Environmental Pollution xxx (2016) 1–7

Contents lists available at ScienceDirect

Environmental Pollution

journal homepage: www.elsevier.com/locate/envpol

Association of maternal serum cadmium level during pregnancy with risk of preterm birth in a Chinese population☆

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ARTICLE INFO

Article history:
Received 4 April 2016
Received in revised form
22 June 2016
Accepted 25 June 2016
Available online xxx

Keywords:
Cadmium
Serum
Preterm birth
Birth cohort study

ABSTRACT

Cadmium (Cd) was a developmental toxicant that induces fetal malformation and growth restriction in mice. However, epidemiological studies about the association of maternal serum Cd level with risk of preterm birth were limited. This study was to investigate whether maternal serum Cd level during pregnancy is associated with risk of preterm birth in a Chinese population. Total 3254 eligible mother-and-singleton-offspring pairs were recruited. Maternal serum Cd level was measured by GFAAS. Based on tertiles, maternal serum Cd concentration was classified as low (L–Cd, <0.65 μg/L), medium (M–Cd, 0.65–0.94 μg/L) and high (H–Cd, ≥0.95 μg/L). Odds ratio (*OR*) for preterm birth was estimated using multiple logistic regression models. Results showed the rate of preterm birth among L–Cd, M-Cd and H–Cd was 3.5%, 3.8%, and 9.4%, respectively. Subjects with H–Cd had a significantly higher risk for preterm birth (*OR*: 2.86; 95%*CI*: 1.95, 4.19; $P < 0.001$) than did those with L–Cd. Adjusted *OR* for preterm birth was 3.02 (95%*CI*: 2.02, 4.50; $P < 0.001$) among subjects with H–Cd compared to subjects with L–Cd. Taken together, the above results suggest that maternal serum Cd level during pregnancy is positively associated with risk of preterm birth.

1. Introduction

Cadmium (Cd) is a ubiquitous occupational and environmental toxicant. Workers in electroplating, pigments, paints, welding, and Ni–Cd batteries are usually exposed to a high concentration of Cd (Beveridge et al., 2010). Environmental Cd pollution has pervaded many parts of the world, especially the developing countries such as China and India. According to First National Soil Pollution Survey (2005–2013) from 31 provinces in China, the geoaccumulation index values for Cd in 17.5% soil samples lay above the moderately contaminated level (Chen et al., 2015). A 19-year follow-up study demonstrated that a significant increase in Cd concentrations of urine and an obviously worsened renal dysfunction were observed in Cd-polluted areas of China (Zhang et al., 2014). In addition, a recent study also found that Cd in natural soils was taken up substantially by crops in southwestern China (Liu et al., 2015). As Cd pollution in soil and cigarette smoke is ubiquitous, the general population is exposed to a low concentration of Cd via food and cigarette smoking (Honda et al., 2010).

There is a growing body of evidence suggesting that Cd is a reproductive toxicant in humans. Several epidemiological investigations show that environmental exposure to a low concentration of Cd is associated with male infertility and poor semen quality in humans (Pant et al., 2003; Telisman et al., 2000; Wu et al., 2008; Xu et al., 1993, 2003). Cd is a testicular toxicant in rodent animals (Siu et al., 2009). Numerous experimental studies indicate that Cd induces germ cell apoptosis in mouse testes (Ji et al., 2011b, 2012a, 2012b, 2013; Kim and Soh, 2009; Ozawa et al., 2002). At a high dose, Cd is also embryotoxic and teratogenic in rodents (Thompson and Bannigan, 2008). Our previous study showed that

Abbreviations: BMI, body mass index; C-ABCS, China-Anhui Birth Cohort Study; Cd, cadmium; *CI*, confidence intervals; FAAS, flame atomic absorption spectrophotometry; GA, gestational age; GFAAS, graphite furnace atomic absorption spectrometry; LBW, low birth weight; LMP, last menstrual period; *OR*, odds ratios; ROS, reactive oxygen species; Zn, zinc.

☆ This paper has been recommended for acceptance by David Carpenter.

