ORIGINAL ARTICLE

Effects of maternal exposure to cadmium on pregnancy outcome and breast milk

M Nishijo, H Nakagawa, R Honda, K Tanebe, S Saito, H Teranishi, K Tawara

Occup Environ Med 2002;**59**:394–397

See end of article for authors' affiliations

Correspondent to: Dr M Nishijo, Department of Public Health, Kanazawa Medical University, 1–1, Daigaku, Uchinada, Ishikawa 920–0293, Japan; ni-koei@kanazawa-med.ac.jp

Accepted
17 October 2001

Objective: The effects of cadmium (Cd) on birth weight have been discussed in the scientific literature. However, investigations on the effects of maternal body burden of Cd on the next generation during pregnancy and lactation have been limited. The relation between maternal exposure to Cd and pregnancy outcome or Cd in breast milk in Japanese mothers was investigated.
Methods: Cd concentrations in urine and colostrum milk samples of 57 mothers were measured by atomic absorption spectrophotometery. The relations between maternal urinary Cd and infant growth, gestational age at birth, and Cd in breast milk were investigated.
Results: The rate of perterm deliveries of mothers with higher urinary Cd (≥2 nmol/mmol creatinine (Cr)) was higher than that of mothers with lower urinary Cd (<2 nmol/mmol Cr). The gestational age was significantly correlated with urinary Cd even after adjustment for maternal age. The height and weight of newborn infants of mothers with higher urinary Cd were significantly lower than those of the newborn infants of mothers with lower urinary Cd, but these decreases were ascribed to early delivery induced by Cd. The Cd in breast milk of mothers with higher urinary Cd was significantly higher than that of mothers with lower urinary Cd. A significant positive correlation was found between maternal urinary Cd and Cd in breast milk.
Conclusion: Maternal exposure to Cd seems to increase early delivery, which leads to a lower birth weight. Also, the Cd is transferred in part to the next generation through breast milk after birth.

Although the reproductive and developmental effects of environmental contaminants have become an issue of great interest recently, neither the female reproductive system nor fetus was considered a critical organ in previous studies on the effects of Cd on human health. In previous studies, the relations between the decreased birth weight of newborn infants and increased Cd concentrations in maternal blood or the placenta due to smoking were pointed out,[1 2] but no effects of Cd on pregnancy outcome or growth and development of infants were detected.[3 4] However, in a more recent report on pregnant women living in an area close to a copper smelter, it was suggested that exposure to lead and cadmium could promote the development of complications in pregnancy such as threatened spontaneous abortion, toxaemia, and anaemia, by increased lipid peroxidation.[5] Laudanski *et al* found that the mean blood concentration of Cd in mothers delivered of preterm infants was higher than that of women who went to full term in an area with high amounts of lead and cadmium in the soil.[6] Also, in an in vitro study of myometrial strips from pregnant women at term, the addition of a low concentration of Cd was found to enhance the contractile activity induced by Ca^{2+} and oxytocin.[7]

Moreover, breast milk is another route by which maternal exposure to Cd has an impact on neonatal infants, but no relation has been found between maternal exposure to Cd and the concentration of Cd in breast milk in previous European studies,[8 9] because of the low concentration of Cd in breast milk. However, a survey of Cd transport to breast milk in Japanese women might give different results, because the concentration of Cd in Japan is known to be higher than that in European countries.[10]

These unanswered questions promoted us to examine the effects of maternal body burden of Cd and the lactational transport of Cd on the next generation during pregnancy and lactation.

MATERIALS AND METHODS

Subjects

Fifty seven women, 58.1 % of all women who delivered infants of gestational age of more than 30 weeks at Toyama Medical Pharmaceutical University Hospital during 6 months, March to August 1999, and their infants were included in this study. The subjects who had enough breast milk to provide samples after feeding their babies, and were interested in their own concentration of Cd in breast milk, were recruited. There were no significant differences in gestational age and birth weight between the infants who took part in the present study and those who did not. The subjects were all Japanese living in the areas close to the hospital including the Jinzu River basin in Toyama which is polluted with Cd, where itai-itai disease, the most severe manifestation of chronic Cd poisoning, used to be found and is still being eliminated. Seventy five per cent of them were housewives whose most common job before marriage was office worker, and others were working as teachers, nurses, pharmacists, and office workers. No significantly different characteristics of socioeconomic status, nutrition, and health management, were found among them. They were not selected for prenatal or intrapartum medical problems. Informed consent for this study was obtained from the subjects in the appropriate manner.

