Elevated total bile acid levels during late pregnancy are associated with the risk of small-for-gestational-age infants

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Abstract

Background Intrahepatic cholestasis of pregnancy (ICP) is common in pregnant women and is diagnosed by detecting serum total bile acid (TBA) levels. We aimed to investigate the association between serum total bile acid (TBA) levels during late pregnancy and the incidence of small-for-gestational-age (SGA) infants in a Chinese population.

Methods The present study was a retrospective cohort study that included 11811 eligible mother-and-singleton-offspring pairs. The correlations between TBA levels and birth sizes, including birth weight, birth length, head circumference and chest circumference, were explored. The relative risk (RR) with 95%CI for SGA infants were estimated among subjects with ICP by multiple logistic regression analysis.

Results Serum TBA levels were inversely linked with birth sizes. According to TBA levels, 11120 pregnant women were controls, 563 mild ICP, and 128 severe ICP. Birth sizes in ICP groups were lower than control group, and were the lowest in severe ICP group. Further analysis showed that 24.51% neonates were SGA infants among subjects with mild ICP (adjusted RR: 3.44; 95%CI: 2.72, 4.34) and 39.06% among subjects with severe ICP (adjusted RR: 6.54; 95%CI: 4.27, 10.02), higher than 7.39% among controls. For adjusted models, linear regression analysis showed that each 1 μ mol/L increase in TBA levels was associated with 11.1g (95%CI: -12.7, -9.5) decrease in birth weight, 0.045cm (95%CI: -0.053, -0.036) decrease in birth length, 0.034cm (95%CI: -0.040, -0.028) decrease in head circumference, and 0.041cm (95%CI: -0.047, -0.034) decrease in chest circumference, respectively.

Conclusion Elevated TBA levels during late pregnancy are associated with an increased risk of SGA infants.

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is one of the most prevalent obstetric diseases. An elevation in serum total bile acid (TBA) levels is the most accurate laboratory diagnostic evidence of ICP [1,2]. ICP occurs usually in the second half of pregnancy until delivery. The incidence of ICP is between 0.4% and 15% in different countries, ethnic populations and climatic conditions [3,4]. The majority of studies had demonstrated that elevated serum TBA levels was linked with adverse maternal outcomes in pregnant women with ICP, including 3-fold increased risks of gestational diabetes mellitus and pre-eclampsia [5-7]. A large cohort study from Sweden showed that women with higher TBA levels had increased risks of later liver and biliary tree cancer, later specifically diabetes mellitus, later autoimmune-mediated and cardiovascular diseases after childbirth [8]. On the other hand, several epidemiological studies reported the association between elevated TBA levels and increased risks of adverse fetal outcomes, including spontaneous and iatrogenic preterm delivery, a low (<7) 5-minute Apgar score, respiratory distress syndrome, meconium-stained fluid, stillbirth and intrauterine fetal death [3,9-11]. In addition, a report in human and rodent animal demonstrated that elevated TBA level was also associated with sex-specific increased susceptibility to severe obese, diabetic phenotype with hepatosteatosis in adult offspring, indicating a programming effect of the high bile acid exposure in utero [12,13].

Fetal growth restriction (FGR), which manifests as lower birth sizes and small for gestational age (SGA) infants, is highly prevalent and one of the leading causes for stillbirth, neonatal deaths and perinatal morbidity [14-16]. Several epidemiological reports showed that the risks of autism in childhood and cardiovascular and metabolic diseases in adulthood were increased in people born SGA [17-19]. Until now, no report analyzed the association between serum TBA levels and SGA infants in a cohort study. Therefore, the association between elevated serum TBA levels during late pregnancy and the risk of SGA infants needs to be determined in a large cohort study.

The objective of the present study was to analyze the association between serum TBA levels during late pregnancy and SGA infants in a large retrospective investigation. Our results found that there were inverse correlations between serum TBA levels and offspring birth sizes, including birth weight, birth length, head circumference and chest circumference. Additionally, birth sizes were significantly lower in the mild and severe ICP groups than in the control group, and were the lowest in the severe ICP group. Further analysis showed that ICP increased a risk of SGA infants. These results suggest that elevated serum TBA levels during late pregnancy are positively associated with the increased risk of SGA infants.