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http://dx.doi.org/10.1016/j.envpol.2016.06.058
0269-7491/

Cd accumulated mainly in maternal liver and kidney, and only trace amounts of Cd could pass from dam to placentas and fetuses (Wang et al., 2016). A large number of experimental studies demonstrate that maternal Cd exposure at middle gestational stage causes fetal malformations (Hovland et al., 1999; Paniagua-Castro et al., 2007; Robinson et al., 2009; Scott et al., 2005; Veeriah et al., 2015; Wang et al., 2012). Several reports indicate that maternal Cd exposure at late gestational stage induces fetal growth restriction in rodents (Ahokas et al., 1980; Ji et al., 2011a; Selvaratnam et al., 2013).

Preterm birth, defined as spontaneous or iatrogenic delivery before gestational week 37 (Englund-Ogge et al., 2014). Numerous epidemiologic data demonstrate that there is an association between preterm birth and childhood asthma (Goyal et al., 2011; Romero et al., 2014). Moreover, preterm birth increases the risk of cardiovascular diseases in young adulthood and is also an important independent risk factor for neurodevelopmental disorders (Crump et al., 2010; Sonnenschein-van der Voort et al., 2014; Ueda et al., 2014). Although some potential risk factors, such as temperature, maternal smoking, maternal zinc deficiency during pregnancy, maternal obesity and inflammation, have been identified, the exact etiology for preterm birth remain obscure (Cnattingius et al., 2013; Savitz et al., 2014; Scharfe-Nugent et al., 2012; Scholl et al., 1993; Strand et al., 2012). Nevertheless, whether maternal Cd exposure during pregnancy induces preterm birth in humans needs to be further determined.

The present study was to analyze the association between maternal serum Cd level during pregnancy and risk of preterm birth in a large population-based birth cohort study. We found that maternal Cd exposure significantly elevated risk of preterm birth. Recently, Our results showed that maternal Cd exposure during pregnancy disrupted zinc (Zn) metabolism in mice (Wang et al., 2016). Thus, the present study also analyzed the association between maternal serum Cd and Zn level.

2. Material and methods

2.1. Study population

China-Anhui Birth Cohort Study (C-ABCS) is a prospective population-based cohort study that recruited 16, 766 pregnant women from six major cities of Anhui province in China between November 2008 and October 2010. A total of 13, 454 singleton live births were followed up from this cohort (Tao et al., 2013). The present study analyzed a sub-study of the C-ABCS cohort that recruited 4, 358 pregnant women from Hefei city of Anhui province from January 1 to December 31 in 2009 (Tao et al., 2013). Exclusion criteria for participation were as follows: inability to provide informed consent, alcohol drinking and cigarette smoking during pregnancy, mental disorders, pregnancy-induced hypertension and preeclampsia, gestational diabetes, heart disease, thyroid-related disease, a history of $\geq$3 previous miscarriages, or plans to leave the locale before delivery (Tao et al., 2013). For this study, eligible participants were mother-and-singleton-offspring pairs in which serum samples from mothers were available for subsequent Cd measurements and offspring had detailed birth records. Total 36 twins, 15 fetal deaths, 2 stillbirths, 58 abortions and 589 withdrew were excluded from the current study (Fig. 1). In addition, 306 with no maternal sera available and 98 with samples collected in the third trimester were also excluded (Fig. 1). As a result of differences in time at entry into Hefei cohort, 1122 serum samples were collected in the first trimester (4–12 weeks of gestation), and 2132 serum samples were collected in the second trimester (13–27 weeks of gestation). As above, the inclusion rate of the current study was 74.7 percent (3254/4358). The present study was approved by the ethics committee of Anhui Medical University (permit 08-1026). The methods were carried out in accordance with the approved guidelines.

