Toxicology and Applied Pharmacology 332 (2017) 75–80

Contents lists available at ScienceDirect

Toxicology and Applied Pharmacology

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

High serum lead concentration in the first trimester is associated with an elevated risk of small-for-gestational-age infants

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ARTICLE INFO

Article history:
Received 22 June 2017
Revised 23 July 2017
Accepted 25 July 2017
Available online 26 July 2017

Keywords:
Lead
Serum
Small-for-gestational-age
Infants
Birth cohort study

ABSTRACT

A recent study found that gestational serum Pb concentration is associated with an increased risk of preterm birth. The purpose of this study was to analyze whether gestational Pb exposure elevates risk of small-for-gestational-age (SGA) births in a Chinese population. In the present study, total 3125 mother-infant pairs were recruited from the China-Anhui Birth Cohort Study (C-ABCS). Pb concentration in maternal serum was detected by GFAAS. All subjects were classified into three groups according to the tertile division of serum Pb concentration: L-Pb (low-Pb, <1.18 μg/dl), M-Pb (medium-Pb, 1.18–1.70 μg/dl), and H-Pb (high-Pb, ≥1.71 μg/dl). There was no difference on birth length, head circumference and chest circumference among different groups. The rate of SGA was 6.2% in subjects with L-Pb, 8.7% in subjects with M-Pb, and 10.1% in subjects with H-Pb, respectively. The adjusted *OR* of SGA was 1.45 (95%*CI*: 1.04, 2.02; $P = 0.03$) in subjects with M-Pb and 1.69 (95%*CI*: 1.22, 2.34; $P = 0.002$) in subjects with H-Pb. Interestingly, the rate of SGA infants was elevated only in subjects with H-Pb in the first trimester (adjusted *OR*: 2.13; 95%*CI*: 1.24, 3.38; $P = 0.007$). Collectively, high serum Pb level in the first trimester is associated with an elevated risk of SGA infants.

1. Introduction

Lead (Pb) is one of the toxic heavy metals and universally present in the environment, such as soil, atmosphere, and water (Bing et al., 2016; Marx et al., 2016; Stromsoe et al., 2015). General population are mainly exposed to Pb through food intake, air inhalation, or drinking water in the Pb-polluted areas (Augustsson et al., 2015; Cheng et al., 2015; Clark et al., 2014; Mohmand et al., 2015). Increasing evidence from epidemiological investigation demonstrates that exposure to high-level Pb results in male reproductive impairments, bone disease, renal dysfunction, neurodevelopmental toxicity, and hematopoietic abnormality (Chen et al., 2011; Dai et al., 2017; Meeker et al., 2008; Skroder et al., 2016; Tsai et al., 2016).

Pregnant women and their embryos/fetuses are more sensitive to low-level Pb exposure. An earlier study showed that high cord blood concentration of Pb was positively related to an increased risk for adverse fetal growth (Bellinger et al., 1991). Another case-control investigation found that maternal and cord blood Pb level was significantly higher in intra-uterine growth retardation (IUGR) cases than in normal subjects (Srivastava et al., 2001). Inconsistent with the above-mentioned results, the Canadian and Saudi Arabian birth cohort study reported no association between risk for SGA infants and maternal blood Pb concentration during gestation (Al-Saleh et al., 2014; Thomas et al., 2015). Recently, we analyzed the association of maternal serum Pb concentration with adverse pregnant outcomes in our cohort study. Our results had shown that maternal Pb exposure during gestational period markedly elevated risk of preterm birth in a Chinese population (Li et al., 2017).

In this study, our purpose was to further analyze the correlation of maternal serum Pb concentration with risk of SGA infants. We observed a positive correlation of maternal serum Pb level during gestational period with an increased risk of SGA infants. Furthermore, we demonstrate that high maternal serum Pb concentration in the first trimester elevates risk of SGA infants.

Abbreviations: C-ABCS, China-Anhui Birth Cohort Study; CI, confidence interval; GFAAS, graphite furnace atomic absorption spectrometry; OR, odds ratio; SGA, small-for-gestational-age.

