3と4)。

D. 考察

今回、妊娠中の母親から得られた母体血、さらに臍帯血と胎盤中の鉛濃度をモニタリングした。その結果、これまでに報告されている諸外国および過去の日本人の血中濃度と比べて、鉛濃度は低いことが改めて明らかとなった。

重金属については、胎盤が障壁となって胎児側への以降を妨げる防御系として機能することが知られ、金属結合タンパク質であるメタロチオネインなどの関与が報告されている。しかしながら、メタロチオネインは鉛との結合能がなく、胎盤についても鉛に対する防御系として機能しないとも考えられている。実際に、本研究でも臍帯血中鉛濃度は、母体血中の濃度と比べ若干低い値を示しているものの、カドミウムの場合になどに比較して、その濃度差は極めて僅かであり、鉛は胎盤を通過し胎児側へ移行していることが本研究でも示唆された。。

次に、タバコの葉には鉛が含まれていることから、喫煙者は血中鉛濃度が高いことが知られている。親の喫煙の影響により、受動喫煙で幼児の血中鉛濃度が高くなることも報告されている(加治正行ほか、わが国の小児の血中鉛濃度、受動喫煙の影響、日本小児科学会雑誌、101:1583-1587、1997;Ballew et al. Blood leadconcentration and children's anthropometric dimensions in the Third National Healthand Nutrition Examination Survey, 1988-1994. J Pediatr. 134: 623-630、1999など)。従って、妊娠中の母親の喫煙による胎児期の鉛曝露影響が懸念された。しかしながら、今回の対象者では、喫煙者の血中鉛濃度(母体血)も臍帯血中の鉛濃度も非喫煙者に比べ、高い値は示さなかった。

鉛中毒の臨床症状は、成人では血中0.8 ppm (800 ng/ml) 以下ならば出現しないとされているが、ヘム合成に関与する酵素のδ-アミノレブリン酸デヒドロゲナーゼの阻害作用は、さらに低レベルでも起こると言われている。本研究では最高15 ng/ml程度の血中鉛が観察されており、低濃度の鉛曝露についても今後注意深く見ていく必要もあるものと思われた。

低濃度曝露における鉛曝露経路については、必ずしも明らかではない。本調査では食物摂取頻度調査を行っており、摂取した食物との関連性について解析を予定している。鉛分析について今後も例数を追加し、健康影響指標、児の心理調査結果等との関連についても調査を進める必要があると考えられた。

E. 結論

本研究において、母体血、臍帯血および胎盤中の鉛濃度の測定方法の確立を行い、少数ながら分析を終えた。その結果、今回の対象者は比較的低濃度の鉛曝露であることが明らかとなったが、低濃度の鉛曝露についても健康影響がでることも考えられるため、今後も分析対象者数を増やすなど更なる検討が必要であると考えられた。

F. 研究発表

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G. 知的所有権の取得状況

なし

Ⅳ. 研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表雑誌	巻名	ページ	出版年
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村田勝敬	妊婦は魚を食べない方がよいか	総合臨床	53	2750-2752	2004

V. 研究成果の刊行物・別刷

EFFECTS OF PERINATAL EXPOSURE TO ENVIRONMENTALLY PERSISTENT ORGANIC POLLUTANTS AND HEAVY METALS ON NEUROBEHAVIORAL DEVELOPMENT IN JAPANESE CHILDREN: IV. THYROID HORMONES AND NEONATAL NEUROBEHAVIORAL STATUS

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Introduction

From several epidemiological studies, it has been reported that there are some associations between perinatal exposures to PCBs, dioxins and heavy metals, and neurobehavioral defects such as postnatal growth delay and poorer cognitive function[1]. We have started a prospective cohort study to examine the effects of perinatal exposures to environmentally persistent organic pollutants on neurobehavioral development in Japanese children[2].

Thyroid hormones (THs) are essential for normal brain development. A lack of THs in pregnancy can result in congenital hypothyroidism, which causes moderate to severe intellectual defects. It has been reported that perinatal exposure to PCBs adversely affects on children's intellectual functions. The chemical structures of some PCBs resembles thyroxine (T4), and therefore, it is suspected that the action mechanism of PCBs is disruption of TH function. Some PCBs and their metabolites are thought to bind with transthyretine (TTR)[3], which is necessary for the transfer of T4 into the brain, and this may cause a shortage of T4 in the developing brain. To examine the effects of perinatal exposure to PCBs on children's development, it is essential to evaluate the functions of THs at a fundamental level.