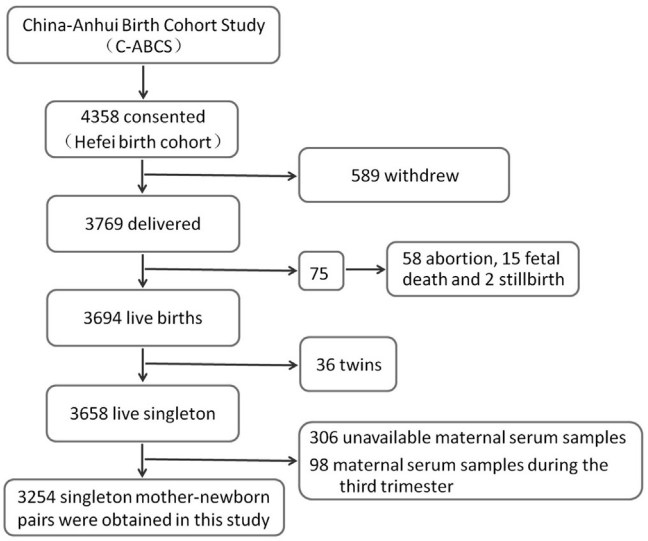

Fig. 1. Flow diagram of recruitment and follow-up in this birth cohort study.

2.2. Outcomes

Gestational age (GA) was calculated using mother's last menstrual period (LMP). In the present study, preterm birth was defined as births at <37 gestational weeks (Athalye-Jape et al., 2014). Total 181 premature infants with spontaneous and non-medical preterm birth were then identified. In addition, preterm birth can be further sub-divided into early preterm birth (<32 weeks), moderate preterm birth (32 to <34 weeks) and late preterm birth (34 to <37 weeks) according to a recently described method (Katz et al., 2013). The present study further analyzed the association between maternal serum Cd level and risks for different sub-categories of preterm birth (early, moderate or late preterm birth).

2.3. Measurement of serum Cd concentration

To avoid contamination of exogenous Cd, all polypropylene tubes and pipette tips were soaked for at least 24 h in 10% ultrapure HNO_3 at room temperature and rinsed persistently in deionized water before use. Maternal fasting blood during pregnancy was collected in the morning. After discarding hemolytic specimens, available sera were stored at −80 °C until analysis. Serum Cd concentration was determined by graphite furnace atomic absorption spectrometry (GFAAS; model: TAS-990; Purkinje General Instrument Co., Ltd, Beijing, China) coupled with a deuterium-lamp background correction system. All samples were prepared and analyzed according to a slightly modified method as previously described(Ji et al., 2011a). Serum samples were diluted with 1% HNO_3 according to 1:4 (v/v). Matrix modifiers colloid palladium (Colpd™, Xinda Measuring & Control Technology Co., Ltd, Chengdu, China) were added to each standard, blank and sample dilution. The following diluted solution was then detected using GFAAS. Each sample was analyzed in triplicate. Precision of the method was measured by coefficients of variation. Mean CV for measurement of serum Cd was 5.16% for within-day determinations and 6.55% for day-to-day determinations. The limit of detection was 0.01 μg/L. In addition, the accuracy of the GFAAS method was also evaluated by the recovery rate of the standard addition method for cadmium. The average recovery rate using standard addition method is

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105.2%. According to a previously described methods (Johnston et al., 2014), maternal serum Cd concentration was classified as low (L–Cd, <0.65 μg/L), medium (M–Cd, 0.65–0.94 μg/L) and high (H–Cd, ≥0.95 μg/L) based on tertiles.

2.4. Measurement of serum Zn concentration

Maternal serum Zn concentration was determined by flame atomic absorption spectr-ophotometry (FAAS; model: TAS-990; Purkinje General Instrument Co., Ltd, Beijing, China). Serum samples were diluted with 1% HNO_3 according to 1:35 (v/v). The diluted solution was then detected using FAAS. Each sample was analyzed in triplicate. Precision of the method was measured by coefficients of variation. Mean CV for measurement of serum zinc was 4.9% for within-day determinations and 4.3% for day-to-day determinations. The detection limit of this method was 0.2 μg/dL.

