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

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 spectrophotometry. The relations between maternal urinary Cd and infant growth, gestational age at birth, and Cd in breast milk were investigated.

Results: The rate of preterm 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.

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 iitai-iitai 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–
Student's Statistical analysis samples were corrected for the creatinine content of urine. No woman had any occupational history of exposure to Cd, smoking after becoming pregnant, or parity between these differences in smoking habits, including women who stopped urinary Cd (<2 nmol/mmol Cr). However, there were no significantly higher than that of the women with lower urinary Cd concentration. 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

### Statistical analysis
Student's $t$ tests or a Welch's test and $\chi^2$ 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 ($\geq$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).

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

<table>
<thead>
<tr>
<th>Maternal urinary Cd</th>
<th>&lt;2 µg/gCr</th>
<th>≥2 µg/gCr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects [n]</td>
<td>45</td>
<td>12</td>
</tr>
<tr>
<td>Maternal age (y, mean (SD))</td>
<td>28.5 (4.1)</td>
<td>33.0 (4.4)**</td>
</tr>
<tr>
<td>Nullipara (n [%])</td>
<td>30 (53.6)</td>
<td>33 (46.3)</td>
</tr>
<tr>
<td>Smoking habit (n [%])</td>
<td>16 (3.3)</td>
<td>2 (16.7)</td>
</tr>
<tr>
<td>Cd in breast milk [nmol/l, mean (SD)]</td>
<td>2.8 (1.7)</td>
<td>4.6 (2.5)*</td>
</tr>
<tr>
<td>Gestational age (weeks, mean (SD))</td>
<td>39.1 (1.3)</td>
<td>37.0 (2.9)**</td>
</tr>
<tr>
<td>Infant growth at birth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (cm, mean (SD))</td>
<td>43.2</td>
<td>41.3*</td>
</tr>
<tr>
<td>Weight (g, mean (SD))</td>
<td>3299 (432)</td>
<td>2663 (680)**</td>
</tr>
<tr>
<td>Head circumference (cm, mean (SD))</td>
<td>33.2 (1.2)</td>
<td>32.3 (2.1)</td>
</tr>
<tr>
<td>Chest circumference (cm, mean (SD))</td>
<td>32.1 (2.0)</td>
<td>31.4 (2.7)</td>
</tr>
<tr>
<td>Low birth weight infant (&lt;2500 g, n [%])</td>
<td>3 (6.7)</td>
<td>5 (14.7)*</td>
</tr>
<tr>
<td>Small for date infant (n [%])</td>
<td>3 (6.7)</td>
<td>1 (3.0)</td>
</tr>
<tr>
<td>Early delivery (gestational age &lt;38 weeks, n [%])</td>
<td>4 (8.9)</td>
<td>5 (14.7)*</td>
</tr>
<tr>
<td>Caesarean section (n [%])</td>
<td>4 (8.9)</td>
<td>7 (15.2)**</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>Partial coefficient controlling for maternal age</th>
<th>Partial coefficient controlling for maternal and gestational age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>-0.309*</td>
<td>-0.237</td>
</tr>
<tr>
<td>Height</td>
<td>-0.252</td>
<td>-0.232</td>
</tr>
<tr>
<td>Chest</td>
<td>-0.171</td>
<td>-0.110</td>
</tr>
<tr>
<td>Head</td>
<td>-0.133</td>
<td>-0.104</td>
</tr>
<tr>
<td>Gestational age</td>
<td>-0.369**</td>
<td>-0.339*</td>
</tr>
</tbody>
</table>

*p<0.05; **p<0.01.
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, 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 Cd body burden 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 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, no significant difference in Cd concentration in breast milk was found between the subjects who did or did not smoke.

A lower birth weight in infants of mothers with higher urinary Cd excretion 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, no significant difference in Cd concentration in breast milk was found between the subjects who did or did not smoke.

**REFERENCES**


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. 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, and it has been hypothesised that Cd significantly compromises the calcium handling ability of trophoblastic cells. 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.

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REFERENCES