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.

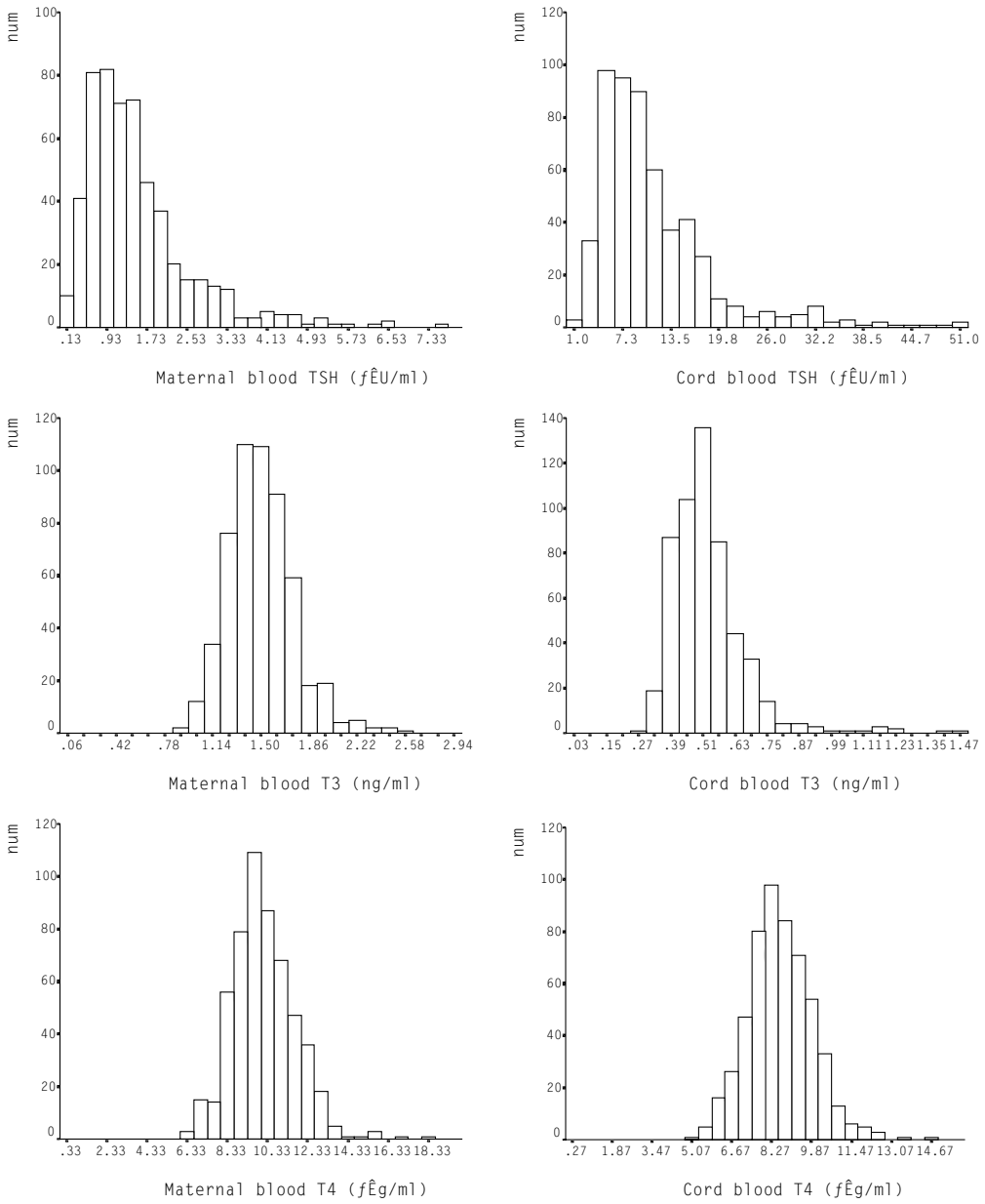

Fig 1. Population distributions of maternal blood and cord blood thyroid hormones