2.5. Confounding factors

According to a previous review (Blencowe et al., 2013; Valero De Bernabe et al., 2004), potential confounding factors that might influence the association between maternal Cd exposure during pregnancy and preterm birth were chosen as follows: maternal age (≤24, 25–29 and ≥ 30 years), pre-pregnancy BMI (<18.5, 18.5–24.9 and ≥25 kg/m^2), average monthly income (Low income for <2000 RMB or 312 US dollars per month; middle income for 2000–4000 RMB or 312–624 US dollars per month; high income for <4000 RMB or 624 US dollars per month), time for collecting serum (first trimester: median 11 weeks of gestation, range 4–12 weeks of gestation; second trimester: median 16 weeks of gestation, range 13–27 weeks of gestation), gravidity (primigravida/multigravida), and parity (nulliparae/multiparae).

2.6. Statistical analysis

The proportions of maternal and neonatal characteristics and the rate for preterm birth among the tertiles of maternal serum Cd concentration were analyzed using the chi-square test. The means of characters and maternal serum Cd concentration between two groups were analyzed using independent-sample *t*-test. For multiple comparisons, we used one-way ANOVA followed by Bonferroni's or Tamhane's T2 *post hoc* test. Next, odds ratios (*OR*) and 95% confidence intervals (*CI*) for the association between maternal serum Cd concentration and risk of preterm birth were estimated using multiple logistic regression models. We calculated unadjusted and adjusted estimates using exact methods and asymptotic methods, respectively. To identify other variables for inclusion in multivariable models, we sequentially tested each maternal characters listed in Table 1 in the basic model, which included maternal age, pre-pregnancy BMI, monthly income, gravidity and parity. Under any definition of tertiles of maternal serum Cd concentration, the variates changed the adjusted *OR* for the association with preterm birth by more than 10% (Yoon et al., 2007). Finally, we adjusted for maternal age, pre-pregnancy BMI, monthly income, maternal serum zinc concentration, gravidity and parity. Because of the low rate of preterm birth, the *OR* is a good approximation of the relative risk (Huybrechts et al., 2014). We preformed all statistical analyses with *Empower Stats* or *SPSS* 16.0. All statistical tests were two-sided using an alpha level of 0.05.

3. Results

In the present study, 3254 pregnant women were recruited for measurement of serum Cd (Fig. 1). The mean serum Cd concentration was 0.89 μg/L (minimum: 0.04 μg/L; maximum: 8.08 μg/L; median: 0.79 μg/L). All alcohol drinkers and cigarette smokers during pregnancy were excluded from this study. The demographic characteristics of pregnant women and their newborns were compared among the tertiles of maternal serum Cd concentrations (L–Cd, M–Cd and H–Cd). No significant difference on mother's age, pre-pregnancy BMI, time for collecting serum and monthly income was observed among the three groups (Table 1). The average birth weight and gestational ages among subjects with H–Cd, but not M–Cd was significantly lower than that of subjects with L-Cd (Table 1). Then, the present study analyzed the influence of maternal characteristics on maternal serum Cd concentration during pregnancy. As shown in Table S1, several maternal characteristics, including maternal age, BMI before pregnancy, monthly income, parity and gravidity, did not influence maternal serum Cd concentration during pregnancy.

The association for maternal serum Cd concentration during pregnancy and the risk of preterm birth was analyzed. As shown in Table 3, the rate of preterm birth among L–Cd, M–Cd and H–Cd was 3.5%, 3.8%, and 9.4%, respectively. Subjects with H–Cd had a significantly higher risk for preterm birth (*OR*: 2.86; 95%*CI*: 1.95, 4.19; $P < 0.001$) than did those with L-Cd. Under any definition of tertiles of maternal serum Cd concentration, three variates (such as pre-pregnancy BMI, gravidity and parity) changed the adjusted OR for the association with preterm birth by more than 10% (Table 2). Adjusted *OR* for preterm birth was 3.02 (95%*CI*: 2.02, 4.50; $P < 0.001$) among subjects with H–Cd compared to subjects with L–Cd (Table 3). The association between maternal Cd concentration at early gestational age and the risk for preterm birth was further analyzed. As shown in Table 4, the rate of preterm birth among L–Cd, M–Cd and H–Cd was 2.3%, 4.0%, and 8.6%, respectively. Subjects with H–Cd had a significantly higher risk for preterm birth (*OR*: 4.46; 95%*CI*: 2.01, 9.93; $P < 0.001$) than did those with L–Cd. Adjusted *OR* for preterm birth was 4.51 (95%*CI*: 2.02, 10.06; $P < 0.001$) among subjects with H–Cd compared to subjects with L–Cd at early gestational age (Table 4). The association between maternal Cd concentration at middle gestational age and the risk of preterm birth was also analyzed. As shown in Table 4, the rate of preterm birth among L–Cd, M–Cd and H–Cd was 4.2%, 3.7%, and 9.8%, respectively. Subjects with H–Cd had a significantly higher risk for preterm birth (*OR*: 2.72; 95%*CI*: 1.71, 4.31; $P < 0.001$) than did those with L–Cd. Adjusted *OR* for preterm birth was 2.68 (95% *CI*: 1.68, 4.27; $P < 0.001$) among subjects with H–Cd compared to subjects with L–Cd at middle gestational age (Table 4).

