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Journal of Steroid Biochemistry & Molecular Biology 93 (2005) 325–330
The Journal of Steroid Biochemistry & Molecular Biology
www.elsevier.com/locate/jsbmb

Assessment of human contamination of estrogenic endocrine-disrupting chemicals and their risk for human reproduction☆

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Abstract

There is broad human exposure to estrogenic endocrine-disrupting chemicals (EDCs), but the data sets that exist are primarily for various environmental media such as food and water rather than the most relevant internal exposure. We have detected various kind of EDC contamination in humans including dioxin and bisphenol A (BPA) widely used for the production of plastic products. BPA was present in serum and follicular fluid at approximately 1–2 ng/ml, as well as in fetal serum and full-term amniotic fluid, confirming passage through the placenta. An approximately five-fold higher concentration, 8.3 ± 8.7 ng/ml, was revealed in amniotic fluid at 15–18 weeks of gestation, compared to other fluids showing increased exposure at the critical developmental period in humans. Interestingly, serum BPA concentrations were significantly higher in normal men and in women with polycystic ovary syndrome (PCOS) compared with normal women possibly due to differences in the androgen-related metabolism of BPA. These findings may provide some insight into the metabolism of EDCs in human and the pathophysiology of endocrine disorders such as PCOS. Dioxin contamination in relationship to development of endometriosis is also discussed.

Keywords: Bisphenol A; Dioxin; Follicular fluid; Amniotic fluid; Gender difference; Polycystic ovary syndrome; Endometriosis

1. Introduction

Endocrine-disrupting chemicals (EDCs) have generated growing scientific concerns and public debate over their potential adverse effects that may result form their exposure. Substantial evidence has reported they have potential to alter the normal function of the endocrine system in wildlife and humans [1]. The International Programme on Chemical Safety provided an objective, global assessment of the current state-of-the-science relative to environmental endocrine disruption in humans, experimental studies, and wildlife species and defined an EDC as an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations [2]. Temporal increases in the incidence of certain cancers in hormonally sensitive tissues in many parts of the industrialized world [3,4] are often cited as evidence that widespread exposure of the general population to EDCs has had adverse impacts on human health. These increases cannot be adequately explained by improved diagnostic techniques, but it has not yet been clarified whether these trends merely coincide with the increased use and release of EDCs into the environment. This problem is a recent controversial topic of science, in part because results of some studies have shown that these chemicals can have adverse effects at very low doses (in the range of human and wildlife environmental exposures to these chemicals) relative to doses normally examined in safety studies [5,6]. However, the elects on reproduction of human exposure to these contaminants in a general environment are largely unknown. In the present review, EDC especially dioxin and bisphenol A (BPA) contamination in humans will be detailed including possible relation between endometriosis and dioxin.

☆ Proceedings of the 16th International Symposium of the Journal of Steroid Biochemistry and Molecular Biology, 'Recent Advances in Steroid Biochemistry and Molecular Biology', Seefeld, Tyrol, Austria, 5–8 June 2004.

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doi:10.1016/j.jsbmb.2004.12.008

2. Contamination of human reproductive fluids

Human exposure to EDCs may affect human reproductive organs. Indeed, some EDCs are detected in ovarian follicular fluid (fluid which composes the environment for the growth and maturation of an ovum). Jarrell et al. determined the extent of contamination of follicular fluid and serum samples in women undergoing in vitro fertilization at three regional clinics in Halifax, Hamilton, Ont., and Vancouver, and studied the effect of the contaminants on reproductive outcome including cleavage rates and time to cleavage of the first egg [7]. They have found that five chlorinated organic chemicals tested were frequently found in two samples: α-chlordane (ALCH), dichlorochlorophenylethylene (DDE), heptachloroepoxide-oxychlordane (OXCH), hexachlorobenzene (HCB), and polychlorinated biphenyl (PCB). The levels of these chemicals were generally low and regional differences between the three clinics were present. Samples from the Halifax clinic had the lowest frequency and lowest level of contamination. The concentrations of the five contaminants did not affect the cleavage rate or the time to cleavage of the first egg. Thus, they concluded that trace amounts of toxic and persistent chlorinated organic chemicals found in the follicular fluid of Canadian women undergoing in vitro fertilization do not seem to have any adverse biologic effect on the rate of fertilization and the time to cleavage.