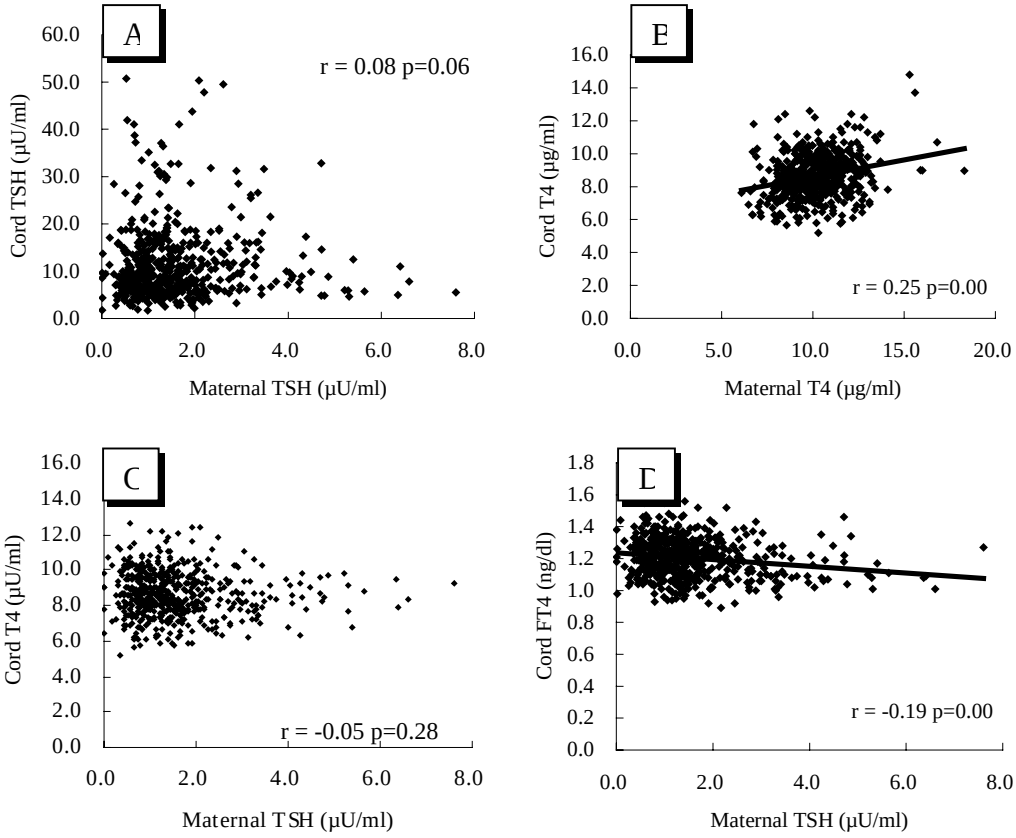

Fig 2. Correlations of thyroid hormones of maternal and cord blood

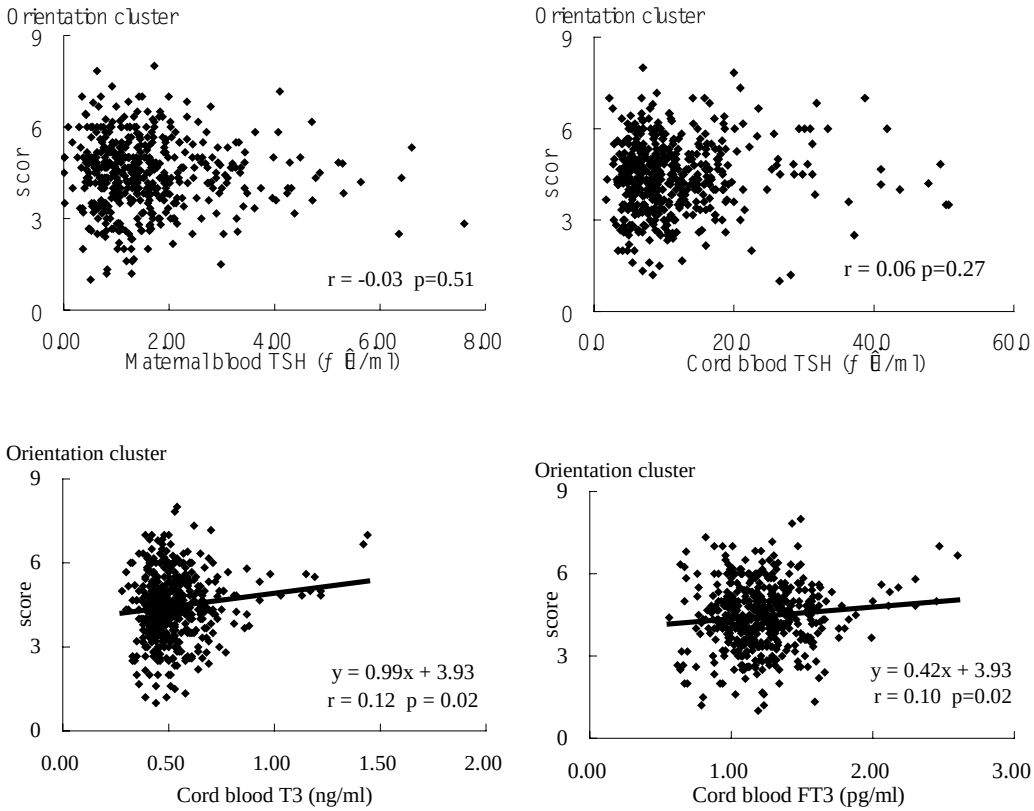

Fig 3. Associations of maternal/cord thyroid hormones with the Orientation cluster score of NBAS

Acknowledgments

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References

1. Nakai K, Satoh H. (2002) Tohoku J Exp Med 196: 89-98
2. Nakai K, Suzuki K, Oka T, Murata K, Sakamoto M, Okamura K, Hosokawa T, Sakai T, Nakamura T, Saito Y, Kurokawa N, Kameo S, Satoh H. (2004) Tohoku J Exp Med 202: 227-237
3. Porterfield S. (2000) Environ Health Perspect. 108: 433-438
4. Brouwer A, Longnecker MP, Brinbaum LS, Cogliano J, Kostyniak P, Moore J, Schantz S, Winneke G. (1999) Environ Health Perspect 107: 639-649.
5. Koopman-Esseboom C, Morse DC, Weisglas-Kuperus N, Lutkeschiplolt IJ, Van der Paauw CG, Tuinstra LG, Brouwer A, Sauer PJ. (1994) Pediatr Res 36(4): 468-473.
6. Longnecker MP, Gladen BC, Patterson DG Jr, Rogan WJ. (2000) Epidemiology 11(3): 239-241.
7. Hagmar L. (2003) Thyroid 13(11): 1021-1028.