The association for maternal serum cadmium concentration during pregnancy and the risk of early preterm birth was first analyzed. As shown in Table S2, 0.6% newborns were with early preterm birth among subjects with L–Cd, In addition, 1.0% newborns were with early preterm birth among subjects with H–Cd (*OR*: 1.74; 95% *CI*: 0.74, 4.13; $P = 0.207$). Adjusted *OR* for early preterm birth was 1.78 (95%*CI*: 0.75, 4.21; $P = 0.193$) among subjects with H–Cd. The association between maternal serum cadmium concentration during pregnancy and the risk of moderate preterm birth was then analyzed. As shown in Table S2, the rate of moderate preterm infants was 2.2% among subjects with H–Cd, significantly higher than 0.8% among subjects with L–Cd. The *OR* was 2.94 (95%*CI*: 1.55, 5.59; $P < 0.001$) among subjects with H–Cd. Adjusted *OR* for moderate preterm birth was 2.95 (95%*CI*: 1.55, 5.62; $P < 0.001$) among subjects with H–Cd. The association between maternal serum cadmium concentration during pregnancy and the risk of late preterm birth was further analyzed. As shown in Table S2, the rate of late preterm infants was 8.4% among subjects with H–Cd, significantly higher than 2.1% among subjects with L-Cd. The *OR* was 4.27 (95%*CI*: 2.95, 6.19; $P < 0.001$) among subjects with H–Cd. Adjusted *OR* for late preterm birth was 4.25 (95%*CI*: 2.93, 6.17; $P < 0.001$) among subjects with H–Cd.

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Table 1
Characteristics of 3254 mothers and their newborns according to maternal serum cadmium level in a Chinese population.[a]

Parameters	Maternal serum cadmium level[b]			*P*-value
	Low (n = 1084)	Medium (n = 1085)	High (n = 1085)	
Maternal characteristics				
Age (*y*)	27.5 ± 3.1	27.5 ± 3.3	27.4 ± 3.2	0.66
≤24	149 (13.8)	177 (16.3)	173 (15.9)	0.24
25–29	712 (65.7)	664 (61.2)	679 (62.6)	
≥30	223 (20.6)	244 (22.5)	233 (21.5)	
Pre-pregnancy BMI (kg/m^2)	20.3 ± 2.3	20.3 ± 2.2	20.2 ± 2.2	0.54
<18.5	221 (20.4)	228 (21.0)	246 (22.7)	0.61
18.5–24.9	825 (76.1)	825 (76.0)	809 (74.6)	
>25	38 (3.5)	32 (3.0)	30 (2.8)	
Parity				
Nulliparae	1066 (98.3)	1042 (96.0)	1053 (97.1)	0.006
Multiparae	18 (1.7)	43 (4.0)	32 (2.9)	
Monthly income				
Low income[c]	487 (44.9)	504 (46.4)	495 (45.6)	0.24
Middle income[c]	440 (40.6)	422 (38.9)	460 (42.4)	
High income[c]	157 (14.5)	159 (14.7)	130 (12.0)	
Time for collecting serum	14.7 ± 4.4	14.8 ± 4.3	14.9 ± 4.4	0.47
First trimester	389 (35.9)	37.4 (34.5)	359 (33.1)	0.39
Second trimester	695 (64.1)	711 (65.5)	726 (66.9)	
Newborn characteristics				
Gestational age (*wk*)	39.1 ± 1.6	39.0 ± 1.6	38.9 ± 1.9	0.006
<37	38 (3.5)	41 (3.8)	102 (9.4)	<0.001
≥37	1046 (96.5)	1044 (96.2)	983 (90.6)	
Birth weight (*g*)	3420 ± 451	3407 ± 434	3375 ± 498	0.07