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http://dx.doi.org/10.1016/j.taap.2017.07.020
0041-008X/

2. Methods

2.1. Subjects

In this work, 4358 pregnant women were enrolled from the China-Anhui Birth Cohort Study (C-ABCS) in 2009 (Tao et al., 2013). Total 589 pregnant women withdrew first were removed. Fifteen pregnant women giving birth to dead fetuses, 36 twins, 2 stillbirths and 58 abortions were then excluded. Also, 439 unavailable for maternal serum and 94 samples at the third trimester were eliminated. Finally, 3125 mother-offspring pairs were analyzed for this work (Fig. 1). No significant difference in population characteristics was observed between mother-newborn pairs who were enrolled in this study and those who were excluded (data not shown). In the first trimester, median time of serum collection is 11 weeks of gestation. In the second trimester, median time of serum collection is 16 weeks of gestation.

2.2. Definition

In the present study, SGA was defined as live-born infants with birth weight below 10th percentile for the babies of the same gestational age according to a global reference (Mikolajczyk et al., 2011). As previously described, the mean birth weight and standard deviation (SD) at 40 gestational weeks were calculated in our birth cohort. The results (mean birth weight: 3511.6 g, the coefficient of variation: 12.31%) were then input into the Excel software, and the different reference percentiles for birth weight at the different gestational ages were generated (Mikolajczyk et al., 2011). The detailed classification was presented in our previous study (Wang et al., 2016a).

2.3. Pb measurement

Maternal serum Pb level was detected as described in our recent study (Li et al., 2017). Based on tertile division of serum Pb concentration, all subjects were divided into three groups: L-Pb (low-Pb, <1.18 μg/dl), M-Pb (medium-Pb, 1.18–1.70 μg/dl), and H-Pb (high-Pb, ≥1.71 μg/dl).

2.4. Statistical analysis

In the current study, one-way ANOVA was used for multiple comparisons. Multivariate logistic regression analysis was used to analyze the odds ratio (*OR*) for correlation of maternal Pb level with risk of SGA infants. To identify the potential confounding factors, we firstly compared maternal characters shown in Supplementary Table 1, which included pre-pregnancy BMI, maternal age, gravidity, monthly income and parity. We also adjusted for the variables that changed the *OR* for SGA infants by >10% when added to the model (Yoon et al., 2007). The potential confounding factors influencing the incidence of SGA infants were chosen according to the previous studies (Blencowe et al., 2013; Valero De Bernabe et al., 2004).

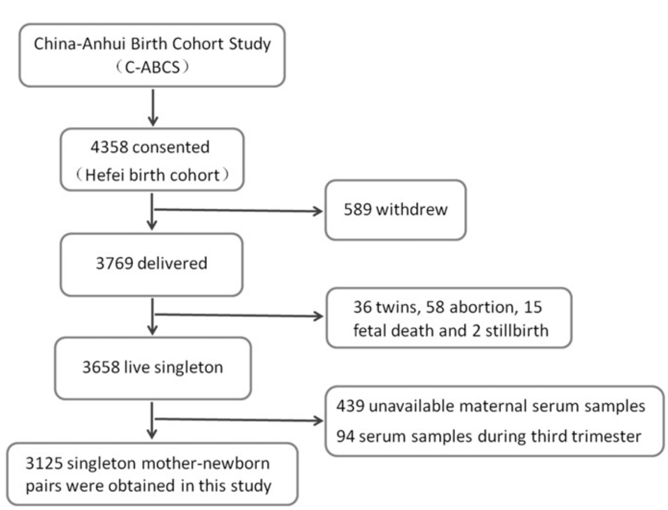

Fig. 1. Flow diagram of recruitment and follow-up in this birth cohort study.

