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Prenatal exposure to PCDDs/PCDFs and dioxin-like PCBs in relation to birth weight ☆, ☆☆

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ABSTRACT

Several human studies have shown that low-level exposure to environmental contaminants, such as polychlorinated biphenyls (PCBs) and organochlorine pesticides, negatively influences birth outcomes. However, the effects of low-level exposure to polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and dioxin-like PCBs (DL-PCBs) on birth outcomes have not been clarified in human studies.

A prospective cohort study was established to investigate the possible adverse effects of PCDDs/PCDFs and DL-PCBs on fetal growth and neurodevelopment. We recruited 514 pregnant women between July 2002 and October 2005 in Sapporo, Japan. We measured 29 congener levels of PCDDs/PCDFs and DL-PCBs in maternal blood.

Using multiple liner regression analysis of the association between birth weight and the levels of PCDDs/PCDFs and DL-PCBs with full adjustments for potential confounders, a significant adverse effect was observed regarding total PCDDs toxic equivalents (TEQ) levels (adjusted $\beta = -231.5$ g, 95% CI: -417.4 to -45.6) and total PCDFs TEQ levels (adjusted $\beta = -258.8$ g, 95% CI: -445.7 to -71.8). Among male infants, significant adverse associations with birth weight were found for total PCDDs TEQ level, total PCDDs/PCDFs TEQ level, and total TEQ level. However, among female infants, these significant adverse associations were not found. With regard to individual congeners of PCDDs/PCDFs and DL-PCBs, we found significantly negative association with the levels of 2,3,4,7,8-PeCDF (adjusted $\beta = -24.5$ g, 95% CI: -387.4 to -61.5).

Our findings suggest that prenatal low-level exposure to PCDDs and PCDFs, especially 2,3,4,7,8-PeCDF, may accumulate in the placenta and retard important placental functions, which result in lower birth weight.

1. Introduction

Polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and polychlorinated biphenyls (PCBs) are highly toxic compounds that have become distributed in all environments worldwide. These compounds may have numerous adverse health effects, including growth retardation in fetuses and infants, neurodevelopmental dysfunction, thyroid deficiency, immune deficiency, reproductive effects, and cancer (Brouwer et al., 1999; Rogan and Ragan, 2003; Schantz et al., 2003; Toft et al., 2004). One of the most significant concerns regarding health effects is the harmful influence of PCBs and PCDDs/PCDFs on future generations, stemming from prenatal and/or postnatal exposure. Pregnant and nursing women pass these pollutants to their babies both trans-placentally and lactationally (Suzuki et al., 2005; Wang et al., 2004).

Abbreviations: DL-PCBs, dioxin-like polychlorinated biphenyls; HRGC/HRMS, high-resolution gas chromatography/high-resolution mass spectrometry; LBW, low birth weight; LOD, limit of detection; Mono-ortho PCBs, mono-ortho coplanar polychlorinated biphenyls; Non-ortho PCBs, non-ortho coplanar polychlorinated biphenyls; OCDD, octachlorodibenzo-*p*-dioxin; OCDF, octachlorodibenzofuran; PCBs, polychlorinated biphenyls; PCDDs, polychlorinated dibenzo-*p*-dioxins; PCDFs, polychlorinated dibenzofurans; TEF, toxic equivalency factor; TEQ, toxic equivalents

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Human trans-placental exposure to high-levels of PCBs and PCDFs is certainly neurotoxic. Yusho and Yu-cheng children, who were trans-placentally exposed to PCBs and PCDFs from rice oil incidents in Japan and Taiwan, displayed growth retardation, delayed cognitive development, and behavioral problems (Rogan et al., 1988; Guo et al., 2004). Moreover, they exhibited a higher proportion of low birth weight (LBW) and premature births than those of the control population (Yamashita and Hayashi, 1985; Yen et al., 1994).