[a] Values were expressed as n (%) or *means* ± *SD*.
[b] According to tertiles, maternal serum Cd level was classified as low (<0.65 μg/L), medium (0.65–0.94 μg/L) and high (≥0.95 μg/L).
[c] Low income for <2000 RMB (312 US dollars) per month; middle income for 2000–4000 RMB (312–624 US dollars) per month; high income for ≥4000 RMB (624 US dollars) per month.

Table 2
Association of maternal characteristics with preterm birth in a Chinese population.

Maternal characteristics	n (%)	Preterm birth	
		Or (95%CI)	*P*-value
Age (*y*)			
≤ 24	499 (15.3)	0.92 (0.59, 1.44)	0.73
25–29	2055 (63.2)	1.00	–
≥ 30	700 (21.5)	1.20 (0.84, 1.72)	0.31
Pre-pregnancy BMI (kg/m^2)			
< 18.5	695 (21.4)	1.42 (1.01, 2.01)	0.046
18.5–24.9	2459 (75.6)	1.00	–
≥ 25	100 (3.1)	2.37 (1.23, 4.55)	<0.01
Gravidity			
Primigravida	1698 (52.2)	1.00	–
Multigravida	1556 (47.8)	0.82 (0.60, 1.11)	0.19
Parity			
Nulliparae	3161 (97.1)	1.00	–
Multiparae	93 (2.9)	1.63 (0.78, 3.41)	0.20
Monthly income			
Low income[a]	1486 (45.7)	1.12 (0.70, 1.79)	0.65
Middle income[a]	1322 (40.6)	1.07 (0.66, 1.74)	0.77
High income[a]	446 (13.7)	1.00	–
Time for collecting serum			
First trimester	1122 (34.5)	1.00	–
Second trimester	2132 (65.5)	1.22 (0.88, 1.69)	0.23

[a] Low income for <2000 RMB (312 US dollars) per month; middle income for 2000–4000 RMB (312–624 US dollars) per month; high income for ≥4000 RMB (624 US dollars) per month.

The association for maternal serum Cd concentration and serum Zn concentration was analyzed. As shown in Fig. S1A, no significant association between maternal serum Cd concentration and serum Zn concentration was observed ($r = 0.025$, $P > 0.05$). Maternal serum Zn concentration during pregnancy was compared between H–Cd and L–Cd groups. As expected, there was no significant difference on serum Zn concentration between two groups (Fig. S1B).

Table 3
The rate and odds ratio (*OR*) for preterm birth based on maternal serum Cd level during pregnancy.

	Maternal serum Cd level[a]			*P*
	Low	Medium	High	
Number of all infants	1084	1085	1085	
Number of preterm birth	38	41	102	
Rate (%)	3.5	3.8	9.4	<0.001
Univariate *OR* (95%*CI*)	1.00	1.08 (0.69, 1.69)	2.86 (1.95, 4.19)[c]	<0.001
Adjusted *OR* (95%*CI*)[b]	1.00	0.96 (0.59, 1.56)	3.02 (2.02, 4.50)[c]	<0.001

[a] According to tertiles, maternal serum Cd level was classified as low (<0.65 μg/L), medium (0.65–0.94 μg/L) and high (≥0.95 μg/L).
[b] Adjusted for pre-pregnancy BMI, maternal age, maternal serum zinc level, monthly income, parity and gravidity.
[c] $P < 0.001$, as compared with low maternal serum Cd level.