Subjects And Methods

Participants

We conducted a retrospective cohort study that included 13801 pregnant women between January 2011 and December 2014 in First Affiliated Hospital of Anhui Medical University for their antenatal care and delivery in Hefei, a central city in China. For this study, eligible participants were mother-and-singleton-offspring pairs in which pregnant women had detailed delivery records. Total 897 pregnant women no detailed delivery records, 270 fetal deaths or stillbirths, 294 pregnant women giving birth to multiple births, 147 induced-abortions and 382 unavailable serum TBA data were excluded from this study. Finally, 11811 (85.6%) mother-and-singleton-offspring pairs were eligible for this study. Data on biochemical parameters (aspartate transaminase, alanine transaminase, and bilirubin) were retrieved from the hospital records. According to serum TBA levels, pregnant women were divided into three groups: $TBA < 10 \mu\text{mol/L}$ for control, $10 \mu\text{mol/L} \leq TBA < 40 \mu\text{mol/L}$ for mild ICP and $TBA \geq 40 \mu\text{mol/L}$ for severe ICP [20]. The present study obtained ethics approval from the ethics committee of Anhui Medical University (No. 20160010). All participants signed a written informed consent for this study. All methods were carried out in accordance with the approved guidelines.

Definition of small-for-gestational age

The cutoff value used for defining the small-for-gestational age (SGA) is birth weight of live-born infants below the 10th percentile for gender and gestational age from a reference population for Chinese [21].

Statistical analysis

The incidence and relative risk (RR) of SGA infants were calculated among different groups. Multiple logistic regression models were used to estimate the risks of SGA infants in relation to ICP by crude and

adjusted RRs with 95% confidence intervals (95% CI). ANOVA and the Student-Newmann-Keuls post hoc test were used to determine differences among different groups. A *p*-value of <0.05 (two-tailed) or a 95%CI not including 1 and 0 (for relative risk) was considered statistically significant.

Results

The demographic characteristics and laboratory measurements of pregnant women

According to maternal serum TBA levels, 11120 pregnant women (94.15%) were control, 563 (4.77%) mild ICP, and 128 (1.08%) severe ICP in this cohort (Table 1). The demographic characteristics of pregnant women were preseaed in Table 1. No subjects were drinking or smoking throughout pregnancy. No significant differences on pre-pregnancy body mass index (BMI), parity and gravidity were observed among three groups. There was also no significant difference on gestational diabetes mellitus among three groups (Table 1). The incidences of gestational hypertension and preeclampsia were significantly higher in pregnant women with mild and severe ICP than controls (Table 1). Maternal serum TBA concentrations, serum aspartate transaminase concentrations, alanine transaminase concentrations, and serum total bilirubin concentrations were significantly higher in pregnant women with mild ICP and severe ICP as compared with controls (Table 2). Moreover, serum TBA concentrations, serum aspartate transaminase concentrations, alanine transaminase concentrations, and serum total bilirubin concentrations were significantly higher in pregnant women with severe ICP than those with mild ICP (Table 2).

