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Prenatal organochlorine pesticide exposure and the disruption of steroids and reproductive hormones in cord blood: The Hokkaido study

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ABSTRACT

Certain organochlorine pesticides (OCPs) are designated as persistent organic pollutants and are regulated in many countries. The effects of OCPs on pediatric endocrinology are a concern; however, only limited data exist from human studies on maternal OCP exposure and its effects on infants' hormone levels. This study was conducted as part of the Hokkaido Study Sapporo Cohort, a prospective birth cohort study in Japan. Participants included 514 women who enrolled at 23–35 weeks of gestation between 2002 and 2005; maternal blood samples were collected in late pregnancy, and 29 OCPs were measured. Reproductive and steroid hormone levels in cord blood were also determined. Characteristics of mothers and their infants were obtained from self-administered questionnaires and medical records. Ultimately, 232 samples with both OCP and hormone data were analyzed. Fifteen of 29 investigated OCPs were detected in over 80% of the samples, with *p,p′*-dichlorodiphenyldichloroethylene showing the highest concentration (median value: 619 pg/g-wet). The association between OCPs and sex hormone levels varied by sex. Linear regression models after sex stratification showed that chlordanes, *cis*-hexachlorobenzene, heptachlor epoxide, Mirex, and toxaphenes in maternal blood were inversely associated with testosterone, cortisol, cortisone, sex hormone-binding globin, prolactin, and androstenedione-dehydroepiandrosterone (DHEA) and testosterone-androstenediones ratios among boys. Furthermore, these OCPs were positively correlated with DHEA, follicle stimulating hormone (FSH), and adrenal androgen-glucocorticoid and FSH-inhibin B ratios among boys. In categorical quartile models, testosterone and DHEA were inversely and positively associated with OCPs, respectively. Estradiol-testosterone and adrenal androgen-glucocorticoid ratios tended to increase with increasing OCP concentrations in the higher quartile, while the testosterone-androstenedione ratio tended to decrease. Sex hormone-binding globulin and prolactin showed an inverse association with OCPs. Among girls, the linear regression model showed that only *p,p′*-dichlorodiphenyltrichloroethane was inversely associated with the level of DHEA and the adrenal androgen-glucocorticoid ratio, but was positively associated with cortisone levels. However, no associations were observed using the quartile categorical model.

Abbreviations: CI, confidence interval; CYP11A1, cytochrome P450 family 11 subfamily A member 1; CYP17A1, cytochrome P450 family 17 subfamily A member 1; CYP19A1, cytochrome P450 family 19 subfamily A member 1; DDD, dichlorodiphenyldichloroethane; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; HCB, hexachlorobenzene; HCE, heptachlor epoxide; HCH, hexachlorocyclohexane; HSD17B1, hydroxysteroid 17-beta dehydrogenase 1; HSD3B1, hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 1; IRMA, immunoradiometric assay; DHEA, dehydroepiandrosterone; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; FSH, follicle stimulation hormone; INSL3, insulin-like factor 3; LC-MSMS, liquid chromatography-tandem mass spectrometry; LH, luteinizing hormone; LSM, least square mean; OCP, organochlorine pesticides; SHBG, sex hormone-binding globulin; StAR, steroidogenic acute regulatory protein

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These results suggest that prenatal exposure to OCPs disrupt reproductive hormones of fetuses in utero among boys, even at relatively low levels.

1. Introduction

Organochlorine pesticides (OCPs) are chlorinated hydrocarbons used extensively in the 1940s for agriculture and pesticide control, and are now designated as persistent organic pollutants by the Stockholm Convention (http://chm.pops.int). Although the Stockholm Convention has issued an exemption for the production and public health use of dichlorodiphenyltrichloroethane (DDT) to control vector-borne diseases, most OCPs were banned in the United States, Europe, and many other countries in the early 1970s (UNEP and WHO, 2012). The use of OCPs has been eliminated or restricted in Japan since the 1970's (Kanazawa et al., 2012). Although most OCPs have been prohibited for over 30 years, they are still detected in the environment and in human populations. According to Japanese monitoring data, the levels of DDT and its metabolites in water and sediment have decreased since 1990 and have consistently remained low since 2000; however, they are still detectable (Ministry of Environment, Japan, 2006). Heptachlor epoxide (HCE), hexachlorocyclohexane (HCH), Mirex, Parlar-26, and Parlar-50 are also above detectable levels in water and sediments, even though the latter three have never been used in Japan (Ministry of Environment, Japan, 2006).

The endocrine disrupting properties of OCPs are considered a health concern. In previous cross-sectional studies among adults, heptachlor and *o,p′*-DDT concentrations were associated with lower testosterone levels in men (Freire et al., 2014). In women, hexachlorobenzene (HCB), *p,p′*-DDT, *p,p′*-dichlorodiphenyldichloroethane (DDD), endosulfan, aldrin, and Mirex showed inverse associations with luteinizing hormone (LH) and follicle stimulation hormone (FSH) while showing positive associations with prolactin (Freire et al., 2014).