Table 1
The demographic characteristics of 3125 pregnant women.[a]

Parameters	Maternal serum lead level[b]			*P*-value
	L-Pb ($n = 1042$)	M-Pb ($n = 1042$)	H-Pb ($n = 1041$)	
Age (y)	27.5 ± 3.1	27.5 ± 3.2	27.5 ± 3.2	0.96
≤24	158 (15.2)	170 (16.3)	157 (15.1)	0.49
25–29	645 (61.9)	653 (62.7)	665 (63.9)	
≥30	239 (22.9)	219 (21.0)	219 (21.0)	
Prepregnancy BMI (kg/m^2)	20.3 ± 2.3	20.3 ± 2.2	20.2 ± 2.2	0.41
<18.5	222 (21.3)	215 (20.6)	234 (22.5)	0.66
18.5–24.9	790 (75.8)	796 (76.4)	774 (74.4)	
>25	30 (2.9)	31 (3.0)	33 (3.2)	
Gravidity				
Primigravida	562 (53.9)	538 (51.6)	525 (50.4)	0.27
Multigravida	480 (46.1)	504 (48.4)	516 (49.6)	
Parity				
Nulliparous	1005 (96.4)	1023 (98.2)	1005 (96.5)	0.03
Multiparous	37 (3.6)	19 (1.8)	36 (3.5)	
Monthly income[c]				
Low	491 (47.1)	483 (46.4)	448 (43.1)	0.11
Middle	416 (39.9)	410 (39.3)	449 (43.1)	
High	135 (13.0)	149 (14.3)	144 (13.8)	
Time of serum collection				
First trimester	363 (34.8)	343 (32.9)	377 (36.2)	0.28
Second trimester	679 (65.2)	699 (67.1)	664 (63.8)	

[a] Values were expressed as n (%) or *means* ± *SD*.
[b] According to tertile division, maternal serum lead level was classified as L-Pb (<1.18 μg/dl), M-Pb (1.18–1.70 μg/dl) and H-Pb (≥1.71 μg/dl).
[c] Low income for <2000 RMB per month; middle income for 2000–4000 RMB per month; high income for ≥4000 RMB per month.

3. Results

3.1. Demographic characteristics

Serum Pb concentration was analyzed among 3125 pregnant women. Mean serum Pb level was 1.50 μg/dl (median: 1.43 μg/dl; minimum: 0.020 μg/dl; maximum: 5.46 μg/dl) among all subjects. All subjects were classified into three groups by tertile division of serum Pb concentration. The demographic characteristics of 3125 pregnant women were compared among different groups. No significant difference on maternal characteristics was observed among three groups (Table 1). Birth sizes were also analyzed among different groups. As shown in Table 2, birth weight was significantly reduced in subjects with H-Pb, but not in subjects with M-Pb, compared with that of subjects with L-Pb. There was no difference in head circumference, birth length and chest circumference among three different groups

Table 2
Association between birth sizes and maternal serum Pb level during pregnancy.[a]

Parameter	Maternal serum lead level[b]			*P*-value
	L-Pb	M-Pb	H-Pb	
Number of newborns	1042	1042	1041	
Birth weight (g)	3418 ± 451	3414 ± 473	3371 ± 462	0.04
Birth length (cm)	50.4 ± 1.6	50.2 ± 3.2	50.2 ± 2.3	0.21
Head circumference (cm)	34.1 ± 1.5	34.3 ± 2.6	34.1 ± 1.6	0.15
Chest circumference (cm)	33.2 ± 1.5	33.4 ± 2.1	33.2 ± 1.5	0.16

[a] Values were expressed as *n* or *mean* ± *SD*.
[b] According to tertile division, maternal serum lead level was classified as L-Pb (<1.18 μg/dl), M-Pb (1.18–1.70 μg/dl) and H-Pb (≥1.71 μg/dl).

Table 3
Association between birth sizes and maternal serum Pb level during pregnancy.