Data collection

Information about occupational exposure to Cd, residence in an area polluted by Cd, and smoking were obtained with a questionnaire filled in by the study subjects themselves, and confirmed by maternity nurses during their stay in the hospital after delivery. Maternal urine and colostrum milk samples were collected into polypropylene tubes on the 5th postpartum day or 8th day in cases with delayed milk excretion because of caesarean section. The urinary and milk samples were frozen and stored at −20°C until analysis. The Cd concentration was measured with a flameless atomic absorption spectrophotometer (AAS; Hitachi Co, Japan, Model 180–

Table 1 Cadmium in breast milk and infant growth at birth according to concentration of maternal urinary cadmium

	Maternal urinary Cd	
	<2 μg/gCr	⩾2 μg/gCr
Subjects (n)	45	12
Maternal age (y, mean (SD))	28.5 (4.1)	33.0 (4.4)**
Nullipara (n (%))	25 (55.6)	4 (30.8)
Smoking habit (n (%))	6 (13.3)	2 (16.7)
Cd in breast milk (nmol/l, mean (SD))	2.8 (1.7)	4.6 (2.5)*
Gestational age (weeks, mean (SD))	39.1 (1.3)	37.0 (2.9)**
Infant growth at birth		
Height (cm, mean (SD))	49.2 (2.6)	47.2 (3.6)*
Weight (g, mean (SD))	3099 (432)	2663 (680)**
Head circumference (cm, mean (SD))	33.2 (1.2)	32.3 (2.1)
Chest circumference (cm, mean (SD))	32.1 (2.0)	31.4 (2.7)
Low birth weight infant (<2500 g, n (%))	3 (6.7)	5 (41.7)**
Small for date infant (n (%))	3 (6.7)	1 (8.3)
Early delivery (gestational age <38 weeks, n (%))	4 (8.9)	5 (41.7)*
Cesarean section (n (%))	4 (8.9)	7 (58.3)***

*p<0.05; **p<0.01; ***p<0.001 subjects with urinary Cd ⩾2 nmol/mmolCr *v* <2 nmol/mmolCr.

80). Urine samples were digested on HNO3/H2SO4/HClO4 and extracted with ammonium-pyrollidine-dithio-carbamate (APDC) (methyl-iso-butyl-ketone (MIBK) before Cd analysis. In breast milk Cd was also analyzed with a flameless atomic absorption spectrophotometer after digestion by $HNO_3/HClO_4$ and dilution with HNO_3. The measurements of urinary samples were corrected for the creatinine content of urine.

Statistical analysis

Student's *t* tests or a Welch's test and χ^2 tests were used in the analysis of data to find significant bivariate differences between groups with and without high urinary excretion. Multiple regression analysis was used to compute the partial correlation coefficient between maternal urinary Cd, birth weight, and gestational age, after adjusting for confounding factors of Cd exposure. These statistical analyses were all performed with the SPSS (version 10.0) package.

RESULTS

When the women were divided into two groups according to urinary Cd concentration, with the cut off point set at 2 nmol/mmol Cr, the rate of the subjects with high urinary Cd excretion (⩾2 nmol/mmolCr) was 21% (12 women). This cut off value was based on the result that a renal effect induced by Cd, 10% proteinuria, was found at 2 nmol/mmol Cr in environmentally exposed people in Belgium.[11]

The average age of the women with high urinary Cd was significantly higher than that of the women with lower urinary Cd (<2 nmol/mmolCr). However, there were no differences in smoking habits, including women who stopped smoking after becoming pregnant, or parity between these two groups according to maternal urinary Cd concentration. No woman had any occupational history of exposure to Cd, but five women had a history of living in the Jinzu River basin, an area environmentally polluted by Cd. However, there was no difference in the urinary Cd concentration between the women with and without a history of residence in the polluted area (table 1).

The mean gestational age at birth of the infants whose mothers showed a high urinary Cd excretion was lower than that of the infants of mothers with urinary Cd concentration below 2 nmol/mmol Cr. The height and weight at birth of the infants of mothers with higher urinary Cd concentration were significantly lower than those of the infants of mothers with lower urinary Cd. Similarly, the rates of low birth weight (less than 2500 g) or early delivery (gestational age at birth less than 38 weeks) of mothers with higher urinary Cd were significantly higher than those of mothers with lower urinary Cd. Also, a significant increase in the rate of delivery by caesarean section among mothers with higher urinary Cd was found compared with the mothers with lower urinary Cd. However, there was no difference in the rates of small for date infants between these two groups (table 1).