In this report, we examined the correlations of THs in maternal peripheral blood and cord blood, and the association between THs and neonatal neurobehavioral status.

Methods and Materials

The subjects of this study were 545 mother-infant pairs. Mean maternal age at the time of delivery was 31.40 (SD4.29). Mothers were recruited with their informed consent at obstetrical wards of two hospitals in Sendai, Japan. The infants consisted of 284 boys and 261 girls, and they were all singleton and born after full-term (36 to 42 weeks) gestation without congenital anomalies or diseases. Birth weight was 2500g or more. Information was obtained about pregnancy, delivery conditions and infant characteristics from their medical records. These protocols were described previously[2].

Maternal peripheral blood samples were collected at 28 weeks of pregnancy; umbilical cord blood samples were collected shortly after delivery. THs, including thyroid-stimulating hormone (TSH), total thyroxine (T4), triiodothyronine (T3), free T4 (FT4) and free T3 (FT3), were measured from plasma by SRL, Inc. (Tokyo, Japan), with the use of radioimmunoassay.

The Neonatal Behavioral Assessment scale (NBAS) was administrated three days after birth. Examiners of the NBAS were trained and certified to administer it at the Training Center for NBAS in the Nagasaki University School of Medicine in Japan. Reliability checks were conducted throughout data collection to maintain a 90% level of agreement.

In statistical analysis, we examined the correlations of THs between maternal and cord blood. Single regression analyses were performed to examine the associations between THs and the seven NBAS cluster scores. When significant associations were observed, multiple regression analyses were performed for controlling the effects of covariates, which included gender, birth weight, gestational age, Apager score 1 minute after delivery, maternal age at the time of delivery, delivery type, parity, alcohol drinking during pregnancy, smoking habit and NBAS examiners.

Results and Discussion

Figure 1 shows the distribution of THs in maternal and cord blood. T3 and T4 in both maternal and cord blood had almost normal distributions. FT3 and FT4 also showed similar distributions (data not shown). The concentration of TSH in the cord blood was about ten times higher than that of maternal blood (11.36 μU/ml in cord blood, 1.54 μU/ml in maternal blood).

There were some significant ($p<0.05$) correlations of THs between maternal and cord blood. Typical correlations are shown in Fig 2. There was a positive correlation between maternal T4 and cord T4, and a negative correlation between maternal TSH and cord FT4. There were no significant correlations of maternal TSH between cord blood TSH and T4.

Although TSH in maternal and cord blood had no significant association with any of the seven NBAS clusters, cord blood T3 and FT3 had significant positive correlations with the Orientation cluster (Fig 3). These remained significant after controlling for covariates. There were no significant associations of T4 and FT4 in maternal and cord blood with any of the NBAS clusters.

One possible hypothesis of the action mechanisms of persistent organic pollutants (POPs) is the disruption of thyroid function. The chemicals have been shown to alter the metabolism of THs in animal experiments[4]. Human data also suggested that background-level exposure to PCBs might have similar effects in newborns in the Netherlands[5], whereas no association between PCB exposure and the status of THs in cord blood was observed among North Carolina children[6]. Several studies have suggested an association of exposure to dioxin-like compounds with increased TSH in young children[7]. These reports suggest that exposure to POPs may disturb the hypothalamic-pituitary-thyroid regulatory system, and then affect the neurobehavioral status of children. In the present study, we examined the relationship between levels of THs and neonatal neurobehavioral status. Single regression analyses showed that there were several significant associations between THs and NBAS cluster scores. Although cord blood T3 and FT3 had significant positive correlations with the Orientation cluster, TSH, T4, and FT4 in the maternal and cord blood had no significant correlation with any of the NBAS cluster scores. These findings suggest that thyroid function is a modulator of the neurobehavioral status in newborns; however, the relation between chemical exposure and neonatal neurobehavioral awaits further investigation.