Parameter	Unadjusted			Adjusted[a]		
	β[b]	95%CI	*P*	β[b]	95%CI	*P*
Birth weight	−2.72	−5.18, −0.26	0.03	−2.74	−5.17, −0.31	0.03
Birth length	−0.013	−0.026, 0.001	0.07	−0.013	−0.026, 0.001	0.06
Head circumference	−0.007	−0.019, 0.004	0.20	−0.008	−0.019, 0.004	0.18
Chest circumference	−0.007	−0.017, 0.003	0.16	−0.008	−0.018, 0.002	0.13

[a] Linear models were performed with adjustment for pre-pregnancy BMI, maternal age, time of serum collection, gravidity, parity and monthly income.
[b] Regression coefficient.

(Table 2). Linear regression was used to explore the correlation of maternal serum Pb concentration during gestation with birth sizes. After adjustment for the potential confounding factors, linear regression analysis showed a negative association of maternal serum Pb concentration with birth weight ($\beta = -2.74$; 95% CI: –5.17, −0.31; $P = 0.03$; Table 3). However, no association was observed between maternal Pb concentration and other birth sizes (Table 3).

3.2. The rate and OR of SGA infants

The correlation of maternal serum Pb concentration during gestation with the risk for SGA was analyzed. As presented in Table 4, the rate of SGA births was 6.2% in subjects with L-Pb, 8.7% in subjects with M-Pb, and 10.1% in subjects with H-Pb, respectively. The *OR* for SGA was 1.69 (95%*CI*: 1.22, 2.33; $P = 0.002$) in subjects with H-Pb and 1.44 (95%*CI*: 1.03, 2.00; $P = 0.03$) in subjects with M-Pb (Table 4). To analyze the influence of confounding factors on the risk for SGA, the correlation of maternal characteristics with risk of SGA births was then analyzed. As shown in Supplementary Table 1, the risk of SGA was negatively associated with pre-pregnancy BMI ($P < 0.001$). No association was observed between the risk of SGA and other factors, such as maternal age, gravidity, parity, monthly income, and time of serum collection (Table S1). Finally, the adjusted *OR* for SGA was 1.45 (95%*CI*: 1.04, 2.02; $P = 0.03$) in subjects with M-Pb and 1.69 (95%*CI*: 1.22, 2.34; $P = 0.002$) in subjects with H-Pb (Table 4). These results suggest that maternal Pb exposure during gestation elevates the risk of SGA births.

Table 4
Association between maternal serum Pb level during pregnancy and risk for SGA infants in different genders.

Parameter	Maternal serum lead level[a]			*P*-value
	L-Pb	M-Pb	H-Pb	
All				
Newborns, n	1042	1042	1041	
SGA, n	65	91	105	
Rate, %	6.2	8.7	10.1	0.006
Univariate *OR* (95% *CI*)	1	1.44 (1.03,2.00)	1.69 (1.22,2.33)	0.006
Adjusted *OR* (95% *CI*)[b]	1	1.45 (1.04,2.02)	1.69 (1.22,2.34)	0.006
Boys				
Newborns, n	542	566	546	
SGA, n	23	33	38	
Rate, %	4.2	5.8	7.0	0.15
Univariate *OR* (95% *CI*)	1.00	1.40 (0.81, 2.41)	1.69 (0.99, 2.87)	0.16
Adjusted *OR* (95% *CI*)[b]	1.00	1.44 (0.83, 2.50)	1.75 (1.03, 2.99)	0.12
Girls				
Newborns, n	500	476	494	
SGA, n	42	58	66	
Rate, %	8.4	12.2	13.4	0.04
Univariate *OR* (95% *CI*)	1.00	1.51 (0.99, 2.30)	1.68 (1.12, 2.53)	0.04
Adjusted *OR* (95% *CI*)[b]	1.00	1.51 (0.99, 2.31)	1.68 (1.12, 2.54)	0.04

[a] According to tertile division, maternal serum lead level was classified as L-Pb (<1.18 μg/dl), M-Pb (1.18–1.70 μg/dl) and H-Pb (≥1.71 μg/dl).
[b] Adjusted for prepregnancy BMI, maternal age, gravidity, parity, time for collection serum and monthly income.