4. Discussion

In the present study, maternal serum Cd concentration was used as a marker for environmental Cd exposure during pregnancy. Urinary Cd concentration is a good marker for Cd exposure (Kippler et al., 2012), but blood Cd concentration has been proposed as a more accurate estimator of the accumulated body burden (Alfven et al., 2002; Kriegel et al., 2006). Although only about 10% of blood Cd is circulating in serum, serum Cd concentration is positively correlated with blood Cd concentration (Lauwerys et al., 1994). The present study used serum Cd concentration rather than blood Cd concentration as a marker for maternal Cd exposure allowing us much greater flexibility in collecting, storing and transporting samples. The present study analyzed serum Cd concentration among 3254 pregnant women. Our results showed that the mean serum Cd concentration was 0.89 μg/L with a range of from 0.04 to 8.08 μg/L. These results are in agreement with those from other studies, in which mean serum Cd concentration was

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Table 4
The rate and odds ratio (*OR*) for preterm birth based on maternal serum Cd level in the first and second trimesters.

	Maternal serum Cd level[a]			*P*
	Low	Medium	High	
First trimester				
Number of all infants	389	374	359	
Number of preterm birth	9	15	31	
Rate (%)	2.3	4.0	8.6	<0.001
Univariate *OR* (95%*CI*)	1.00	1.91 (0.79, 4.62)	4.46 (2.01, 9.93) [c]	<0.001
Adjusted *OR* (95%*CI*) [b]	1.00	1.91 (0.79, 4.63)	4.51 (2.02, 10.06) [c]	<0.001
Second trimester				
Number of all infants	695	711	726	
Number of preterm birth	29	26	71	
Rate (%)	4.2	3.7	9.8	<0.001
Univariate *OR* (95%*CI*)	1.00	0.73 (0.41, 1.32)	2.72 (1.71, 4.31)[c]	<0.001
Adjusted *OR* (95%*CI*)[b]	1.00	0.71 (0.39, 1.27)	2.68 (1.68, 4.27)[c]	<0.001

[a] According to tertiles, maternal serum Cd level was classified as low (<0.65 μg/L), medium (0.65–0.94 μg/L) and high (≥0.95 μg/L).
[b] Adjusted for pre-pregnancy BMI, maternal age, maternal serum zinc level, gestational week for collecting serum, monthly income per person, parity and gravidity.
[c] $P < 0.001$, as compared with low maternal serum Cd level.

with a range of from 0.462 to 7.1 μg/L among non-occupational population (Ikeh-Tawari et al., 2013; Kim et al., 2014; Kriegel et al., 2006; Osada et al., 2011; Satarug et al., 2005). As cigarette smoking is an important risk factor for preterm birth (Balazs et al., 2013; Mercer et al., 2008), as well as associated with the increased Cd exposure (Sorkun et al., 2007), cigarette smokers during pregnancy were excluded from this study.

Until now, no report investigated the association between maternal Cd level during pregnancy and preterm birth. The present study analyzed the association between maternal serum Cd level and risk of preterm birth in a large population-based birth cohort study. We found that higher maternal serum Cd level during pregnancy was positively associated with increased rate and risk of preterm birth. We further analyzed the association between maternal serum Cd level at different gestational ages and preterm birth. Our results showed that maternal serum Cd level in the first and second trimesters was positively associated with risk of preterm birth. The above-mentioned results might be interesting, worth discussing and guarantee to further studies. The association between maternal serum cadmium level during pregnancy and risks of early, moderate and late preterm births was then analyzed. As expected, maternal Cd exposure during pregnancy significantly elevated risks for moderate and late preterm births. To our knowledge, the present study is the first to demonstrate that maternal serum Cd level at different gestational stages is positively associated with risk of preterm birth.