Dozens of studies concerning low-level exposure to these contaminants in recent years have primarily looked at organochlorine pesticides and PCBs, but there are very few studies on prenatal exposure to PCDDs/PCDFs and dioxin-like PCBs (DL-PCBs) exposure. Several studies of lower-level PCBs exposure during pregnancy observed associations with decreased birth weight and other growth parameters (Fein et al., 1984; Rylander et al., 1996, 1998; Patandin et al., 1998; Karmaus and Zhu, 2004; Hertz-Picciotto et al., 2005; Sagiv et al., 2007; Sonneborn et al., 2008). In the Lake Michigan fish consumer study, cord serum PCBs levels predicted LBW and smaller birth head circumference (Fein et al., 1984). Furthermore, in the Netherlands general population study, both cord and maternal plasma PCBs levels were negatively associated with birth weight (Patandin et al., 1998). However, these associations have not been demonstrated in other studies (Rogan et al., 1986; Dar et al., 1992; Grandjean et al., 2001; Longnecker et al., 2005; Weisskopf et al., 2005; Baibergenova et al., 2003). Higher PCBs exposure correlated with higher birth weight in fish consumers from the Green Bay, Wisconsin, area (Dar et al., 1992). Moreover, the US Collaborative Perinatal Project study found that maternal PCBs levels during pregnancy were essentially unrelated to premature birth, birth weight, or length of gestation, although an association of PCBs with SGA birth was observed (Longnecker et al., 2005). Thus, consistent results regarding the influence of prenatal low-level exposure to PCBs on birth outcomes have not been obtained.

The influence of low-level exposure to PCDDs/PCDFs and DL-PCBs on birth size has not been reported as frequently as exposure to organochlorine pesticides and PCBs. A Finnish study reported that birth weight, especially of boys, correlated negatively with TEQ levels of PCDDs/PCDFs in breast milk (Vartiainen et al., 1998). Another recent study examining the effects of individual congeners of PCDDs/PCDFs and DL-PCBs on birth weight reported that only OCDD levels in breast milk had a significant negative correlation (Tajimi et al., 2005). However, there were no significant relationships between birth weight and PCDDs/PCDFs congeners in maternal breast milk (Nishijo et al., 2008). Thus, reported results on the relationship between birth weight and the levels of PCDDs/PCDFs and DL-PCBs are currently limited and inconsistent. Furthermore, some studies have reported a difference between genders with regard to the effects of PCBs and PCDDs/PCDFs on birth outcomes (Rylander et al., 1996; Baibergenova et al., 2003; Sonneborn et al., 2008; Hertz-Picciotto et al., 2005; Vartiainen et al., 1998).

Taking the above considerations into account, the aim of the present study was to examine the influence of low-level PCDDs/PCDFs and DL-PCBs on birth weight, and also identified which individual congeners of PCDDs/PCDFs and DL-PCBs have harmful effects on birth weight.

2. Materials and methods

2.1. Study, subjects, and data collection

In 2002, the Hokkaido University Graduate School of Medicine established a hospital-based prospective cohort study entitled the "Hokkaido Study on Environment and Children's Health" to investigate the possible adverse effects of PCBs, PCDDs/PCDFs, perfluorinated chemicals, and many other environmental contaminants on fetal growth and neurodevelopment (Sasaki et al., 2006, 2008; Nakajima et al., 2006; Washino et al., 2009). This birth cohort study is based on the inborn infants delivered at the Sapporo Toho Hospital in Sapporo, Hokkaido, Japan, which is an obstetrics and gynecology hospital and treated the largest number of deliveries in Sapporo City. Between July 2002 and October 2005, we approached pregnant women who were between the 23rd and 35th weeks of gestation, and no serious illness or any other medical complications. All potential subjects were native Japanese living in Sapporo and the surrounding industrialized areas. The following were exclusion criteria for study subjects: the women had incomplete partner's information, the women had decided to enroll in the Japanese cord blood bank (22% of those of approached), or the women decided to deliver the baby at another hospital (3% of those of approached). Some of the women we approached did not express interest in our study, and some were unable or unwilling to participate in this study. Ultimately, 514 pregnant women (30% of those approached) were enrolled in this cohort study. All of these women have been taking medical examination during pregnancy at the hospital. This study was conducted after all participating women provided written informed consent and was approved by the institutional ethical board for epidemiological studies at the Hokkaido University Graduate School of Medicine.

