Original Article

Urinary Cadmium in Relation to Neonatal Anthropometric Indices during Pregnancy

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Abstract

Aim: This study aims to determine the concentrations of urinary Cadmium (Cd) in a group of pregnant women and its association with neonatal anthropometric Indices. **Materials and Methods:** This cross-sectional study was conducted, involving 136 pregnant women in the first trimester, as a sub-study of the PERSIAN Birth Cohort in Isfahan in 2020. Cadmium exposure was assessed by urinary concentrations using atomic absorption spectrometry. The socioeconomic information and neonatal anthropometric indices were documented. Data were analyzed using the SPSS statistical package. $P < 0.05$ was considered statistically significant. **Results:** The results of the study revealed the mean (standard deviation) concentration of urinary Cd (U-Cd) was 0.16 (0.11) μg/L. The U-Cd by Creatinine ranged from 0.06 to 1.24 with a median (interquartile range) of 0.18 (0.12–0.26) (μg/g creatinine). The mean age of participants was 30.26 (4.92) years. Although the association between birth height and birth head circumference was inverse, it was not significant after using the adjusted model for confounder variables, including maternal anthropometric measurements, maternal body mass index, passive smoking status, and socioeconomic demographic. **Conclusion:** The current findings show that maternal Cd exposure was reversely associated with physical growth at birth. Hence, reduction of maternal Cd exposure is essential to improve infant health. Further research is required to investigate the effect of maternal exposure to Cd on adverse health outcomes in long-term periods considering other cofounders and metal pollutants.

Keywords: Birth weight, cadmium, infant health, newborn, pregnancy

Introduction

Cadmium (Cd) is a toxic metal found in nature including food, drinking water, soil, dust, and air. In addition, it is found in fertilizer applicants, burning of fossil fuels, seafood as well as rice and leafy green and root vegetables, and cigarette smoke.[1,2]

Studies have found the average concentration of Cd has increased two or threefold in farmland and urban soil from 0.097 mg/kg to 0.29 mg/kg during two recent decades.[3] Furthermore, high contamination of Cd in Iranian food and blood samples among the general population has been found.[4] So, it ranged between 0.0031 ± 0.0004 mg/L and 0.049 ± 0.04 mg/kg^{-1} wet weight in raw milk and rice samples.[5,6] This concentration in the north and rivers has been reported as 0.273–1.387 μg/g per dry weight.[7] The mean dietary intake of Cd has been reported 9.3 ± 3.5 μg/day in Iranian pregnant women,[8] and its concentration in urine samples has been found 0.13 mg/L during pregnancy.[2] While Environmental Protection Agency has established 5 μg/L^{-1} of cd as the standard value for drinking water.[9]

Pregnancy is a critical period in that environmental toxicants can threaten maternal and fetal health.[10] Cd is a considerable public health concern, low molecule, and fat-soluble that can quickly cross mothers to offspring via fluids to the placenta, depending on blood flow.[2] Cd exposure tends to decrease

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blood flow, disrupt steroid and polypeptide placental hormones, and alter trophoblast cell integrity.[11] In addition, Cd affects the fetus's cellular division and differentiation via declining zinc bioavailability.[12]

Prior studies have shown these changes lead to negative effects on child growth and neurodevelopment in humans,[13,14] especially anthropometric indices. One of the most common indicators to assess neonatal health, intrauterine condition, mortality, and morbidity of infants is anthropometric indices.[15]

Controversial information about Cd exposure in early life and neonates' anthropometric indices has been reported. For example, doubling maternal blood Cd during the third trimester of pregnancy was associated with a reduction of birth weight by 95 gr in Mongolia (95% confidence interval [CI]: 34, 155 g).[16] On the other hand, some studies haven't proven any association between Cd exposure and the outcome of pregnancy.[17] In Thomas *et al*.'s study, exposure to heavy metals, including maternal blood Cd at the first and third trimester was not associated with small for gestational age (SGA).[18] Additionally, Khoshhali *et al*. found that Cd exposure was not significantly correlated with low birth weight.[19]

The aim of this study was to determine the concentrations of urinary Cd in a group of pregnant women and its association with neonatal anthropometric Indices.

