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# Sex-related differences in the associations between maternal dioxin-like compounds and reproductive and steroid hormones in cord blood: The Hokkaido study

Chihiro Miyashita[a], Atsuko Araki[a], Takahiko Mitsui[b], Sachiko Itoh[a], Houman Goudarzi[a,c], Seiko Sasaki[d], Jumboku Kajiwara[e], Tsuguhide Hori[e], Kazutoshi Cho[f], Kimihiko Moriya[g], Nobuo Shinohara[g], Katsuya Nonomura[g,h], Reiko Kishi[a,*]

[a] Center for Environmental and Health Sciences, Hokkaido University, Sapporo, Japan
[b] Department of Urology, Hokkaido University Hospital, Sapporo, Japan
[c] First Department of Medicine, Hokkaido University School of Medicine, Sapporo, Japan
[d] Department of Public Health Sciences, Hokkaido University Graduate School of Medicine, Sapporo, Japan
[e] Fukuoka Institute of Health and Environmental Sciences, Dazaifu, Japan
[f] Department of Obstetrics and Genecology, Hokkaido University Hospital, Sapporo, Japan
[g] Department of Renal and Genitourinary Surgery, Hokkaido University Graduate School of Medicine, Sapporo, Japan
[h] Kushiro Rosai Hospital, Kushiro, Japan

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ABSTRACT

*Background:* Prenatal exposure to dioxin-like compounds (DLCs) irreversibly affects fetal reproductive and steroid hormone synthesis.

*Objective:* This study aimed to assess the relationships between maternal DLCs and cord blood reproductive and steroid hormones.

*Methods:* Participants in this study were pregnant women who enrolled in the Sapporo Cohort of the Hokkaido Study between 2002 and 2005. We quantified 29 DLCs during the 2nd and 3rd trimesters in maternal blood. Additionally, we measured the concentrations of progesterone, estradiol (E2), testosterone (T), androstenedione, dehydroepiandrosterone (DHEA), cortisol, cortisone, sex hormone-binding globulin (SHBG), luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin, inhibin B, and insulin-like factor-3 (INSL3) in cord blood samples.

*Results:* Data from 183 mother-child pairs were analyzed. We observed sex-dependent associations of DLCs on T/E2 ratios, DHEA, cortisol, cortisone, adrenal androgen/glucocorticoid (AA/GC: sum of DHEA and androstenedione)/(sum of cortisol and cortisone) ratios and SHBG. An increase in maternal DLCs related to decreased T/E2 ratios and SHBG and inhibin B levels, and increased AA/GC ratios and FSH and DHEA levels in male cord blood samples. However, an increase in maternal mono-ortho polychlorinated biphenyls related to increased cortisol, cortisone, and SHBG levels, and decreased DHEA levels and AA/GC ratios in female cord blood samples.

*Conclusions:* Prenatal exposure to DLCs alters steroidogenesis and suppresses the secretion of inhibin B in male cord blood. Relationships between maternal DLCs and cord blood hormones differ between boys and girls. Further studies are required to clarify whether the effects of *in utero* exposure to DLCs on adrenal hormones extend into infancy and puberty.

*Abbreviations:* AA/GG, adrenal androgen/glucocorticoid (sum of dehydroepiandrosterone and androstenedione)/(sum of cortisol and cortisone); AHR, aromatic hydrocarbon receptor; B, regression coefficient; CI, confidence interval; DHEA, dehydroepiandrosterone; LOD, limit of detection; DLC, dioxin-like compound; E2, estradiol; ER, estrogen receptor; FSH, follicle-stimulating hormone; HRGC/HRMS, chromatography/high-resolution mass spectrometry; INSL3, insulin-like factor 3; LC-MS/MS, Liquid chromatography-tandem mass spectrometry; LH, luteinizing hormone; LOQ, limit of quantification; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzo-*p*-dioxins; PCDF, polychlorinated dibenzofuran; SHBG, sex hormone-binding globulin; T, testosterone; TEQ, toxic equivalent

* Corresponding author at: Center for Environmental and Health Sciences, Hokkaido University, North 12 West 7 Kita-ku, Sapporo 060-0812, Japan.
*E-mail address:* rkishi@med.hokudai.ac.jp (R. Kishi).

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## 1. Introduction

Human exposure to persistent organic pollutants, including polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and polychlorinated biphenyls (PCBs), is widespread from environmental sources and daily food intake (Todaka et al., 2008). Seventeen PCDDs/PCDFs and 12 PCBs have been categorized as dioxin-like compounds (DLCs) (Van den Berg et al., 2006). Aromatic hydrocarbon receptors (AHRs) regulate xenobiotic metabolism, cell proliferation, and cell cycle control in fetal tissues. DLCs bind to AHRs and disrupt normal fetal development (Van den Berg et al., 2006). Exposure to DLCs *in utero* inhibits fetal reproductive development and steroid hormone synthesis (Cao et al., 2008; Hsu et al., 2005). Consequently, the immature endocrine system results in dyshomeostatic endocrine and reproductive development during adolescents (WHO, 2012). Sex-related differences in the susceptibility to DLC toxicity on birth size, immunity, and neurobehavioral disorders are reported (Kishi et al., 2017). Therefore, it is worthwhile to identify the underlying mechanisms.