The self-administered questionnaire survey provided us with potential confounding variables in relation to the past medical history of the mothers and their partners, demographic characteristics, health status during pregnancy, smoking habits (including environmental tobacco smoke), educational level, economic status, work history during pregnancy, dietary intake during pregnancy (including inshore fish and deep-sea fish), caffeine intake, alcohol intake, and exposure to chemical compounds in their daily life. For estimating caffeine and alcohol intake, we used the modified self-administered questionnaire described by Nagata et al. (1998). Dietary intake during pregnancy was obtained from the food frequency questionnaire, which is divided into five categories: never, 1–2 times/month, 1–2 times/week, 3–4 times/week, or almost every day. With regard to maternal smoking habits during pregnancy, 21% of the women quit smoking in the first trimester and most of them quit smoking before 10 weeks of gestation, which is quite soon after cognition of their pregnancy. Therefore, the women who quit smoking in the first trimester were included in the group of non-smokers. Maternal smoking status during pregnancy was categorized into two groups: women who were non-smokers during pregnancy and those who quit smoking during the first trimester (non-smoking group), and women who smoked during pregnancy and those who quit smoking after the first trimester (smoking group).

Maternal and infant medical information, including multiple births, infant gender, gestational age, birth weight, birth length, birth head circumference, maternal age, maternal height, maternal weight before pregnancy, parity, and medical history during pregnancy, were collected from their medical records at the hospital.

2.2. Exposure measures

Analyses of PCDDs/PCDFs and DL-PCBs were performed according to a previously published method (Iida and Todaka, 2003; Todaka et al., 2003). Briefly, a 40-ml blood sample was taken from the maternal peripheral vein at the time of the next prenatal hospital examination after recruitment. If we were not able to take the blood during pregnancy due to maternal anemia, we took the blood during hospitalization within a week after delivery. All samples were stored at −80 °C until analysis. The levels of PCDDs/PCDFs and DL-PCBs in the maternal blood samples were measured using high-resolution gas chromatography/high-resolution mass spectrometry (HRGC/HRMS) equipped with a solvent-cut large-volume injection system (SGE Ltd., Victoria, Australia) at Fukuoka Institute of Health and Environmental Sciences. The gas chromatograph was an Agilent 6890 (Agilent Technologies Inc., Palo Alto, CA, USA) equipped with an AutoSpecUltima NT (Micromass Ltd., Manchester, UK). Specific congeners of seven PCDDs, ten PCDFs, four non-ortho PCBs, and eight mono-ortho PCBs were analyzed. The World Health Organization (WHO) toxic equivalent factor approach was used to express the toxic potency of the mixture of PCDDs, PCDFs, non-ortho PCBs, and mono-ortho PCBs. The TEQ levels were calculated by multiplying the levels of individual congeners by its toxic equivalency factor (TEF) values of WHO 1998 (Van den Berg et al., 1998) and WHO 2006 (Van den Berg et al., 2006). We measured the levels of PCDDs/PCDFs and DL-PCBs in 426 maternal blood samples. The remaining maternal blood samples in this study were not analyzed because they were not available or lacked sufficient blood volume for the measurement. One mother's sample was excluded from the study because the PCDFs levels were extremely high. The blood sampling period was categorized into four groups: 23–31 weeks of gestation, 32–34 weeks of gestation, 35–41 weeks of gestation, within a week after delivery.

2.3. Data analysis and statistical methods

Ten registered women were lost from the study due to miscarriage, stillbirth, removal before delivery, or dropping out from the study at the beginning of the follow-up period. The following subjects were excluded from analysis: those with