Materials and Methods

This study was a cross-sectional study conducted as a sub-study of the PERSIAN Birth Cohort (PBC),[20] following the ethical standards of the Helsinki Declaration. The study design and goals were explained to all study participants before inclusion. Written informed consent was taken from all mothers before enrollment in the Isfahan Birth Cohort study. Using the correlation coefficient formula in estimating the sample size, at a significance level of 5% and with a power of 80%, the maximum sample size of the study was 136. Data collection of PBC is based on physical examinations, and questionnaires. The distribution of participants' living is demonstrated in Figure 1.

The Cd concentration was determined using graphite furnace atomic absorption spectrometry (AA240 Agilent Zeeman Atomic Absorption Spectrometer). The limit of detection was 0.005 μg/L, and no samples were below it. Quality control was certified using the standards, and measured in duplicate. To make samples comparable, Cd concentration was corrected using creatinine content in the urine samples that were determined using the colorimetric method (Mindray-BF800).

Birth weight in grams; birth length and head circumference in centimeters were measured at least 2 h after birth in hospitals, with experienced midwives using standardized procedures. Ponderal index ([birth weight g/birth length $cm^3 \times 100$]). The ponderal index might be used to identify the symmetrical or asymmetrical infant's growth status. Covariate data including demographic data (weight, age, and height of mother), socioeconomic (education, occupation, self-evaluation of household income), maternal smoking, and passive smoking. A trained interviewer at the first meeting acquired all of this information. Infants' birth date, gender, and gestational age were recorded after the birth. Gestational age was calculated by subtracting the date of the last menstrual period from the date of birth. After comparing with ultra-sonographic data. It must be <1-week difference.

Statistical analysis

We assess the normality of data by using the one-sample Kolmogorov-Smirnov. Data were expressed as mean (standard deviation [SD]) for continuous variables and as frequency (percent) for categorical variables. For continuous data with abnormal distribution, Median and interquartile range (IQR) for Cd by Creatinine (Cd/Cr), and Cd were used. The association between the concentration of urine Cd with dependent variables was assessed by multiple binomial logistic regression and multiple linear regression based on the type of outcome. Maternal body mass index, age, passive smoking status, and socioeconomic (e.g., education, income, and occupation) were adjusted as confounders. Data were analyzed using the SPSS statistical package (SPSS, Chicago, IL, USA; version 18:0). $P < 0.05$ was considered statistically significant.

Results

The detailed demographic characteristics of 136 mother-newborn pairs are shown in Table 1. The mean (SD) age of mothers was 30.26 (4.92) years. About 55.9% of newborns were boy, 10.6% had low birth weight, and 12.6% was SGA.

The median (IQR) concentration of U-Cd was 0.11 (0.1–0.2) μg/L and ranged between 0.1 and 0.8. Moreover, the U-Cd/Cr ranged from 0.06 to 1.24 with a median (IQR) of 0.18 (0.12–0.26) (μg/g creatinine).

The bivariate correlation between maternal and newborn characteristics is presented in Table 2. Overall, maternal U-Cd/Cr was not significantly correlated with birth weight, length, head circumference, and ponderal index ($P > 0.05$). Additionally, this association was not significant in boy or girl infants. However, gestational age was weakly correlated with birth outcomes (spearman correlation coefficient for birth weight: 0.376, for birth-head circumference: 0.330, and ponderal index: 0.200) ($P < 0.05$).

As shown in Table 3, there was no significant association between maternal U-Cd/Cr and newborn anthropometric measurements after controlled potential confounders ($P > 0.05$). We observed slight and nonsignificant decreases in birth height (−0.030 cm; 95% CI: −4.47 to 2.48) and birth-head circumference (−0.049 cm; 95% CI: −2.70 to 1.94) with increasing maternal U-Cd/Cr.