A significant negative correlation between maternal urinary Cd and weight, height, and gestational age at birth were found by simple correlation analysis (table 2). Multiple regression analysis was applied to find the partial correlation between urinary Cd and indices of infant growth or gestational age to adjust for maternal age which is strongly correlated with urinary Cd concentration (r=0.470, $p<0.001$). The results showed that the increase of urinary Cd was related to a decrease in gestational age after adjustment for maternal age (table 2). Although a partial correlation between urinary Cd and indices of infant growth to control for the maternal and gestational age was computed by multiple regression analysis, no significant correlation between them was found after adjustment for gestational age (table 2). Therefore, the

Table 2 Relations between infant growth and urinary cadmium after adjusting for maternal and gestational age

	Coefficient	Partial coefficient controlling for maternal age	Partial coefficient controlling for maternal and gestational age
Weight	–0.309*	–0.237	–0.015
Height	–0.252	–0.232	–0.015
Chest	–0.171	–0.110	0.089
Head	–0.133	–0.104	0.094
Gestational age	–0.369**	–0.339*	–

*p<0.05; **p<0.01.

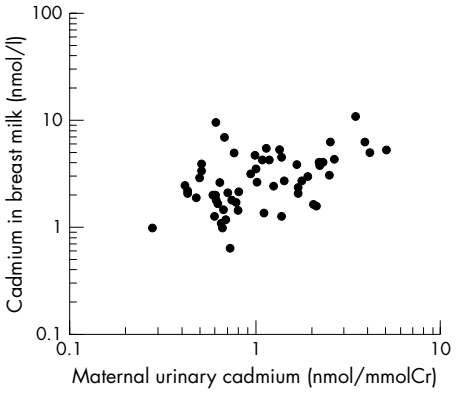

Figure 1 Correlation between maternal urinary Cd and Cd concentration in breast milk. Correlation coefficient = 0.472, p<0.001.

decreased birth weight was thought to be due to earlier delivery related to increased urinary Cd.

The mean Cd concentration of breast milk of mothers with a urinary Cd concentration more than 2 nmol/mmol Cr was significantly higher than that of those with a urinary Cd concentration below 2 nmol/mmol Cr (table 1). A significant positive correlation between Cd concentration in breast milk and maternal urinary Cd concentration was found in the correlation analysis, and Cd excretion into breast milk in proportion to maternal Cd body burden was found (fig 1). However, Cd concentration in breast milk did not show a significant correlation (r=0.160) with maternal age, which is highly related to urinary Cd concentration. At this time, there were no significant differences between Cd concentrations in breast milk of women with a first or subsequent infant, or between delivery with and without caesarean section. Although smoking is reported to cause an increase in Cd concentration in breast milk,[5] no significant difference in Cd concentration in breast milk was found between the subjects who did or did not smoke.

DISCUSSION

A lower birth weight in infants of mothers with higher urinary Cd excretion was found in the present survey compared with infants of mothers with lower urinary Cd. However, the relation between birth weight and urinary Cd was based on the relation between birth weight and gestational age, which was significantly related to the increased urinary Cd. These results suggest that Cd exposure might induce preterm birth. The lack of any difference in the rate of small for date infants between the two maternal groups divided according to urinary Cd also suggested that Cd exposure does not greatly affect fetal development, but it does affect pregnancy outcome. However, the placenta is known to accumulate Cd, which may cause placental toxicity and disturbance of fetal development. A study of the relation between placental Cd and infant growth is necessary to clarify the effect of Cd on fetal development.

In this survey, urinary Cd during the postpartum period (5th day after delivery) was used as an index of Cd body burden, because no significant changes in urinary Cd concentrations before pregnancy, during gestation, and after birth were reported by Hernandez *et al*.[12] In this study also, no significant difference between the geometric means of urinary Cd concentrations in the 30th to 32nd weeks of pregnancy, 5th day, and 1 month after delivery were noted among eight subjects. Moreover in the present study, in the 24 women during the 30th to 32nd weeks of pregnancy whose whole blood could be examined, the urinary Cd during the postpartum period and blood Cd concentration were highly correlated (r=0.735, p<0.0001). These results showed that the urinary Cd concentration during the postpartum period is a good indicator of maternal body burden of Cd, as is the urinary Cd concentration before pregnancy or blood Cd.

A significant relation was found between Cd concentration of breast milk and maternal urinary Cd, which showed the existence of maternal-fetal transfer of Cd by breast milk. In previous studies that focused on the subjects living in Europe, no relation between maternal exposure to Cd and Cd in breast milk was detected, because the concentration of Cd in breast milk in European countries was under 0.9 nmol/l,[8 9 13] and much lower than the level noted in our subjects, which was on average 4.6 nmol/l.