Table 1 Maternal demographic characteristics

Demographic variables	Control	Mild ICP	Severe ICP	<i>P</i> -value
Pregnant women [n (%)]	11120 (94.15)	563 (4.77)	128 (1.08)	
Maternal age (years, mean $\pm$ SD)	28.2 $\pm$ 5.6	28.4 $\pm$ 5.1	28.9 $\pm$ 4.5	
<25 [n (%)]	1636 (14.71)	121 (21.49)	37 (28.91)	<0.001
25-34 [n (%)]	8227 (73.98)	371 (65.90)	71 (55.47)	
≥ 35 [n (%)]	1257 (11.30)	71 (12.61)	20 (15.63)	
Maternal BMI [kg/m ² , n (%)]	21.0 $\pm$ 2.9	21.0 $\pm$ 3.1	20.6 $\pm$ 3.4	
<18.5 [n (%)]	1916 (17.23)	113 (20.07)	29 (22.66)	0.159
18.5-22.9 [n (%)]	6875 (61.83)	328 (58.26)	79 (61.72)	
23.0-27.4 [n (%)]	2003 (18.01)	102 (18.12)	15 (11.72)	
≥ 27.5 [n (%)]	326 (2.93)	20 (3.55)	5 (3.90)	
Maternal education (years)				
≤ 9 (Junior school)	3527 (31.72)	298 (52.93)	74 (57.81)	<0.001
10-15 (High school)	3457 (31.09)	149 (26.47)	31 (24.22)	
≥ 16 (University)	3669 (32.99)	107 (19.00)	15 (11.72)	
Data missing	467 (4.20)	9 (1.60)	8 (6.25)	
Mode of delivery [n (%)]				
Vaginal delivery	6276 (56.44)	342 (60.75)	81 (63.28)	0.042
Cesarean delivery	4844 (43.56)	221 (39.25)	47 (36.72)	
Parity [n(%)]				
1	8288 (74.53)	418 (74.25)	89 (69.53)	0.432
≥ 2	2832 (25.47)	145 (25.75)	39 (30.47)	
Gravidity				
1	5931 (53.34)	297 (52.75)	61 (47.66)	0.428
≥ 2	5189 (46.66)	266 (47.25)	67 (52.34)	
Gestational diabetes mellitus [n(%)]				
Yes	922 (8.29)	55 (9.77)	12 (9.38)	0.429
No	10198 (91.71)	508 (90.23)	116 (90.62)	
Gestational hypertension [n(%)]				
Yes	614 (3.18)	74 (4.62)	8 (6.25)	0.029
No	10766 (96.82)	537 (95.38)	120 (93.75)	
Preeclampsia [n(%)]				
Yes	614 (5.52)	74 (13.14)	18 (14.06)	<0.001
No	10506 (94.48)	489 (86.86)	110 (85.94)	

Table 2 Laboratory measurements within the study population

Demographic variables	Control	Mild ICP	Severe ICP	P_{trend}
	(mean $\pm$ SD)	(mean $\pm$ SD)	(mean $\pm$ SD)	
Total bile acid (TBA), $\mu\text{mol/L}$	3.35 $\pm$ 1.98	17.19 $\pm$ 7.06	62.56 $\pm$ 23.01	<0.001
Aspartate transaminase, IU/L	23.1 $\pm$ 25.1	93.2 $\pm$ 128.8	168.7 $\pm$ 167.0	<0.001
Alanine transaminase, IU/L	18.3 $\pm$ 30.4	110.2 $\pm$ 152.6	189.3 $\pm$ 171.4	<0.001
Total bilirubin, $\mu\text{mol/L}$	8.04 $\pm$ 7.70	12.60 $\pm$ 11.41	33.92 $\pm$ 68.66	<0.001
Direct bilirubin, $\mu\text{mol/L}$	6.19 $\pm$ 2.84	7.52 $\pm$ 5.18	24.39 $\pm$ 33.80	<0.001
Indirect bilirubin, $\mu\text{mol/L}$	1.85 $\pm$ 2.41	4.08 $\pm$ 5.81	9.53 $\pm$ 10.30	<0.001

