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Maternal exposure to high levels of dioxins in relation to birth weight in women affected by Yusho disease ☆

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ABSTRACT

Background: Studies on the association of maternal exposure to polychlorinated dibenzo-*p*-dioxin (PCDDs), polychlorinated dibenzofurans (PCDFs), and polychlorinated biphenyls (PCBs) with decreased birth weight in humans have produced conflicting results. In Japan in 1968, an accidental human exposure to rice oil contaminated with PCDDs, PCDFs, and PCBs, led to the development of Yusho disease.
Objective: The Yusho cohort was used to evaluate the effect of maternal exposure to PCDDs, PCDFs, and PCBs on birth weight.
Methods: Blood samples, obtained from 101 Yusho women (190 births) who gave birth after exposure, were analyzed for congeners of seven PCDDs, ten PCDFs, and four non-*ortho* PCBs.
Results: Total PCDD TEQ (adjusted beta = −161.9 g; 95% CI, −265.3 to −58.6), total PCDF TEQ (adjusted beta = −105.9 g; 95% CI, −179.5 to −32.2), and total non-*ortho* PCBs (adjusted beta = −178.4 g; 95% CI, −318.3 to −38.5) levels were inversely associated with birth weight. Significant inverse associations with birth weight were also found for total PCDD TEQ, total PCDF TEQ, and total non-*ortho* PCB TEQ levels among male, but not female, infants. Significant inverse associations with birth weight were also found for nine congeners among all infants; the adjusted beta coefficients were largest for 1,2,3,6,7,8-HxCDD and smallest for 2,3,4,7,8-PeCDF.
Conclusion: In the setting of exposure to high levels of dioxins, maternal blood levels of PCDDs, PCDFs and PCBs are associated with lower birth weight in Yusho patients. The association exhibited gender-specific differences, as male infants are more susceptible than females to growth restriction induced by *in utero* dioxin exposures.

1. Introduction

Polychlorinated dibenzo-*p*-dioxin (PCDDs), polychlorinated dibenzofurans (PCDFs), and dioxin-like polychlorinated biphenyls (PCBs) are highly toxic compounds that are widespread in the environment. Several human studies have suggested that maternal exposure to PCDDs, PCDFs, and PCBs may affect fetal growth and infant development (Rogan et al., 1988; Rylander et al., 2000). Birth weight is considered a predictor of a variety of adverse developments in childhood and beyond, including poor school performance (Weindrich et al., 2003), high blood pressure (Law et al., 2002) and cardiovascular diseases (Barker, 2002; Barker et al., 2009). Thus, it is important to assess whether exposure to PCDDs, PCDFs, and PCBs contributes to reduced birth weight.

Several studies of low-level exposure to dioxins during pregnancy have found associations with decreased birth weight (Fein et al., 1984; Hertz-Picciotto et al., 2005; Konishi et al., 2009; Patandin et al., 1998; Sagiv et al., 2007; Sonneborn et al., 2008; Tajimi et al., 2005; Vartiainen et al., 1998). In a general population study in the Netherlands, the birth weight of 207 infants negatively correlated with plasma PCB levels of both maternal blood (range 0.59–7.35 μg/l) and cord blood (range 0.08–2.08 μg/l) (Patandin et al., 1998). A Japanese study reported that the birth weight of 514 infants

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was negatively associated with the maternal blood toxic equivalent (TEQ) levels of total PCDDs (range 1.7–29.3 TEQ pg/g lipid) and total PCDFs (range 0.6–7.8 TEQ pg/g lipid) (Konishi et al., 2009). However, these associations have not been demonstrated in other studies (Longnecker et al., 2005; Nishijo et al., 2008: Rogan et al., 1986; Tawara et al., 2009; Weisskopf et al., 2005). Moreover, some studies have reported gender-specific differences (Hertz-Picciotto et al., 2005; Konishi et al., 2009; Sonneborn et al., 2008; Vartiainen et al., 1998). Thus, the controversy over whether maternal exposure to polychlorinated organic compounds is associated with decreased birth weight in humans continues.

Although few studies have evaluated groups with high levels of exposure, they are particularly informative with regard to the association between maternal exposure to PCDDs, PCDFs, and PCBs and birth weight. In Western Japan in 1968, an accidental human exposure to rice oil contaminated with PCBs led to the development of what was later referred to as Yusho oil disease (Kunita et al., 1985). It was later discovered that the rice oil had also been contaminated with PCDFs and PCDDs (Furue et al., 2005). PCDFs, now considered the primary causative agent of Yusho, have also been implicated in the Yu-cheng incident in central Taiwan in 1979 (Furue et al., 2005; Masuda et al., 1985). Over 1900 people have been diagnosed with Yusho.