In 1979, several pregnant women were accidently exposed to high levels of DLCs after consuming DLC-contaminated rice oil; this accident was called the Yucheng accident. Increased free testosterone (fT) levels and elevated fT/estradiol (E2) ratios in the serum of boys (aged 8–12 years), born to these women, were observed compared to those in age-matched boys born to women who were not exposed to DLC during their pregnancy (Hsu et al., 2005). In a birth cohort from Duisburg (Germany), fT and E2 concentrations in the cord blood inversely correlated with maternal PCDD/PCDF concentrations. The decrease in fT levels was more pronounced among females, whereas that of E2 levels was more pronounced among males (Cao et al., 2008). These studies suggest that *in utero* exposure to DLCs may be associated with the sex-dependent adverse effects of DLCs on reproductive and steroid hormone levels.

The fetal adrenal gland produces adrenal androgenic steroids,

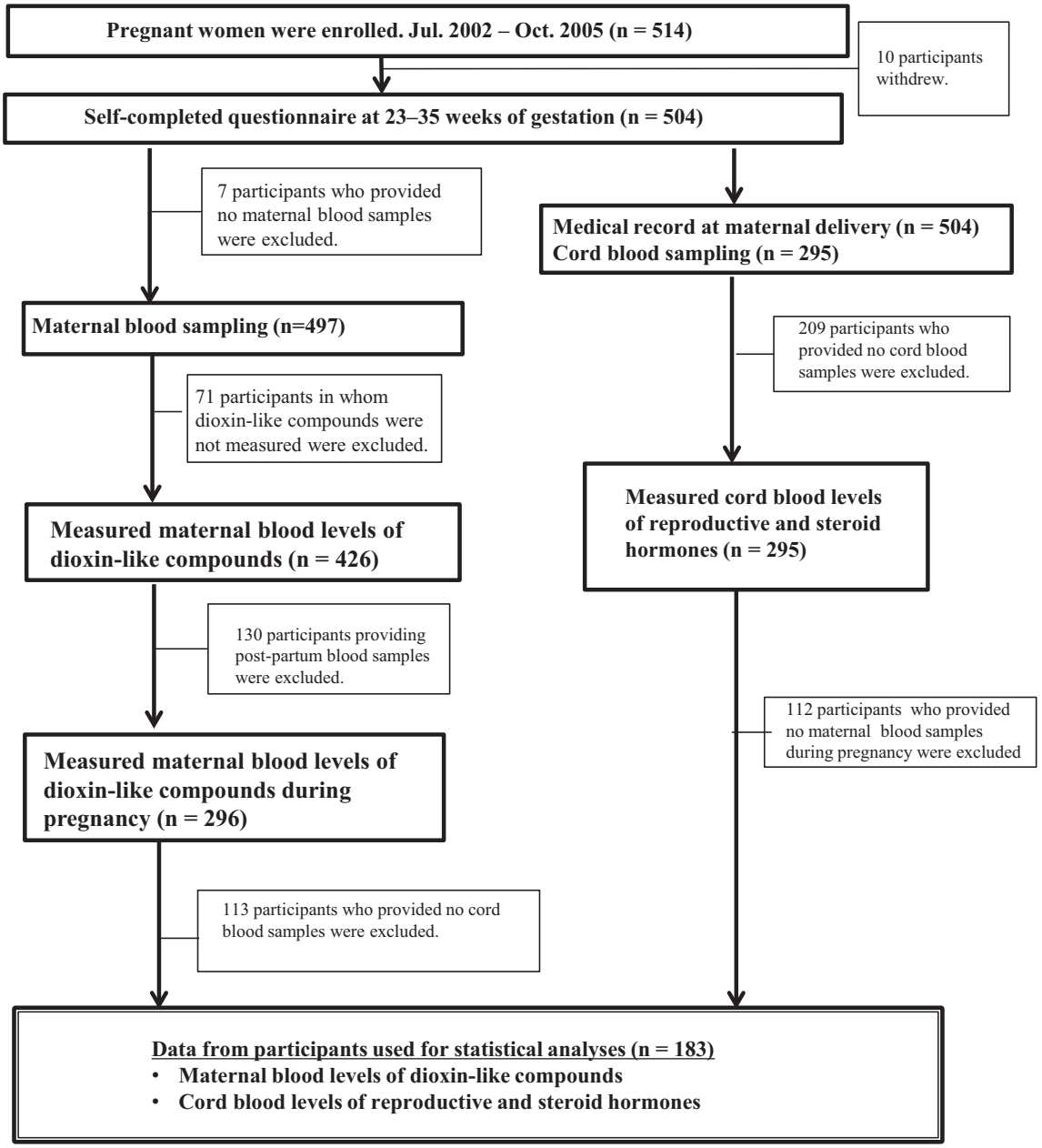


**Fig. 1.** Participant recruitment flowchart.