3.3. The rate and OR of SGA boys and girls

The correlation of maternal serum Pb concentration with the risk of SGA boys was analyzed. As shown in Table 4, the rate of SGA in boys was 4.2%, 5.8% and 7.0% in subjects with L-Pb, M-Pb, and H-Pb, respectively. The *OR* for male SGA was 1.40 (95%*CI*: 0.81, 2.41; $P = 0.23$) in subjects with M-Pb and 1.69 (95%*CI*: 0.99, 2.87; $P = 0.054$) in subjects with H-Pb (Table 4). After controlling the confounding factors, the adjusted *OR* of SGA boys was 1.44 (95%*CI*: 0.83, 2.50; $P = 0.19$) in subjects with M-Pb and 1.75 (95%*CI*: 1.03, 2.99; $P = 0.04$) in subjects with H-Pb (Table 4). The correlation of maternal serum Pb concentration with the risk of SGA girls was then analyzed. As presented in Table 4, the rate of SGA girls was 8.4%, 12.2% and 13.4% in subjects with L-Pb, M-Pb, and H-Pb, respectively. The *OR* of SGA girls was 1.51 (95%*CI*: 0.99, 2.30; $P = 0.053$) in subjects with M-Pb and 1.68 (95%*CI*: 1.12, 2.54; $P = 0.013$) in subjects with H-Pb. The adjusted *OR* of SGA girls was 1.51 (95%*CI*: 0.99, 2.31; $P = 0.054$) in subjects with M-Pb and 1.68 (95%*CI*: 1.12, 2.54; $P = 0.013$) in subjects with H-Pb (Table 4). The above-mentioned results suggest that maternal Pb exposure during gestation elevates the risk of SGA girls, but not SGA boys.

3.4. The rate and OR of SGA infants based on maternal serum Pb concentration in the first trimester

Serum Pb concentration in the first trimester was analyzed among 1083 pregnant women. Mean serum Pb level in the first trimester was 1.52 μg/dl (median: 1.43 μg/dl; minimum: 0.025 μg/L; maximum: 5.16 μg/dl). All subjects were classified into three groups according to above-mentioned criteria. Maternal characteristics were compared among three groups. Gravidity was significantly reduced in subjects with H-Pb, but not in subjects with M-Pb, compared with that of subjects with L-Pb (Supplementary Table 2). There was no difference in other demographic characteristics among three different groups (Supplementary Table 2). Birth sizes were compared among different groups. As shown in Table 5, birth weight was significantly reduced in subjects with H-Pb in the first trimester, but not in subjects with M-Pb, as compared with that of subjects with L-Pb. No significant difference in birth length, head circumference and chest circumference was found among the three groups (Table 5). The correlation of birth sizes with maternal serum Pb concentration in the first trimester is presented in Table 6. Multivariable-adjusted linear regression analyses showed a negative association of maternal serum Pb level in the first trimester with birth weight ($\beta = -4.40$; 95% CI: –8.22, −0.58; $P = 0.02$) and chest circumference ($\beta = -0.015$; 95% CI: –0.030, <0; $P = 0.04$). However, no relation was found maternal serum Pb concentration in the first trimester and head circumference and birth length (Table 6). The correlation of maternal serum Pb concentration in the first trimester with the risk for SGA births was then analyzed. As shown in Table 7, the rate of SGA infants was 5.8% in subjects with L-Pb, 7.0% in subjects with M-Pb, and 11.7% in subjects with H-Pb, respectively. The *OR* for SGA was 2.15 (95%*CI*: 1.25, 3.70; $P = 0.006$) in subjects with H-Pb in the first trimester. The adjusted *OR* for SGA was 2.13 (95%*CI*: 1.24, 3.38; $P = 0.007$) in subjects with H-Pb in the first trimester (Table 7).