We have reported that Yusho women have had a higher proportion of spontaneous abortions, preterm deliveries, and pregnancy losses (Tsukimori et al., 2008). This study demonstrated a significant relationship between these adverse pregnancy outcomes and the estimated blood concentrations of PCDFs and PCBs at the time of pregnancy. Low birth weight Yusho children have also been born to exposed mothers (Yamashita and Hayashi, 1985), and Yu-cheng children exhibited a higher proportion of low birth weights than those in a control population (Rogan et al., 1988; Yen et al., 1994). However, the association between birth weight and level of maternal exposure to dioxins in Yusho or Yu-cheng women has not been studied.

The aim of this study was to investigate the association between birth weight and maternal exposure levels of PCDDs, PCDFs, and PCBs in Yusho patients, and to identify which individual congeners of these compounds have harmful effects on birth weight.

2. Materials and methods

2.1. Subjects

A nationwide health examination of Yusho survivors has been conducted annually since 1986. Its purpose is to provide health maintenance services to, and monitor the health status of, chronic Yusho patients (Hirota et al., 1996). The examination is open not only to officially registered Yusho patients, but also to those who regard themselves as potential victims. The serum dioxin-related compound levels were also measured as part of the examination. Blood samples of participants who were willing to have their dioxin levels measured were collected beginning in 2001. As of April 2009, the Study Group for Yusho had registered 737 women based on signs and symptoms of the illness, a history of consumption of contaminated oil, or the composition and concentration of blood PCBs and polychlorinated quarterphenyls (PCQs). In April 2009, the Study Group for Yusho obtained data on the health status of Yusho patients from mailed questionnaires. Questions about maternal and infant outcomes addressed parity, maternal age at delivery, date of delivery, gestational age at delivery, birth weight, infant gender, smoking status during pregnancy and age at interview. Date of delivery, gestational age at delivery and birth weight were collected from the record of pregnancy care (maternity health record book) provided by each patient. Of the 737 officially registered Yusho patients, 581 (78.8%) answered the questionnaires, 206 of which had given birth after the Yusho incident. Of the 206 women, 104 (50.5%) had their dioxin levels measured. Three women who gave incomplete information on maternal and infant outcomes were excluded. Therefore, 101 of registered patients (49.0%) were eligible for participation. These 101 subjects had a total of 190 births following the Yusho incident. The study design (No. 20–58) was approved by the Institutional Ethics Committee, and informed consent was obtained from all subjects prior to the study.

2.2. Analysis of PCDDs, PCDFs and non-ortho PCBs

Analyses of PCDDs, PCDFs and non-*ortho* PCBs were performed according to a previously published method (Iida and Todaka, 2003; Todaka et al., 2007). Briefly, 10 ml blood samples were collected using a vacuum blood-collecting tube containing heparin and stored at 4 °C. PCDD, PCDF and non-*ortho* PCB levels in the 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, and four non-*ortho* PCBs were analyzed.

Table 1
Characteristics of study subjects.

Characteristics	Number (%)
Mothers	101 (100)
Age at exposure (years)	
Prenatal	4 (4.0)
0–10	25 (24.8)
11–20	37 (36.6)
21–35	35 (34.6)
Age at blood sampling (years)	54.2 ± 9.3 (32–75)[a]
Date of blood sampling (years)	2006 (2002–2008)[b]
Number of birth	
1	36 (35.6)
2	48 (47.5)
3	12 (11.9)
4	3 (3.0)
5	2 (2.0)
Breast fed their children	59 (58.4)
Duration of breast feeding (years)	1.93 ± 1.36 (0.1–6)[a]
Frequency of seafood consumption	
Every day	18 (17.8)
3–4 Times/week	42 (41.6)
1–2 Times/week	37 (36.6)
1–2 Times/month	4 (4.0)
Almost never	0 (0)
Age at delivery (years)	28.4 ± 4.3 (18–41)[a]
Date of delivery (year)	
1968–1977	82 (43.2)
1978–1988	61 (32.1)
1988–1997	38 (20.0)
1998–2006	9 (4.7)
Interval between delivery and blood sampling (years)	25.8 ± 9.1 (0–38)[a]
Maternal smoking status during pregnancy	
Non-smoking	93 (92.1)
Smoking	8 (7.9)
Infants	190 (100)
Gestational age at delivery (weeks)	39.1 ± 1.1 (32–42)[a]
Preterm birth	6 (3.2)
Term birth	184 (96.8)
Birth weight (g)	3024 ± 403 (1900–4000)[a]
<2500	17 (8.9)
>=2500	173 (91.3)
Gender	
Male	109 (57.4)
Female	81 (42.6)

[a] Mean ± SD (range).
[b] Median (range).