Birth sizes among different groups

The correlation between maternal serum TBA levels and birth sizes were analyzed. There were inverse correlations between maternal serum TBA levels and birth weight ($r=-0.173$, $P<0.001$), birth length ($r=-0.139$, $P<0.001$), head circumference ($r=-0.136$, $P<0.001$) and chest circumference ($r=-0.151$, $P<0.001$). Subjects were divided into three groups according to maternal serum TBA levels. Birth weight was compared among three groups. As shown in Figure 1A, birth weight was significantly decreased in mild ICP and severe ICP groups as compared with control group. Moreover, birth weight was significantly lower in pregnant women with severe ICP than pregnant women with mild ICP (Figure 1A). Stratification analyses based on neonates' gender was used to further compare birth weight among three groups. Results also showed that birth weight in both boys and girls were lower in the mild ICP and severe ICP groups than in the control group, whereas were the lowest in the severe ICP group (Figure 1A). Birth length, head circumference and chest circumference were then compared among three groups. As shown in Figure 1B-D, birth length, head circumference and chest circumference were significantly lower in the mild ICP and severe ICP groups than in the control group, and were the lowest in the severe ICP group. Stratification analyses based on neonates' gender was used to further compare birth length, head circumference and chest circumference among three groups. As shown in Figure 1B-D, birth length, head circumference and chest circumference in both boys and girls were lower in the mild ICP and severe ICP groups than in the control group, and were the lowest in the severe ICP group.

Association between ICP and the risk of SGA infants

The association between ICP and the risk of SGA infants was analyzed. As shown in Table 3, 24.51% neonates were SGA infants among subjects with mild ICP (RR: 4.07; 95%CI: 3.32, 4.99) and 39.06% among

subjects with severe ICP (RR: 8.03; 95%CI: 5.59, 11.54), higher than 7.39% among controls. After adjustment for maternal age, pre-pregnancy BMI, maternal education, parity, gestational diabetes mellitus, gestational hypertension and preeclampsia, RRs for SGA infants were 3.44 (2.72, 4.34) among subjects with mild ICP and 6.54 (4.27, 10.02) among subjects with severe ICP using multiple logistic regression model.

Stratification analyses based on neonates' gender was used to further explore the association between ICP and the risk of SGA infants using multiple logistic regression models. For boys, 25.00% neonates were SGA infants among subjects with mild ICP (RR: 4.69; 95%CI: 3.54, 6.19) and 34.72% among subjects with severe ICP (RR: 7.48; 95%CI: 4.55, 12.28), significantly higher than 6.64% among controls (Table 3). After adjustment for maternal age, pre-pregnancy BMI, maternal education parity, gestational diabetes mellitus, gestational hypertension and preeclampsia, RRs for SGA infants were 4.03 (2.92, 5.55) among subjects with mild ICP and 5.04 (2.83, 8.97) among subjects with severe ICP (Table 3). For girls, 23.94% neonates were SGA infants among subjects with mild ICP (RR: 3.50; 95%CI: 2.59, 4.74) and 44.64% among subjects with severe ICP (RR: 8.97; 95%CI: 5.25, 15.34), significantly higher than 8.25% among controls (Table 3). After adjustment for maternal age, pre-pregnancy BMI, maternal education parity, gestational diabetes mellitus, gestational hypertension and preeclampsia, RRs for SGA infants were 2.94 (2.08, 4.15) among subjects with mild ICP and 9.94 (5.21, 18.93) among subjects with severe ICP (Table 3).

Table 3 Crude and adjusted RRs for SGA in different groups

Demographic variables	Control (n=11120)	Mild ICP (n=563)	Severe ICP (n=128)
SGA [n (%)]	822 (7.39)	138 (24.51)	50 (39.06)
Crude <i>RR</i> (95% <i>CI</i>)	1.00	4.07 (3.32, 4.99)**	8.03 (5.59, 11.54)**
Adjusted <i>RR</i> (95% <i>CI</i>) ¹	1.00	3.44 (2.72, 4.34)**	6.54 (4.27, 10.02)**
Stratification analyses based on neonates' gender			
Boys (n)	5917	304	72
SGA [n (%)]	393 (6.64)	76 (25.00)	25 (34.72)
Crude <i>RR</i> (95% <i>CI</i>)	1.00	4.69 (3.54, 6.19)**	7.48 (4.55, 12.28)**
Adjusted <i>RR</i> (95% <i>CI</i>) ¹	1.00	4.03 (2.92, 5.55)**	5.04 (2.83, 8.97)**
Girls (n)	5203	259	56
SGA [n (%)]	429 (8.25)	62 (23.94)	25 (44.64)
Crude <i>RR</i> (95% <i>CI</i>)	1.00	3.50 (2.59, 4.74)**	8.97 (5.25, 15.34)**
Adjusted <i>RR</i> (95% <i>CI</i>) ¹	1.00	2.94 (2.08, 4.15)**	9.94 (5.21, 18.93)**

Adjustment for maternal age, pre-pregnancy BMI, maternal education, parity, gestational diabetes mellitus, gestational hypertension and preeclampsia.