Table 5
Association between birth sizes and maternal serum Pb level at different gestational stages.[a]

Parameter	Maternal serum lead level[b]			P-value
	L-Pb	M-Pb	H-Pb	
First trimester				
Number of newborns	363	343	377	
Birth weight (g)	3436 ± 452	3451 ± 452	3368 ± 475	0.04
Birth length (cm)	50.4 ± 1.7	50.2 ± 4.2	50.1 ± 3.1	0.49
Head circumference (cm)	34.2 ± 1.4	34.3 ± 1.6	34.1 ± 1.6	0.23
Chest circumference (cm)	33.4 ± 1.6	33.4 ± 1.7	33.2 ± 1.5	0.20
Second trimester				
Number of newborns	679	699	664	
Birth weight (g)	3408 ± 451	3395 ± 483	3373 ± 456	0.38
Birth length (cm)	50.4 ± 1.6	50.2 ± 2.5	50.3 ± 1.6	0.34
Head circumference (cm)	34.1 ± 1.5	34.2 ± 3.0	34.1 ± 1.6	0.41
Chest circumference (cm)	33.2 ± 1.5	33.3 ± 2.3	33.2 ± 1.5	0.22

[a] Values were expressed as *mean* ± *SD*.
[b] Maternal serum lead level was classified as L-Pb (<1.18 μg/dl), M-Pb (1.18–1.70 μg/dl) and H-Pb (≥1.71 μg/dl).

These results suggest that higher serum lead concentration in the first trimester is positively associated with an elevated risk of SGA infants.

3.5. The rate and OR of SGA infants based on maternal serum Pb concentration in the second trimester

Serum Pb concentration in the second trimester was analyzed among 2042 pregnant women. Mean serum Pb level in the second trimester was 1.49 μg/dl (median: 1.43 μg/dl; minimum: 0.022 μg/dl; maximum: 5.46 μg/dl). The subjects were classified into three groups according to above-mentioned criteria. Demographic characteristics of 2042 pregnant women were compared among different groups. No difference in maternal characteristics was observed among three groups (Supplementary Table 3). Birth sizes were compared among different groups. As presented in Table 5, no difference in birth sizes was found among three groups. The correlation of birth sizes with maternal serum Pb concentration in the second trimester was presented in Table 6. Unexpectedly, no association was found between maternal serum Pb concentration in the second trimester and birth sizes. The association of maternal serum Pb level in the second trimester with the risk for SGA was shown in Table 7. The rate of SGA infants was 6.5% in subjects with L-Pb in the second trimester, 9.6% in subjects with M-Pb, and 9.2% in subjects with H-Pb, respectively. No difference was found among three groups (Table 7). The above-mentioned results suggest that no association is observed between maternal serum Pb level in the second trimester and the risk of SGA infants.

4. Discussion

Maternal Pb exposure during gestational period is related to some adverse pregnant outcomes. A matched case-control study showed that Pb concentration in maternal urine was positively correlated with an increased risk of preterm low birth weight (Zhang et al., 2015). According to a large cohort study, an inverse association of maternal blood Pb level with birth sizes, including birth weight, head circumference and crown-heel length, was observed (Taylor et al., 2015). Recently, we found that maternal serum Pb concentration was positively correlated with risk of preterm delivery in a large birth cohort study (Li et al., 2017). In this work, we firstly analyzed the correlation of maternal serum Pb concentration with neonatal sizes at birth. Our results demonstrated that birth weight, but not other birth sizes, was reduced in subjects with H-Pb when compared to that of subjects with L-Pb. To investigate the influence of maternal Pb exposure in different gestational periods on fetal development, the current work analyzed the correlation of neonate sizes at birth with maternal serum Pb concentration in different trimesters. Our results showed that birth weight was reduced in subjects with H-Pb in the first trimester. In addition, chest circumference was reduced in subjects with H-Pb in the first trimester. However, no difference on birth sizes was found among subjects with different levels of Pb in the second trimester. Taken together, the findings suggest that a reduction of birth weight and chest circumference is associated with maternal serum Pb level in the first trimester.