The mechanism through which maternal Cd exposure during pregnancy results in preterm birth remains obscure. An earlier small birth cohort study showed that maternal Zn deficiency during pregnancy is associated with the increased risk of preterm birth (Scholl et al., 1993). Indeed, maternal Cd exposure during pregnancy caused Zn retention in maternal liver and kidney, thus reducing serum Zn concentration (Sorell and Graziano, 1990). The present study analyzed the association between maternal serum Cd and Zn concentration. Unexpectedly, no association between maternal serum Cd and Zn concentration was observed. Moreover, there was no significant difference on maternal serum Zn concentration between subjects with H–Cd and subjects with L–Cd. Several earlier studies showed that maternal Cd exposure during pregnancy impaired placental Zn transport from maternal circulation to the fetuses (Daston, 1982; Sowa and Steibert, 1985). According to an in vitro report, Cd-induced metallothionein binds Zn^{2+} in the cytosol of the trophoblast, making Zn^{2+} less available to the fetal circulation (Torreblanca et al., 1992). Therefore, we guess that insufficient placental Zn^{2+} transfer from maternal circulation to the fetuses may be one of the main mechanisms for Cd-related preterm birth. Additional study is necessary to explore the exact mechanism through which Cd inhibits placental Zn transport from maternal circulation to the fetuses.

A growing body of evidence demonstrates that excessive production of reactive oxygen species (ROS) or pro-inflammatory cytokines can result in adverse pregnancy outcomes (Burdet et al., 2014; Cotechini et al., 2014; Xu et al., 2006). A recent birth cohort study indicated that maternal Cd exposure significantly elevated serum malondialdehyde concentrations, and was linked with risk of small for gestational age infants (Al-Saleh et al., 2015). An earlier animal experiment demonstrated that maternal exposure to Cd in drinking water obviously triggered oxidative stress in rat placentas, fetal livers and kidneys (Enli et al., 2010). According to an in vitro study, glycine could effectively protect against Cd-induced growth restriction and neural tube defects in mouse embryos through alleviating lipid peroxidation (Paniagua-Castro et al., 2008). Our previous study indicated that ROS-mediated endoplasmic reticulum stress was involved in Cd-induced impairment of placental and fetal development in mice (Wang et al., 2012). On the other hand, Cd is also a pro-inflammatory agent. Numerous data showed that the expression of several pro-inflammatory cytokines was selectively up-regulated in Cd-exposed lung, liver and kidney tissues (Olszowski et al., 2012). An earlier study found that maternal Cd exposure through drinking water obviously increased the expression of placental NF-κB, a key mediator of immune and inflammatory response (Ronco et al., 2011). Another in vitro study found that inflammation-related MAPK pathways, namely ERK, JNK and p38, were activated by Cd in human umbilical vein endothelial cells (Kim et al., 2012). Taken together, these results suggest that Cd induces preterm birth, at least partially, via excess production of ROS and pro-inflammatory cytokines.

In this study, we laid emphasis on the association of maternal serum Cd concentration during pregnancy and risk of preterm birth. The present study has several limitations. First, the present study did not analyze the effects of other heavy metals (including lead and mercury) exposure on adverse pregnancy outcomes. Second, gestational age was calculated using mother's last menstrual period, but not color ultrasonography. Third, the present study did not explore the mechanism of Cd-associated with preterm birth. Additional work is required to determine whether environmental lead and mercury exposure during pregnancy elevates risk of preterm birth. In addition, the mechanism by which maternal Cd exposure during pregnancy induces preterm birth needs to be explored in animal experiments.

Please cite this article in press as: Wang, H., et al., Association of maternal serum cadmium level during pregnancy with risk of preterm birth in a Chinese population, Environmental Pollution (2016), http://dx.doi.org/10.1016/j.envpol.2016.06.058

5. Conclusions

In summary, maternal serum Cd level during pregnancy is positively associated with risk of preterm birth.

Conflict of interest

All authors declare that there is not conflict of interest.

Acknowledgements

We are grateful to Hai-Yan Zhang and Yuan-Yuan Yang for assistance in cadmium measurement. This study was supported by National Natural Science Foundation of China (81473016), National Key Technology R & D Program (2006BAI05A03 to C-ABCS), Key Projects of outstanding Youth Talent Support Program in Anhui Provincial University (gxyqZD2016056), Grants for Scientific Research of BSKY (XJ201522) and Top-notch Youth Talent Support Program from Anhui Medical University.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.envpol.2016.06.058.

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