<0.01 as compared with control.

Correlation between maternal serum TBA levels and birth sizes

Linear regression was used to explore the correlation between maternal serum TBA levels and birth weight. As shown in Figure 2A, for crude models, each 1 $\mu\text{mol/L}$ increase in maternal serum TBA levels was associated with a 14.6g (95%CI: -16.1, -13.1) decrease in birth weight among all subjects, 46.1g (95%CI: -51.9, -40.3) decrease in birth weight among controls, 21.9g (95%CI: -30.8, -13.0) decrease in birth weight among subjects with mild ICP, and 4.0g (95%CI: -9.3, 1.3) decrease in birth weight among subjects with severe ICP, respectively. After adjustment for maternal age, pre-pregnancy BMI, maternal education parity, gestational diabetes mellitus, gestational hypertension and preeclampsia, each 1 $\mu\text{mol/L}$ increase in maternal serum TBA levels was associated with a 11.1g (95%CI: -12.8, -9.4) decrease in birth weight among all subjects, 35.1g (95%CI: -41.2, -29.0) decrease in birth weight among controls, 19.1g (95%CI: -26.6, -11.6) decrease in birth weight among subjects with mild ICP, and 4.9g (95%CI: -11.3, 1.5) decrease in birth weight among subjects with severe ICP, respectively (Figure 2A). Stratification analyses based on neonates' gender was used to further explore the correlation between maternal serum TBA levels and birth weight using linear regression models. As shown in Figure 2A, an inverse correlation was observed between maternal serum TBA levels and birth weight in both boys and girls. The correlation between maternal serum TBA levels and birth length, head circumference and chest circumference were then analyzed based on linear regression models. After adjustment for maternal age, pre-pregnancy BMI, maternal education parity, gestational diabetes mellitus, gestational hypertension and preeclampsia, the birth length decreased by 0.045cm (95%CI: -0.054, -0.036) among all subjects, by 0.130cm (95%CI: -0.162, -0.098) among controls, by 0.064cm (95%CI: -0.105, -0.023) among subjects with mild ICP and by 0.047cm (95%CI: -0.086, -0.008) among subjects with severe ICP for each 1 $\mu\text{mol/L}$ increase of serum TBA levels, respectively (Figure 2B). The head circumference decreased by 0.034cm (95%CI: -0.040, -0.028) among all subjects, by 0.070cm (95%CI: -0.092, -0.048) among controls, by 0.067cm (95%CI: -0.098, -0.036) among subjects with mild ICP and by 0.012cm (95%CI: -0.040, 0.016) among subjects with severe ICP for each 1 $\mu\text{mol/L}$ increase of TBA levels, respectively (Figure 2C). The chest circumference decreased by 0.041cm (95%CI: -0.048, -0.034) among all subjects, by 0.121cm (95%CI: -0.147, -0.095) among controls, by 0.091cm (95%CI: -0.124, -0.058) among subjects with mild ICP and by 0.025cm (95%CI: -0.056, 0.006) among subjects with severe ICP for each 1 $\mu\text{mol/L}$ increase of TBA levels, respectively (Figure 2D). Stratification analyses based on neonates' gender was used to further explore the correlation between maternal serum TBA levels and birth length, head circumference and chest circumference. As shown in Figure 2B-D, inverse correlations were observed between maternal serum TBA levels and birth length, head circumference and chest circumference in both boys and girls.