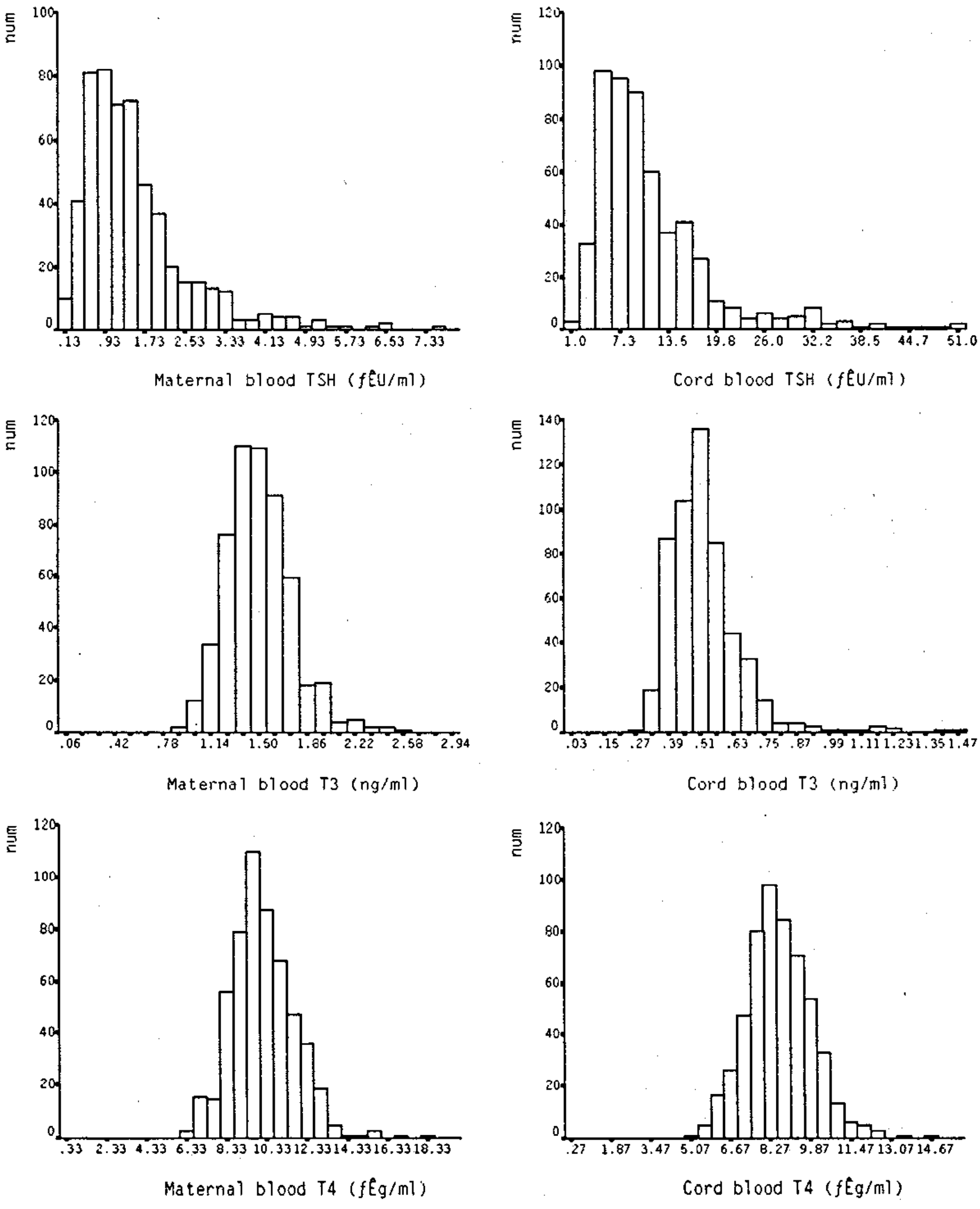

Fig 1. Population distributions of maternal blood and cord blood thyroid hormones