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) is the most toxic of the halogenated aromatic hydrocarbons. TCDD has been shown to interact with a cytosolic receptor, the aryl hydrocarbon receptor (AhR) [8]. It was recently reported that AhR mRNA and AhR protein are present in mouse preimplantation embryos [9]. TCDD and other dioxins (PCDDs), furans (PCDFs), and PCBs originate from numerous sources including emissions from incinerators, effluents and solid wastes from pulp and paper processing, petroleum refining, wood preservation, and the production of many chemical compounds. We have found that PCDDs and PCDFs were detected in the follicular fluid from the infertile women who were undergoing in vitro fertilization [10]. Various PCDDs and PCDFs were identified and quantified using the labeled internal standard. The level of TCDD, the most toxic congener, was below the limit of detection for both samples. The total concentration of these compounds was about 1 pg/ml. The toxic equivalency (TEQ) value, which is used to express the toxic potency of complex mixtures of PCDDs and PCDFs [11], was approximately 0.01 pg of TEQ/ml, equivalent to 0.031 pM TCDD. The level of these substances in the follicular fluid was relatively low as compared with those in other biological fluids such as breast milk and plasma.

Bisphenol A, an estrogenic endocrine-disrupting chemical with two unsaturated phenol rings, is widely used in the production of polycarbonate plastics and epoxy resins, which are used in dentistry, food packaging, and as lacquers to coat food cans, bottletops, and water pipes [12,13]. A significant amount of BPA was detected in liquid from canned vegetables that are exposed to high temperature during autoclaving

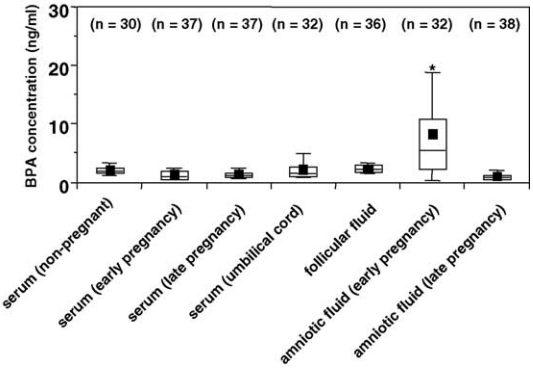

Fig. 1. Bisphenol A concentrations in human biological fluids. Data are presented as box and whisker plots, where boxes encompass values between the 25th and 75th percentiles, horizontal lines represent median values, and "whiskers" give the 95% range of the values. Dots (■) represent mean values. Number of samples appears in parentheses. (*) Denotes $P < 0.0001$ compared with other biological fluids.

[14] and in saliva of dental patients fitted with restorative materials [15]. BPA has been reported to bind estrogen receptors (ERα and ERβ) and play either estrogenic or antiestrogenic roles in vitro [16]. BPA has been shown to have several actions such as uterotrophic effects [17], decreasing sperm production [18], stimulation of prolactin release [19], promotion of cell proliferation in a breast cancer cell line [14], and influence on preimplantation development [20], by animal experiments. It was reported the promotion effect of growth and puberty by fetal or preimplantation exposure of BPA in mouse [21,22]. To study human contamination of BPA, we employed enzyme-linked immunosorbent assay (ELISA) and found that BPA contaminates the follicular fluids at a concentration 2.4 ± 0.8 ng/ml showing that oocytes themselves are exposed to BPA [23]. Of note, these BPA levels were higher than the level (1 nM) reported to affect preimplantation development [20]. As shown in Fig. 1, BPA was also present in serum at 2.0 ± 0.8 ng/ml (non-pregnant), 1.5 ± 1.2 ng/ml (early pregnancy), 1.4 ± 0.9 ng/ml (late pregnancy), as well as in fetal serum (2.2 ± 1.8 ng/ml) and amniotic fluids. There was a significant correlation between maternal and fetal serum concentrations, confirming passage through the placenta. There was approximately a five-fold difference in BPA concentrations between amniotic fluid obtained at 15–18 weeks of gestation (8.3 ± 8.9 ng/ml) and other fluids ($P < 0.0001$). However, amniotic fluid levels decreased significantly at term (1.1 ± 1.0 ng/ml) and no longer differed from the levels of other fluids.

To verify the results of our ELISA for BPA in the amniotic fluid samples, we compared BPA values obtained by our ELISA with those by the conventional reverse-phase HPLC analysis. The results showed the significant linear correlation between the two procedures ($R = 0.93$, $P < 0.0001$). Although its metabolism in the human body is largely unknown, BPA may be glucuronidated by a liver enzyme, uridine diphosphate-glucuronosyl transferase (UGT) [24]. Significantly higher levels of BPA in the mid-term amniotic fluid