Discussion

The present study, after controlling for probable confounders demonstrated that maternal U-Cd wasn't significantly

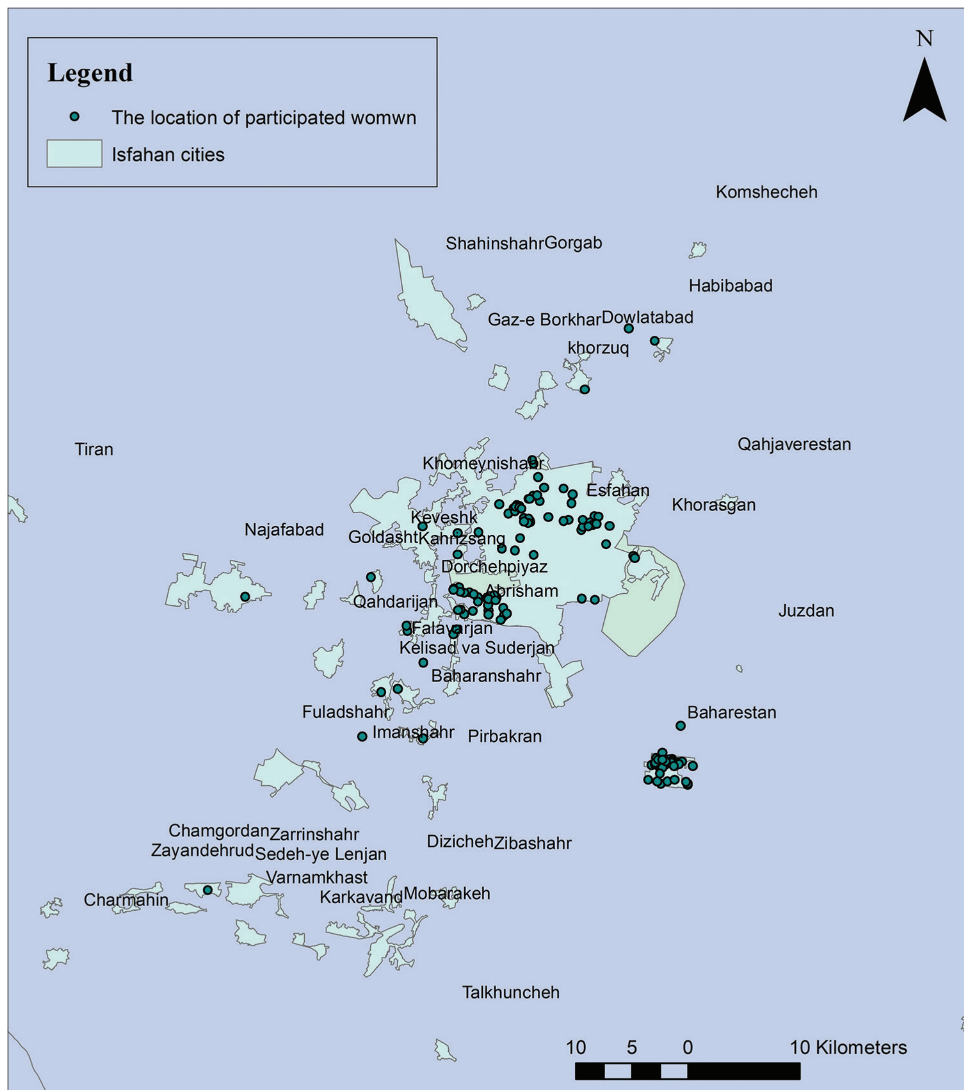

Figure 1: The distribution of participants' living in the study

associated with birth weight. As well, this association was not significant in boys or girls ($P > 0.05$). Furthermore, there was a nonsignificant negative association between U-Cd and birth length and head circumference.

Median (IQR) cadmium concentration in pregnant women was different values. In the current study, Cd was 0.11 (0.1–0.2) μg/L which is lower than Cd levels reported in other studies.[21,22] In some studies, it's rather similar to the current study (0.10 μg/L) in Swedish pregnant women.[2] While it is greater in some studies from 1.09 μg/L (0.72–1.31 μg/L) to 1.21 μg/L (0.76–1.84 μg/L) among Chinese,[23] or <0.70 (0.52–0.95) μg/L in Japanese pregnant women.[24] This difference may stem from the quality and quantity of food consumption, dietary intake of minerals like iron and calcium, different races and ethnicities, cultural practices such as using traditional lead-glazed pottery and traditional medicines, occupational exposures, geographical differences due to presence of Cd in soil, air and crops, and different time of measurement.[25]