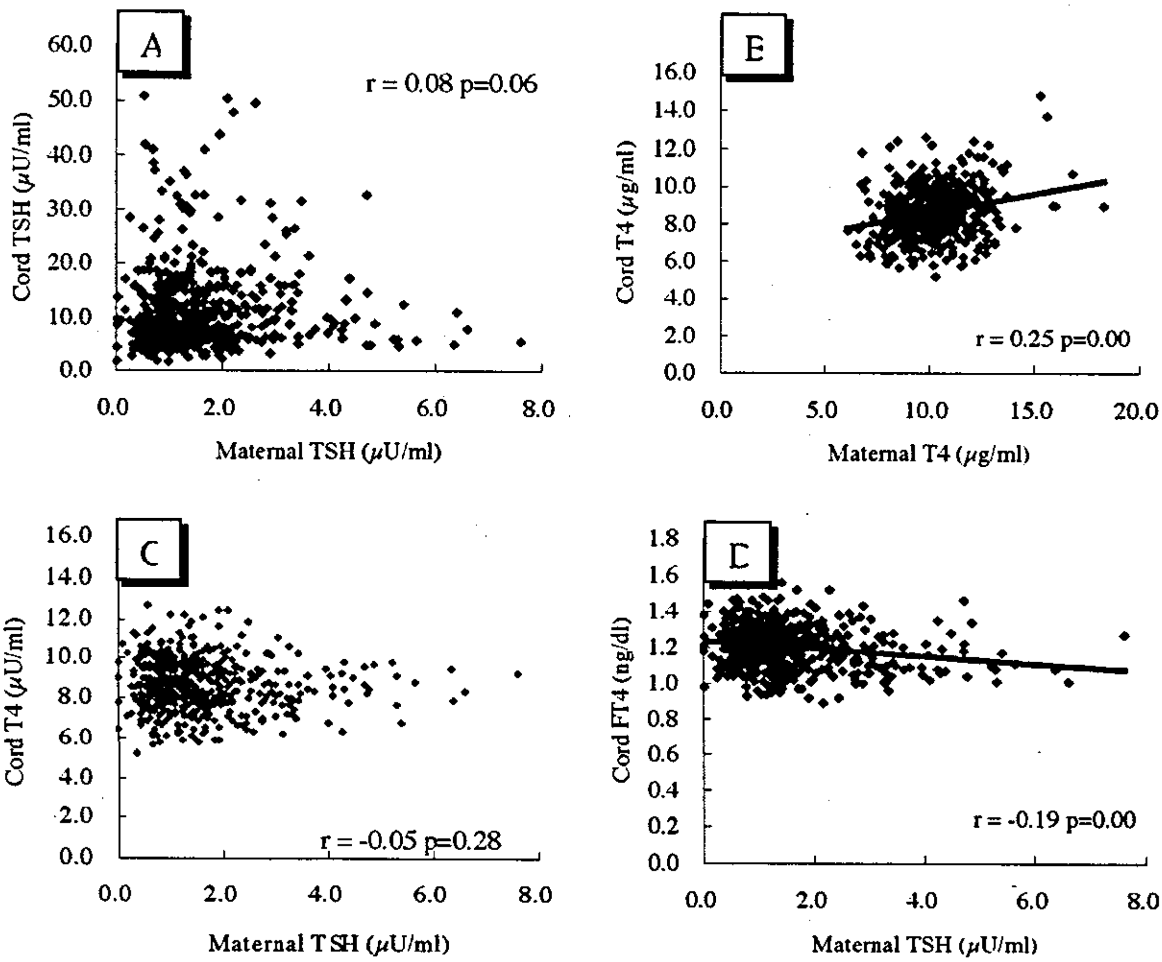

Fig 2. Correlations of thyroid hormones of maternal and cord blood

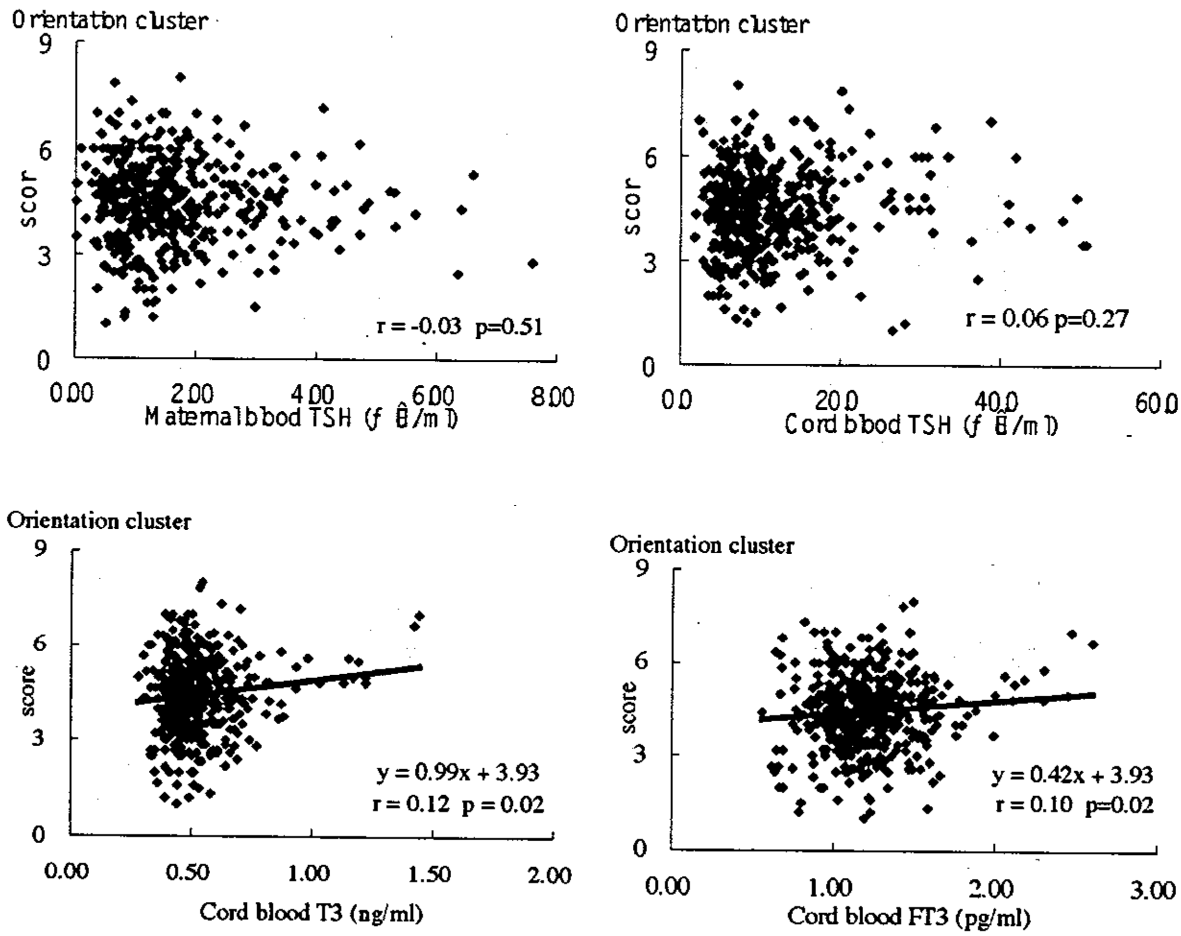

Fig 3. Associations of maternal/cord thyroid hormones with the Orientation cluster score of NBAS

Acknowledgments

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Organochlorine Pesticide Residues in Human Breast Milk and Placenta in Tohoku, Japan

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Introduction

Organochlorine pesticides are compounds widespread in the environment due to their persistence and highly lipophilic nature, and they accumulate in biological systems. Newborns are exposed to these organochlorine compounds across the placenta and through breastfeeding. Perinatal exposure to these compounds may induce several adverse effects such as lower birth weight [1], neurodevelopmental delay [2], and disturbance of thyroid hormone status [3]. DDT, especially, has been suggested to be a neuroendocrine disruptor as well as a functional teratogen in humans [4 5]. Other pesticides such as dieldrin and endosulfan were also recognized to have estrogenic hormonal activity in animal studies.

Recently, we have started a birth cohort study to examine the effects of exposure to persistent organochemical pollutants and heavy metals on neurodevelopment in Japanese children, The Tohoku Study of Child Development [6]. In this cohort study, biological samples, including maternal peripheral blood, cord blood, placenta, cord tissue, and breast milk have been collected from more than six hundred mother-infant pairs for chemical determinations. The growth of infants has been monitored using neurodevelopmental tests, including the Brazelton Neonatal Behavioral Assessment Scale, the Bayley Scale of Infant Development, the Kyoto Scale of Psychological Development, and others. Exposures to dioxin and related compounds, polychlorinated biphenyls, methylmercury, and several heavy metals were assessed. Additionally, since perinatal exposure to organochlorine pesticides may affect the neurodevelopment of children, we examined the effects of those pesticides in the cohort study.