Whether gestational Pb exposure elevates the risk of SGA births remains contradictory. An early report from case-control study with 262 mother-infant pairs showed that pregnant women with blood Pb levels ≥10 μg/dl were more than a fourfold increase in SGA risk (adjusted *OR* = 4.2, 1.3–13.9) (Jelliffe-Pawlowski et al., 2006). According to a large retrospective cohort study, pregnant women with blood Pb levels of 5 and 10 μg/dl were with an average of 61-g and 87-g reduction of birth weight, but were not related to the rate of SGA infants (Zhu et al., 2010). Another report from birth cohort with 1835 subjects showed no association of maternal blood Pb concentration with risk of SGA infants (Thomas et al., 2015). In the current study, we explored the correlation of maternal serum Pb concentration with risk of SGA births. We showed that rate of SGA births was 10.1% in subjects with H-Pb, significantly higher than 8.7% in subjects with M-Pb and 6.2% in subjects with L-Pb. The adjusted *OR* for SGA was 1.69 in subjects with H-Pb and 1.45 in subjects with M-Pb. The association of risk of SGA infants with maternal serum Pb concentration in different trimesters was then analyzed. Our results showed that the subjects with H-Pb in the first trimester elevated risk of SGA infants. By contrast, no difference on rate of SGA infants was found among the subjects with H-Pb in the second trimester. Our results suggest that risk of SGA infants is associated with maternal serum Pb level in the first trimester but not in the second trimester.

Table 6
Association between birth sizes and maternal serum Pb level at different gestational stages.

Parameter	Unadjusted			Adjusted[a]		
	β[b]	95%CI	P	β[b]	95%CI	P
First trimester						
Birth weight	−4.41	−8.25, −0.57	0.02	−4.40	−8.22, −0.58	0.02
Birth length	−0.022	−0.049, 0.004	0.10	−0.022	−0.048, 0.005	0.10
Head circumference	−0.007	−0.021, 0.007	0.31	−0.007	−0.022, 0.007	0.30
Chest circumference	−0.015	−0.030, < 0	0.04	−0.015	−0.030, < 0	0.04
Second trimester						
Birth weight	−1.61	−4.81, 1.59	0.33	−1.64	−4.80, 1.53	0.31
Birth length	−0.006	−0.020, 0.009	0.44	−0.006	−0.020, 0.009	0.42
Head circumference	−0.008	−0.024, 0.008	0.35	−0.008	−0.024, 0.008	0.34
Chest circumference	−0.002	−0.016, 0.011	0.75	−0.002	−0.016, 0.011	0.72

[a] Linear models were performed with adjustment for pre-pregnancy BMI, maternal age, time of serum collection, gravidity, parity and monthly income.
[b] Regression coefficient.

Table 7
Association between risk for SGA and maternal serum Pb level at different gestational stages.

Parameter	Maternal serum lead level[a]			P-value
	L-Pb	M-Pb	H-Pb	
First trimester				
Newborns, n	363	343	377	
SGA, n	21	24	44	
Rate, %	5.8	7.0	11.7	0.009
Univariate *OR* (95% *CI*)	1.00	1.23 (0.67, 2.24)	2.15 (1.25, 3.70)	0.0101
Adjusted *OR* (95% *CI*)[b]	1.00	1.19 (0.65, 2.19)	2.13 (1.24, 3.38)	0.011
Second trimester				
Newborns, n	679	699	664	
SGA, n	44	67	61	
Rate, %	6.5	9.6	9.2	0.08
Univariate *OR* (95% *CI*)	1.00	1.53 (1.03, 2.27)	1.46 (0.98, 2.19)	0.082
Adjusted *OR* (95% *CI*)[b]	1.00	1.57 (1.05, 2.34)	1.48 (0.98, 2.21)	0.066

[a] According to tertile division, maternal serum lead level was classified as L-Pb (<1.18 μg/dl), M-Pb (1.18–1.70 μg/dl) and H-Pb (≥1.71 μg/dl).
[b] Adjusted for prepregnancy BMI, maternal age, gravidity, parity and monthly income.