In the current study, there was a nonsignificant positive relationship between U-Cd and birth weight and ponderal index. This association was reversed between U-Cd and birth length and head circumference. Consistent with our findings, adjusted odds ratio showed a reverse association between U-Cd, and head circumference.[2,17,26,27] Furthermore, some studies pointed to significant differences between anthropometric indices of girls in comparison to boy infants concerning Cd exposure. The reverse association between Cd and birth weight, ponderal, and head circumference only in female children at birth,[17,28,29] and length at birth in male neonates[26] have been reported. This difference has been attributed to sex variations in the toxico-kinetics and toxico-dynamics of Cd.[28]

Contrarily, Cd concentration in cord blood was negatively associated with ponderal index at birth only in males ($\beta = -0.06$ g/cm^3, 95% CI: −0.11, −0.02; $p < 0.01$).[21] Additionally, in another study, U-Cd wasn't related to birth weight, length, ponderal index, and head circumference.[30]

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Table 1: Demographic and anthropometric characteristic of the mothers and their newborns

Quantitative variables	Minimum–maximum	Median (Q1–Q3)
Urinary Cd	0.1–0.8	0.11 (0.1–0.2) μg/L
Urinary Cd/Cr	0.06–1.24	0.18 (0.12–0.26) (μg/g creatinine)
	Mean±SD	
Urinary Cd/Cr log	−2.75±0.470	
Weight	65.02±11.93	
BMI (kg/m²)	24.93±3.95	
HiC (cm)	99.81±18.02	
WC (cm)	90.15±21.23	
Newborn characteristics		
Gestational age (week)	39.18±4.53	
Birth-weight (g)	3104.51±501.73	
Birth-height (cm)	53.76±39.36	
Birth-head circumference (cm)	37.17±27.80	
Ponderal index	2.47±0.38	
Qualitative variables	**Frequency (%)**	
BMI (kg/m²)		
Underweight (below 18.5)	5 (3.6)	
Normal (18.5–24.9)	67 (50)	
Overweight (25–29.9)	48 (35.29)	
Obese (30.0 and above)	15 (11.11)	
Maternal education (years)		
≤12	83 (61.02)	
>12 (academic)	53 (38.98)	
Occupation		
Housewife	124 (91.17)	
Freelance or official work	12 (8.83)	
Self-evaluation of income		
Low	24 (17.6)	
Moderate	102 (75)	
High	10 (7.4)	
Maternal passive smoking status		
Yes	30 (25.6)	
No	87 (74.4)	
Newborn gender		
Girl	60 (44.1)	
Boy	76 (55.9)	
Preterm		
Yes	10 (7.7)	
No	121 (92.3)	
LBW		
Yes	14 (10.6)	
No	118 (89.4)	
SGA		
Yes	17 (12.9)	
No	114 (87.1)	

Data presented as mean±SD for continuous normal data, and median (Q1–Q3) for continuous nonnormal data. SD: Standard deviation, HiC: Hip circumference, WC: Waist circumference, LBW: Low birth weight, SGA: Small for gestational age, BMI: Body mass index, Cd/Cr: Cadmium by creatinine

These discrepancies might have occurred due to considering the diversity of contributing essential micronutrients including Zn, Fe, and other related factors to neonatal growth,[31] or the effect of other medical complications on anthropometric indices at birth such as hypertension.[2] On the other hand, we didn't assess the interaction of other metals or micronutrients with neonatal growth.[30] Moreover, differences in results might reflect the impact of the cumulative effect of cadmium along with other heavy metals such as lead and mercury on newborns. For example, the place of residence of pregnant women in the neighborhood of e-waste recycling tended to cause significant negative association.[22,24] As well, in other studies, U-Cd concentration was higher than in our study.[23] Moreover, different types of evaluated samples[2,21,31] in different times of sampling

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Table 2: Spearman's rank correlation coefficients between maternal urinary cazdmium by creatinine, age, body mass index, gestational age and newborn anthropometry measurements