Maternal exposure to OCPs may affect fetal hormone levels. Sex steroid hormones including testosterone, progesterone, and estradiol exert their functions predominantly in the gonads, and dehydroepiandrosterone (DHEA) and androstenedione are activated to form androgens and estrogens that have important roles in sex differentiation and maturation (Labrie et al., 2001). Cortisol and cortisone are synthesized within the adrenal cortex, are involved in a wide range of physiological processes, and are essential for regulating and/or modulating homeostasis in metabolism, growth, neurodevelopment, and the immune system (Braun et al., 2013; Reynolds, 2010). LH and FSH play critical roles in the development and regulation of numerous body functions via the hypothalamic-pituitary-gonadal (HPG) axis (Kuiri-Hänninen et al., 2014). Inhibin B and insulin-like factor-3 (INSL3) are major products secreted by the Leydig and Sertoli cells, respectively, and the establishment of sufficient numbers of these cells is critical for the production of sperms in adulthood (Ivell et al., 2013; Orth and Boehm, 1990). In response to gonadotropins, testosterone (via LH signaling) and inhibin B together act to regulate the secretion of FSH; these constitute the major negative feedback signals that maintain the physiological function of the HPG axis (Carlson, 2009). However, only limited data exist regarding human studies on prenatal exposure to OCPs and their effects on steroids and reproductive hormone levels in offspring. There is only one study in France that found that prenatal α-endosulfan and HCE increase estradiol and sex hormone-binding globulin (SHBG), whereas these same agents reduce testosterone levels at birth (Warembourg et al., 2016).

We have previously reported that 21 of 29 tested OCPs were detected in maternal blood acquired between 2002 and 2005 in Japan (Kanazawa et al., 2012). The impact of relatively low levels of OCP exposure on hormones at birth has still not been well-investigated in epidemiological studies. In particular, the effects of OCPs other than DDTs are rarely investigated. Thus, we hypothesized that prenatal exposure to even relatively low levels of these agents may alter hormone levels in infants. To that end, the aim of this study was to examine the associations between prenatal OCP exposure and cord blood steroid and reproductive hormone levels.

2. Methods

2.1. Participants

This investigation was based on the Sapporo Cohort of the Hokkaido Study on Environment and Children's Health. Details of this study, including the population, data collection, sampling of the biological specimens, and contents of the administered questionnaire, were described previously (Kishi et al., 2017; Kishi et al., 2013; Kishi et al., 2011). Briefly, Japanese pregnant women who lived in Sapporo City or surrounding areas were recruited at 23–35 weeks of gestation between July 2002 and October 2005 at an obstetrics and gynecology hospital in Sapporo, Hokkaido, Japan. Among the 1796 eligible women approached, 25% were excluded because they were enrolled in the Japanese Cord Blood Bank or planned to deliver at another hospital. Ultimately, 514 pregnant women (28.6% of those approached) were enrolled in this study.

2.2. OCP measurement

Maternal blood samples were obtained at the time of patients' hospital examinations following recruitment (n = 296). If a blood sample could not be obtained during pregnancy because of maternal anemia, a sample was collected during post-partum hospitalization within a week after delivery (n = 130). All samples were stored at − 80 °C until analysis. OCPs in whole blood were measured by gas chromatography/high-resolution mass spectrometry and gas chromatography/negative-ion chemical-ionization mass spectrometry at IDEA Consultants, Inc. (Shizuoka, Japan) The 29 OCPs evaluated in this study were 5 chlordanes (*cis*-chlordane, *trans*-chlordane, *cis*-nonachlor, *trans*-nonachlor, and oxychlordane), 6 DDTs (*o,p′*-DDT, *p,p′*-DDT, *o,p′*-DDE, *p,p′*-DDE, *o,p′*-DDD, and *p,p′*-DDD), 3 ‘drins’ (aldrin, dieldrin, and endrin), 3 heptachlors (heptachlors, *cis*-HCE, and *trans*-HCE), HCB, 4 HCH isomers (α-HCH, β-HCH, γ-HCH, and δ-HCH), Mirex, and 6 toxaphenes (Parlar-26, Parlar-41, Parlar-40, Parlar-44, Parlar-50, and Parlar-62). Details of the measurement methods have been described previously (Kanazawa et al., 2012).

2.3. Measurement of steroids and reproductive hormones

The methods used to measure steroids and reproductive hormones were described previously (Araki et al., 2017; Araki et al., 2014; Goudarzi et al., 2017). Briefly, the concentrations of 7 steroid hormones including progesterone, estradiol, testosterone, DHEA, androstenedione, cortisol, and cortisone in cord blood were measured using liquid chromatography-tandem mass spectrometry (LC-MSMS) (Yamashita et al., 2007a; Yamashita et al., 2007b). An immunoradiometric assay (IRMA) was used to measure the concentrations of LH, FSH, and prolactin (Spac-S LH Kit, Spac-S FSH Kit, and Spac-Prolactin Kit, respectively, TFB, Inc., Tokyo Japan). SHBG was also measured using IRMA-Count SHBG (Siemens, Berlin, Germany). Concentrations of inhibin B were measured by using an enzyme-linked immunosorbent assay (ELISA) (Inhibin B Gen ELISA, Beckman Coulter, Inc., CA, USA), while INSL3 was measured by using an enzyme immunoassay (EIA) (INSL3/