An earlier cohort study reported that maternal cadmium exposure during gestational period was inversely related to birth sizes in girls, but not in boys (Kippler et al., 2012). However, whether there is inverse correlation of maternal serum Pb concentration with risk of SGA infants in a gender-dependent manner remains unknown. In the current study, we further analyzed the correlation of maternal serum Pb concentration with risks of SGA boys or girls. Our results showed that gestational serum Pb level was negatively correlated with risk of SGA infants in girls, but not in boys. We hypothesize that Pb may interfere with growth hormone (GH)/insulin-like growth factor (IGF) axis and thus inhibit fetal growth in a gender-dependent manner. Indeed, an early animal experiment showed that maternal rats administrated daily with Pb during the whole pregnancy had lower serum IGF-1 level (Dearth et al., 2002). For human pregnancies, IGF-1 plays an important role in fetal growth and development (Walenkamp et al., 2013). A previous epidemiologic investigation observed that umbilical cord plasma IGF-1 concentrations were higher in female infants than in male infants (Geary et al., 2003). Thus, additional work is required to explore the effects of maternal Pb exposure on GH/IGF axis.

Several animal experiments found that gestational exposure to heavy metals, such as cadmium, at middle and late gestational stages induced fetal IUGR in mice (Ji et al., 2011; Wang et al., 2016b, 2012). Until now, no report analyzed the association of maternal Pb exposure at different gestational stages with risk of SGA infants. In this work, we measured serum Pb concentration in different trimesters. Although there was no difference on serum Pb concentration between the first trimester and the second trimester, the rate of SGA infants was elevated only in the subjects with H-Pb in the first trimester. The adjusted *OR* for SGA was 2.13 (95%*CI*: 1.24, 3.38) in subjects with H-Pb in the first trimester. In contrast, no difference in the rate of SGA infants was found between the subjects with H-Pb and L-Pb in the second trimester. Our findings suggest that maternal Pb exposure in the first trimester, but not in the second trimester, elevates the risk of SGA births. These results are completely opposite to those of previous reports, in which maternal cadmium exposure at middle gestational stage, but not at early gestational stage, elevates risk of SGA infants (Wang et al., 2016a). Thus, it is especially interesting and worth further exploration in future works.

This study has several limitations. Firstly, this study had not analyzed the correlation of maternal serum Pb concentration with maternal Pb concentration in the whole blood in different trimesters. Secondly, the present study did not rule out the influence of other metals, such as cadmium, arsenic, mercury, zinc and selenium, on neonatal sizes at birth. Indeed, several studies showed that gestational cadmium and arsenic exposure was inversely corrected with neonatal sizes at birth (Kippler et al., 2012; Thomas et al., 2015). In contrast, gestational serum zinc level was positively correlated with neonatal sizes at birth (Wang et al., 2015). Thirdly, although cigarette smokers were excluded from this study, the present study had not quantitatively evaluated the influence of environmental tobacco smoke exposure on SGA as a confounding factor. Finally, the present study had not explored the mechanism through which maternal Pb exposure elevates the risk of SGA infants. An early study showed an evidence of endoplasmic reticulum stress in IUGR placentas (Yung et al., 2008). A recent animal experiment showed that prolonged endoplasmic reticulum stress impaired not only placental development and morphogenesis but also placental transport and endocrine functions (Kawakami et al., 2014). Indeed, several heavy metals including cadmium and Pb are inducers of ER stress (Mostafalou et al., 2015; Wang et al., 2012). Thus, additional work is required to explore the association among Pb-induced ER stress, placental development and IUGR.

5. Conclusion

High maternal serum Pb concentration in the first trimester, but not in the second trimester, is associated with elevated risk for SGA infants.

Author contributions

DXX and FBT designed the research; JL, HW, LL and JHH conducted the research, HW, JL, YHC, ZY and LF analyzed data; DXX and HW wrote this manuscript. All authors have read and approved the final version of the manuscript.

Conflict of interest

All authors have no conflicts of interest to declare.

Acknowledgements

We thank Yuan-Yuan Yang for providing guidance on Pb measurement. The present study was supported by the National Natural Science Foundation of China (81473016, 81630084, and 81471467) and the National Key Technology R & D Program (2006BAI05A03 to C-ABCS).

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.taap.2017.07.020.

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