In the present study, several organochlorine pesticides were analyzed in human breast milk and placenta from 20 mothers to identify the major pesticide compounds found in the cohort subjects. The relationship between pesticides in breast milk and the placenta was analyzed to examine the utilization of the placenta as the material for exposure assessment. Some information regarding the factors affecting the contamination of breast milk and the placenta with organochlorine pesticides are also discussed.

Methods and Materials

This study was performed as part of our prospective cohort study [6]. Healthy pregnant women were recruited with their informed consent at obstetrical wards of two hospitals in Tohoku between January 2001 and September 2003. Twenty subjects were randomly selected from the registered subjects of the cohort study, and pairs of breast milk samples and placenta samples were used. The ages of mothers ranged from 21 to 39. The placenta was taken immediately after the delivery, and divided into 20-30 pieces that were randomly separated into 4 groups. Each bottle contained 50-100 g of tissue. The representative samples were finally prepared by homogenization. The mothers were asked to provide breast milk one month after the delivery. The breast milk sample was taken directly into a clean glass bottle. These samples were frozen at –80°C until analysis. Each mother completed a questionnaire to provide personal information such as the number of births, smoking, alcohol consumption during pregnancy, occupation, educational background, food intake, and place of residence. The study protocol was approved by the Medical Ethics Committee of the Tohoku University Graduate School of Medicine.

The pesticides examined were hexachlorobenzene (HCB), α-hexachlorocyclohexane (HCH), β-HCH, γ-HCH, δ-HCH, cis-chlordane, trans-chlordane, oxy-chlordane, cis-nonachlor, trans-nonachlor, p,p'-DDT, o,p'-DDT, p,p'-DDE, o,p'-DDE, p,p'-DDD, o,p'-DDD, aldrin, endrin, dieldrin, α-endosulfun, β-endosulfun, heptachlor, heptachlorepoxide, and methoxychlor. Gas chromatographic determination of these organochlorine pesticides was performed with the collaboration of SRL, Inc. (Tokyo, Japan) for sample extraction and Toray Research Center (Tokyo, Japan) for gas chromatography. Briefly, after the samples were spiked with $^{13}C_6$-HCB, $^{13}C_6$-β-HCH, $^{13}C_{12}$-p,p'-DDT, $^{13}C_{12}$-endosulfun, and $^{13}C_{10}$-chlordane, they were extracted with ethanol/hexane. The organic extracts were finally purified with the use of a Florisil column, and the eluates were concentrated and spiked with $^{13}C_{12}$-pentaPCB(#118). A mass spectrometer (AutoSpec, Micromass) coupled to a Hewlett-Packard model HP6800 capillary gas chromatograph equipped with a capillary column (BPX-35, 0.25 mm ID x 25 m, film thickness 0.33 μm, SGE) was used for determination of pesticides. Residue levels were expressed as ng/g extracted fat.

Results and Discussion

HCB, β-HCH, oxy-chlordane, cis-nonachlor, trans-nonachlor, p,p'-DDT, p,p'-DDE, dieldrin, and heptachlorepoxide were found from all breast milk samples and placenta samples as shown in Table 1, whereas levels of α-HCH, γ-HCH, δ-HCH, cis-chlordane, trans-chlordane, o,p'-DDT, o,p'-DDE, p,p'-DDD, o,p'-DDD, aldrin, endrin, α-endosulfun, β-endosulfun, heptachlor, and methoxychlor were very low or below the detection limit (data not shown). Since using of these organochlorine compounds had been prohibited in the field in the 1970-1980s in Japan, these results reconfirmed their environmentally persistent nature. In Japan, the concentrations of PCBs, β-HCH, and DDTs in breast milk declined gradually from the peak levels observed at the mid-1970s and almost reached equilibrium states [7]. However, it remains to be elucidated whether the current low levels of organochlorine pesticides affect the neurodevelopment of children.