	Newborn anthropometric measurements											
	Birth-weight			Birth-length			Head circumference			Ponderal index		
	Overall	Girl	Boy	Overall	Girl	Boy	Overall	Girl	Boy	Overall	Girl	Boy
Urinary Cd/Cr	0.101	−0.003	0.220	−0.016	0.105	0.024	0.002	−0.135	0.124	0.044	−0.009	0.136
	0.251	0.983	0.067	0.853	0.439	0.847	0.983	0.320	0.30	0.617	0.948	0.026
Maternal age	−0.116	−0.157	−0.079	−0.106	0.024	−0.253	−0.053	−0.218	0.042	0.020	−0.122	0.116
	0.186	0.248	0.517	0.230	0.861	0.035	0.574	0.106	0.729	0.816	0.371	0.034
Maternal BMI	0.066	0.081	0.038	0.147	0.060	0.187	0.053	0.044	0.063	−0.056	−0.047	−0.077
	0.453	0.552	0.756	0.092	0.658	0.119	0.543	0.750	0.600	0.525	0.731	0.052
Gestational age	0.376	0.530	0.264	0.100	0.134	0.115	0.330	0.522	0.212	0.200	0.323	0.098
	0.000	0.000	0.031	0.284	0.370	0.354	0.000	0.000	0.084	0.030	0.027	0.42

*Correlation is significant at the 0.05 level. BMI: Body mass index, Cd/Cr: Cadmium by creatinine

Table 3: Multivariate linear regression analyses of the associations between newborn anthropometric measurements and urinary Cadmium by creatinine

Outcomes	Maternal urinary Cd/Cr (μg/g)		
	B	*P*	Upper and lower limits of beta coefficient
Birth-weight (g)	0.052	0.649	−2.43–2.53
Birth-height (cm)	−0.030	0.814	−4.47–2.48
Birth-HC (cm)	−0.049	0.671	−2.70–1.94
Ponderal index (kg/m^3)	0.091	0.488	−1.98–2.162

*P<0.05 considered as statistically significant. Model adjusted for maternal anthropometric measurements (waist, hip, and chest circumference), BMI, age, gender, preterm, passive smoking status and socio economic situation. HC: Head circumference, BMI: Body mass index, Cd/Cr: Cadmium by creatinine

during pregnancy[2,24] or stratified analyses by sex or trimesters of pregnancy[28,29] could be justified in the controversial findings.

Furthermore, considering the diversity of contributing essential micronutrients including Zn, and Fe related to neonatal growth,[31] or the effect of other medical complications on anthropometric indices at birth such as hypertension[2] can explain these variations. In other words, we did not have any assessment the interaction of other metals[29] or micronutrients with neonatal growth in our study.

Overall, previous studies have found maternal exposure to environmental pollution and its adverse effect on neonatal birth size.[2,19,22] Probable mechanisms of Cd exposure to reduce birth size parameters may include endocrine toxicity,[32] influencing the metallothionein protein expression and Zn transfer to the fetus,[33] sex-specific alteration of DNA methylation,[26] lowering the levels of insulin-like growth factor I (IGF-I) and IGF-binding protein 3, and the negative effect on human placental trophoblast cells.[34]

One of the major sources of Cd exposure is smoking,[21] but we did not find any significant difference between the passive smoker women and the nonexposed in terms of maternal urine Cd concentrations which is in good agreement with Guo *et al*.[21] On the other hand, environmental tobacco smoke exposure is the most important determinant of Cd status in children. Gunier *et al*. 's study reported that lifetime intensity-years of passive smoking for nonsmokers is one of the factors for explaining the U-Cd variability.[35] In the mentioned studies, the effect of Cd was dependent on smoking status.[36]

Study strengths and limitations

Several strengths in our study include the following: First, the present study was the sub-study of the from different centers to decrease selective bias. Good prospective birth cohort study design. Participant recruitment was done control of confounders was another positive point of our study.

One of the potential weaknesses of the present study may be that spot urine sampling may lead to incorrect classifications that potentially cause a bias in the risk assessment.[21] Another limitation was other heavy metals or diets that can affect birth outcomes that have not been assessed in our study.

Conclusion

Elevated maternal Cd levels are associated with a decreased birth length and head circumference at birth. As anthropometric indices are an indicator of neonate well-being, Reduction of maternal Cd exposure is essential to improve infant health. Further research is required to investigate the effect of maternal exposure to Cd on adverse health outcomes in long-term periods considering other cofounders and metal pollutants.

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Data availability statement

All data collected, without personally identifiable information, is available as electronic supplementary material.

Ethics code

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Conflicts of interest

The authors declare no conflict of interest.

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