However, a high body burden of Cd in Japan was suspected to be due to the high Cd intake mainly from rice, but the Japanese lifestyle has been changing, especially with a decreased intake of rice reported in the younger generation. A further survey to determine dietary intake of Cd in these subjects will be required.

Smoking is also a known source of exposure to Cd in breast milk.[8] However, smoking did not significantly affect the increased Cd concentration in breast milk in the present study. This result may be attributable to the fact that there were only eight women who had smoked, six of whom had stopped smoking in early pregnancy. Accordingly, the effect of smoking on Cd concentrations in breast milk should be investigated in the populations with a higher rate of smoking.

ACKNOWLEDGEMENTS

We thank the nursing and medical staff at Toyama Medical Pharmaceutical University Hospital; Makiko Ebie, Mutumi Katsuo, Aki Ohta. This work was supported by a grant for project research from the High-Technology Center of Kanazawa Medical University (H2000-4).

Authors' affiliations
M Nishijo, H Nakagawa, K Tawara, Department of Public Health, Kanazawa Medical University, Uchinada, Ishikawa, Japan
R Honda , Department of Hygiene, Kanazawa Medical University, Uchinada, Ishikawa, Japan
K Tanebe, S Saito, Department of Obstetrics and Gynecology, Faculty of Medicine, Toyama Medical Pharmaceutical University, Toyama, Japan
H Teranishi , Department of Public Health, Faculty of Medicine, Toyama Medical Pharmaceutical University, Toyama, Japan

REFERENCES

1 **Kuhnert PM**, Kuhnert BR, Bottoms SF, *et al*. Cadmium levels in maternal blood, fetal cord blood, and placental tissues of pregnant women who smoke. *Am J Obstet Gynecol* 1982;**142**:1021–5.
2 **Kuhnert BR**, Kuhnert PM, Debanne S, *et al*. The relationship between cadmium, zinc, and birth weight in pregnant women who smoke. *Am J Obstet Gynecol* 1987;**157**:1247–1251.
3 **Odland JO**, Nieboer E, Romanova N, *et al*. Blood lead and cadmium and birth weight among sub-arctic and arctic populations of Norway and Russia. *Acta Obstet Gynecol Scand* 1999;**78**:852–60.
4 **Loiacono NJ**, Graziano JH, Kline JK, *et al*. Placental cadmium and birthweight in women living near a lead smelter. *Arch Environ Health* 1992;**47**:250–5.
5 **Tabacova S**, Little RE, Balabaeva L, *et al*. Complications of pregnancy in relation to maternal lipid peroxides, glutathione, and exposure to metals. *Reproduct Toxicol* 1994;**8**:217–24.
6 **Laudanski T**, Sipowicz P, Modzelewski J, *et al*. Influence of high lead and cadmium soil content on human reproductive outcome. *Int J Gynecol Obstet* 1991;**366**:309–15.
7 **Sipowicz M**, Kostrzewska A, Laudanski T, *et al*. Effects of cadmium on myometrial activity of the nonpregnant human. Interactions with calcium and oxytocin. *Acta Obstet Gynecol Scand* 1995;**74**:93–6.
8 **Radisch B**, Werner L, Nau H. Cadmium concentration in milk and blood of smoking mothers. *Toxicol Lett* 1987;**36**:147–52.
9 **Oskarsson A**, Hallen IP, Sundberg J, *et al*. Risk assessment in relation to neonatal metal exposure. *Analyst* 1998;**123**:19–23.
10 **World Health Organisation**. *Environmental Health Criteria 134, Cadmium*. Geneva: WHO, 1992.
11 **Buchet JP**, Lauwerys R, Roels H, *et al*. Renal effects of cadmium body burden of the general population. *Lancet* 1990;**336**:699–702.
12 **Hernandez M**, Schuhmacher M, Fernandez JD, *et al*. Urinary cadmium levels during pregnancy and postpartum, a longitudinal study. *Biol Trace Elem Res* 1996;**53**:205–12.
13 **Schramel P**, Hasse S, Ovcar-Pavlu J. Selenium, cadmium, lead, and mercury concentrations in human breast milk, in placenta, maternal blood, and the blood of the newborn. *Biol Trace Elem Res* 1988;**15**:111–24.