The concentration of organochlorine pesticides in breast milk mainly depends on their accumulation in the maternal fatty tissue and their subsequent mobilization. Indeed, numerous studies around the world have used human breast milk samples to determine maternal body burden and lactational transfer of pesticides to infants. Since there were excellent correlations of all major pesticides between breast milk samples and placenta samples (Table 1, and the two typical relationships in Fig. 1), placenta is also suggested to be the useful material to estimate the maternal body burden. In addition, the concentrations of some organochlorine pesticides such as HCB, oxy-chlordane, and trans-nonachlor, in the placenta samples had significant negative correlations with parity (Table 2). This finding clearly shows that the mothers eliminate these pesticides during pregnancy and by breastfeeding them into their children. Considering that the concentration of pesticides in breast milk samples had no significant correlation with parity, monitoring of the placental pesticide concentration may contribute to determining the prenatal exposure of infants to organochlorine pesticides. The placenta is a relatively large organ, and is usually discarded after delivery. Utilization of the placenta is possibly suggested for the purpose of assessment of exposure to chemicals.

Table 1: Organochlorine pesticide concentrations in the human milk samples and placenta samples, and the relationship between the 2 samples.

Pesticide	Milk (ng/g-fat)	Placenta (ng/g-fat)	Correlation Coefficient Milk x Placenta
Hexachlorobenzene	17.1±10.1	9.9±4.1	0.693**
β-HCH	83.4±55.1	21.5±12.6	0.919**
oxy-Chlordane	7.2±3.4	2.3±0.9	0.644**
cis-Nonachlor	3.7±1.7	0.8±0.4	0.589**
trans-Nonachlor	18.8±8.6	3.8±2.2	0.679**
p.p'-DDT	6.2±3.5	1.4±0.6	0.746**
p.p'-DDE	142.3±73.5	46.0±34.6	0.569**
Dieldrin	5.0±3.6	1.7±1.1	0.808**
Heptachlorepoxide	3.7±1.4	1.4±0.3	0.881**

Spearman's correlation analysis, ** $p<0.01$, * $p<0.05$

Table 2: Correlation coefficient values of organochlorine pesticides with fish intake, maternal age at delivery, and parity.

Pesticide	Fish consumption Milk	Fish consumption Placenta	Maternal age Milk	Maternal age Placenta	Parity Milk	Parity Placenta
Hexachlorobenzene	0.023	-0.127	-0.421	-0.223	-0.429	-0.625**
β-HCH	0.064	0.034	0.244	0.375	0.025	-0.064
oxy-Chlordane	0.609**	0.515*	-0.208	0.033	-0.428	-0.521*
cis-Nonachlor	0.486*	0.356	-0.085	0.234	-0.093	-0.354
trans-Nonachlor	0.701**	0.475*	-0.133	0.155	-0.282	-0.471*
p.p'-DDT	0.341	0.267	-0.179	0.06	-0.053	0.089
p.p'-DDE	0.054	0.412	-0.165	0.169	-0.174	-0.131
Dieldrin	0.463*	0.518*	-0.109	0.004	0.12	0.033
Heptachlorepoxide	0.566**	0.711**	-0.185	-0.169	-0.054	-0.235

Spearman's correlation analysis, ** $p<0.01$, * $p<0.05$

Some organochlorine pesticides have been thought to be introduced to humans partly through the consumption of fish and related products [8]. The concentrations of oxy-chlordane, nonachlors, dieldrin, and heptachlorepoxide in breast milk samples and placenta samples were indeed correlated with fish consumption; however, HCB, HCH, and DDE had no association. These results indicated that the contribution of fish consumption to the intake of pesticides was dependent on the kind of pesticide. More information regarding risk analysis of pesticide intake is needed for risk management. Maternal age at the time of delivery and parity have been shown to be important factors affecting the concentration of pesticides in breast milk samples [8]. Although parity was a potent factor in our data (Table 2), maternal age had no significant relationship with the concentrations of pesticides in breast milk samples and placenta samples. However, since parity correlated significantly with maternal age (data not shown), multiple regression analysis should be performed to control for the effects of covariates. These issues, and identification of the factors affecting the contamination levels of organochlorine pesticides in breast milk and placenta will be readdressed when we increase the sample size.

