyclic hydrocarbons, aromatic amines, heavy metals, and nitrosamines [51, 82].

These chemicals affect each stage of reproductive function: uterine myometrium and uterine blood flow, folliculogenesis, steroidogenesis, endometrial angiogenesis, endometrial receptivity, and embryo transport [51].

Adult exposure to cigarette smoke leads to decreased fecundity, reduced ovarian reserve, decreased success rates of in vitro fertilization (IVF), increased miscarriage rate, and earlier menopause by 1–4 years [29, 84, 85].

**Marijuana consumption**- leads to a decreased number of oocytes harvested during in vitro fertilization and impairs the menstrual cycle [51].

**Air pollutants**

Several studies found that air pollutants may act as endocrine disruptors, affecting female fertility. Thus, ozone and nitrogen dioxide were associated with a decreased live birth rate among women.
undergoing in vitro fertilization. Furthermore, carbon monoxide, sulfur dioxide, and nitrogen dioxide led to stillbirths and miscarriages [86].

Conclusions
Endocrine-disrupting chemicals (EDCs) are negatively associated with reproductive outcomes in women, affecting fertility through multiple mechanisms.

Several disorders, such as endometriosis, uterine fibroids, and polycystic ovary syndrome, indorse an important pathway towards infertility. Some endocrine disruptors interfere with the etiopathogenesis of these conditions.

A lot of fecundity and fertility markers are used to evaluate the effects of endocrine-disrupting chemicals on women's reproductive function. Thus, there are compounds which lead to:
- increased time to pregnancy (organochlorine pesticide, MXC, lead, TCDD, PCB, triclosan, PFC),
- increased risk of spontaneous abortion (DDT,DDE,CB-153,MXC,lead,arsenic, phthalates, BPA),
- shorter menstrual cycles (organochlorine pesticides, lead, butylparaben) and menstrual cycle irregularity (heavy metals),
- early age at menopause (pesticides, TCDD),
- anovulation or delayed ovulation (BPA, phthalates, PCB),
- longer estrous cycles, smaller preovulatory follicles, increased serum FSH, decreased synthesis of estradiol and progesterone (phthalates),
- low plasma levels of anti-Müllerian hormone (pyrethroids, PCB) and decreased antral follicle count (BPA, triclosan, parabens), which are markers of ovarian reserve.

Endocrine-disrupting chemicals may also interfere with in vitro fertilization outcomes. They are responsible for:
- reduced total and mature oocyte yield during in vitro fertilization (phthalates),
- reduced fertilization rates (phthalates, PCB),
- diminished probability of clinical pregnancy and live birth after in vitro fertilization (phthalates, BPA, ozone, and nitrogen dioxide),
- lower probability of implantation (BPA),
- alteration of the oocyte quality, ovarian steroidogenesis, and estradiol response to gonadotropin stimulation (BPA).

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