COMMENTARY

The study by Nishijo *et al* consisted of 57 women who gave birth at a hospital in the Toyama prefecture, Japan. Some of the women lived in the cadmium contaminated Jinzu River Valley, where the itai-itai disease occurred some 55 years ago. Occupational, residential, and smoking histories were obtained through a self completed questionnaire. Maternal urine and colostrum milk samples were analysed for cadmium (Cd) content, and a positive correlation between the two was observed. The authors report an inverse relation between maternal urinary Cd level and gestational age, after adjustment for maternal age. More preterm and caesarean section deliveries were reported in the group of women with high levels of urinary Cd (>2 nmol/mmol Cr), and the weights and heights of these infants were significantly lower as well. However, birth weight (BW) was not directly related to maternal urinary Cd after adjustment for maternal and gestational age. There was no difference in the proportions of small for date (SFD) infants in terms of maternal urinary Cd concentration. These findings led the authors to postulate that exposure to Cd might induce preterm births which, in turn, were responsible for decreased BW. The authors suggest that Cd exposure significantly affects pregnancy outcome but not fetal development.

A number of previous studies have reported an inverse relation between maternal CD exposure and BW, while other studies have not.[1–6] The investigation by Nishijo *et al* provides some new insights into the complex relation between maternal Cd exposure and reproductive outcome. Several aspects of the study merit further discussion. In the Nishijo *et al* investigation, Cd exposure from smoking seems to have played only a minor role, because of the small number of smokers and the almost equal proportions of smokers in the two groups classified by maternal urinary Cd concentration. But smoking histories were self reported and might not be reliable. A more objective approach would have been based on plasma cotinine, a major metabolite of nicotine. Furthermore, because of the small number of smokers, the study provided little information on the impact of smoking.

None of the women in the study reported any occupational Cd exposure. A detailed characterisation of the sources of exposure (for example, environmental, dietary, smoking) would have been highly desirable. As a biomarker to assess CD exposure, Nishijo *et al* relied on maternal urinary samples, which were non-invasive and easy to obtain, while other investigators have preferred maternal whole blood, umbilical cord blood, placenta, mothers' hair, and infants' hair. Different biomarkers may be better suited for measuring different specific exposures. For example, Cd in blood is more influenced by recent exposure than Cd in urine.

It has been reported that Cd accumulates in the placenta during the first trimester,[7] and it has been hypothesised that Cd significantly compromises the calcium handling ability of trophoblastic cells.[8] Nishijo *et al* did not investigate the possible role of the placenta but acknowledge that study of the relation between placental Cd and infant growth is needed.

Exposure to Cd is a serious public health concern. In addition to occupational and environmental exposure, pregnant women are exposed through smoking and diet. While more research is needed to increase our understanding of the underlying mechanisms, the overall message from the literature is that maternal Cd exposure can produce several adverse reproductive outcomes, including preterm deliveries and reduced BW. The public health challenge is to educate the public about the importance of avoiding exposure, especially by not smoking during pregnancy.

Otto Wong
Applied Health Sciences, Inc., 181 Second Avenue, Suite 628, PO Box 2078, San Mateo, California 94401, USA; ottowong@aol.com

REFERENCES

1 **Huel G**, Boudene C, Ibrahim MA. Cadmium and lead content of maternal and newborn hair: relationship to parity, birth weight, and hypertension. *Arch Environ Health* 1981;**36**:221–7.
2 **Sikorski R**, Radomanski T, Paszkowski T, *et al*. Smoking during pregnancy and the perinatal cadmium burden. *J Perinat Med* 1988;**16**:225–31.
3 **Kuhnert BR**, Kuhnert PM, Debanne S, *et al*. The relationship between cadmium, zinc, and birth weight in pregnant women who smoke. *Am J Obstet Gynecol* 1987;**157**:1247–51.
4 **Laudanski T**, Sipowicz M, Modzelewski P, *et al*. Influence of high lead and cadmium soil content on human reproductive outcome. *Int J Gynaecol Obstet* 1991;**36**:309–15.
5 **Berlin M**, Blanks R, Catton M, *et al*. Birth weight of children and cadmium accumulation in placentas of female nickel cadmium (long-life) battery workers. *IARC Sci Publ* 1992;**118**:257–62.
6 **Odland JO**, Nieboer E, Romanova N, *et al*. Blood lead and cadmium and birth weight among sub-arctic and arctic populations of Norway and Russia. *Acta Obstet Gynecol Scand* 1999;**78**:852–60.
7 **Kantola M**, Purkunen R, Kroger P, *et al*. Accumulation of cadmium, zinc, and copper in maternal blood and developmental placental tissue: differences between Finland, Estonia, and St. Petersburg. *Environ Res* 2000;**83**:54–66.
8 **Lin FJ**, Fitzpatrick JW, Iannotti CA, *et al*. Effects of cadmium on trophoblast calcium transport. *Placenta* 1997;**18**:341–56.