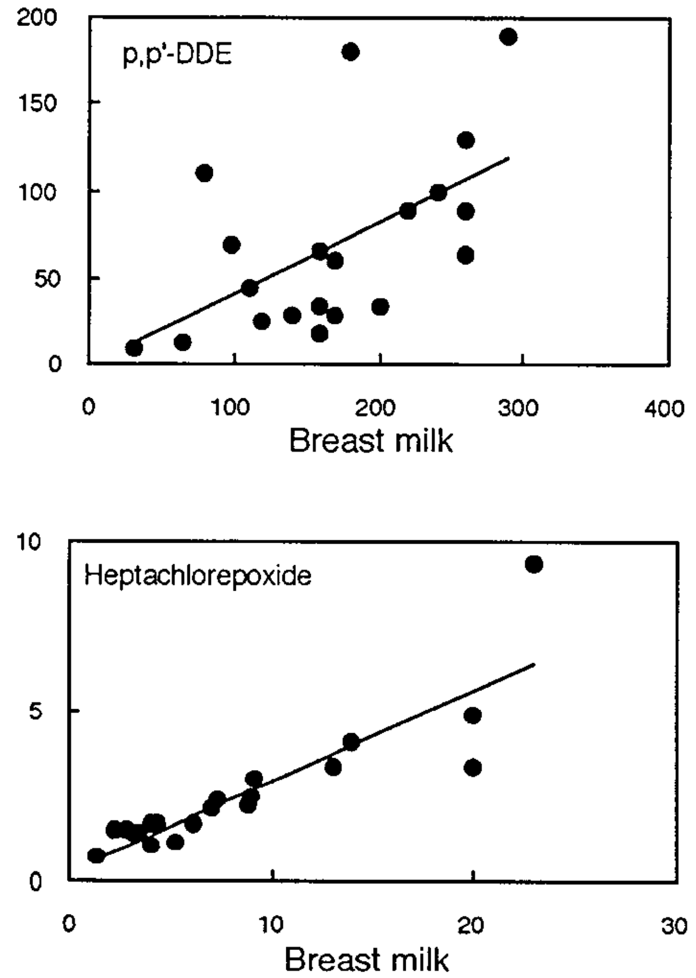

Fig. 1.: Relationship of p,p'-DDE (upper) and heptachlorepoxide (lower) between breast milk and placenta. ng/g-fat, N=20.

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A Cohort Study of Effects of Perinatal Exposures to Methylmercury and Environmentally Persistent Organic Pollutants on Neurobehavioral Development in Japanese Children: Study design and status report

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Abstract: Adverse effects of perinatal exposures to methylmercury (MeHg) and environmentally persistent organic pollutants (POPs) have been apparent from several birth cohort studies, but little is known about the hazardous effects in Japanese, whose fish consumption is high. The present study was designed to examine the effects of perinatal exposures to MeHg, polychlorinated biphenyls (PCB), dioxins, pesticides, and other chemicals in Japanese children. Six hundred eighty-seven pregnant women were participated in this study with their written informed consent. Maternal peripheral blood, cord blood, cord tissue, placenta, and breast milk samples were collected for chemical analysis. Maternal hair was also taken for MeHg analysis. Infants born at full term were assessed by a battery of neurobehavioral tests. The children will be continuously followed up to ages 6-7. The results of this cohort study will allow us to evaluate associations between the neurobehavioral development of children and perinatal exposures to MeHg and environmentally POPs in Japan.

Key words: epidemiology, methylmercury, pregnant women

INTRODUCTION

The neurobehavioral effects of prenatal exposures to methylmercury (MeHg) and environmentally persistent organic pollutants (POPs) including polychlorinated biphenyls (PCBs), dioxins, and pesticides are of great concern worldwide (NAKAI, 2002). It was shown that prenatal MeHg exposure causes the delay of development of cognitive functions in Faroe Islands (GRANDJEAN, 1997), although studies conducted in the Seychelles showed the absence of toxic effects of prenatal exposures to MeHg (DAVIDSON, 1998). Several epidemiological studies have also shown the evidence of the adverse effects of perinatal PCB exposure on neurodevelopment.