Discussion

The present study analyzed the association between maternal serum TBA levels and birth sizes including birth weight, birth length, head circumference and chest circumference in a retrospective cohort study that included 11811 eligible mother-and-singleton-offspring pairs. Results showed that there was an inverse correlation between maternal serum TBA levels and birth sizes. The present study found that birth sizes

were significantly lower in the mild ICP and severe ICP groups than in the control group, and were the lowest in the severe ICP group. These results provide evidence that ICP is positively associated with SGA infants.

Maternal demographic characteristics, such as maternal age, pre-pregnancy BMI, parity and maternal education, were associated with birth weight and the risk of SGA. A number of epidemiological studies demonstrated that advanced maternal age, primiparity and low BMI before pregnancy elevated the risks of SGA and low birth weight infants [22-24]. Several reports indicated that the risk of SGA was higher in low educational subjects compared with high educational subjects [25,26]. On the other hand, pregnancy complications, such as gestational diabetes mellitus, gestational hypertension and pre-eclampsia, were also associated with birth weight and the risk of SGA. Several reports showed that gestational hypertension and pre-eclampsia elevated risk of SGA infants [27,28]. In contrast, gestational diabetes mellitus was significantly associated with higher birth weight and 2-fold increased risk of large for gestational age (LGA) infants and macrosomia [29,30]. In the present study, there were significant differences on maternal age and education among three groups. In addition, the incidences of gestational hypertension and preeclampsia were significantly higher in pregnant women with mild and severe ICP than those without cholestasis. Thus, the present study further estimated the adjusted RRs with 95%CI with respect to the incidence of SGA infants using multiple logistic regression models. After adjustment for maternal age, pre-pregnancy BMI, gestational diabetes mellitus, gestational hypertension and pre-eclampsia, the present study found that birth sizes were significantly lower in the mild ICP and severe ICP groups than in the control group, and were the lowest in the severe ICP group. There were a 3.4-fold increased risk of SGA infants among subjects with mild ICP and a 6.5-fold increased risk of SGA infants among subjects with severe ICP. These results suggest that differences of maternal demographics and pregnancy complications in the present cohort have little influence on the relationship between ICP and SGA infants.

The mechanism by which ICP elevates the risk of SGA infants remains obscure. Several case-control studies showed that the levels of proinflammatory cytokines and chemokines in placenta and maternal serum were significantly higher in the cholestasis group as compared to the control group [31,32]. Reports *in vivo* and *in vitro* found that bile acids stimulated the expression of a series of inflammatory cytokines and chemokines via activating both signal 1 and 2 of the NLRP3 inflammasome and NF- κ B pathway [33,34]. These studies indicated that cholestasis was associated with inflammation. Indeed, many epidemiological studies showed that maternal serum and umbilical cord serum TNF- α , C-reactive protein and IL-8 levels were significantly higher in the SGA group than in the control group [35]. According to a recent nest case-control study, strongly nuclear NF- κ B p65 immunoreactivity was observed in placentas from pregnant women with SGA infants [36]. Animal experiments also found that maternal inflammation resulted in FGR in rodents [37]. Therefore, we guess that maternal and placental inflammation may play a vital role in ICP-mediated SGA infants. On the other hand, a recent study reported that maternal serum TBA levels at diagnosis and at delivery were correlated positively with umbilical cord blood TBA levels, which provides evidence that bile acids could transport across the placenta [38]. Recently, numerous reports found that bile acids induced oncosis, necrotic cell death and apoptosis [39,40]. Thus, the present study does not exclude that ICP-associated SGA infants is due to the direct toxic effect of bile acids.

The present study laid emphasis on whether ICP was positively associated with SGA infants in a cohort study. However, the present study has three faults. First, as this was a retrospective study, the data of the treatment to mothers diagnosed with ICP were unavailable for analysis. Second, the present cohort included only Chinese population, so our results should be treated cautiously when branched out to other ethnic populations.

In summary, the present study investigated the association between serum TBA levels and the incidence of SGA infants in a large retrospective cohort study. Our results found that serum TBA levels were inversely linked with birth sizes. ICP elevated the risk of SGA infants. These results provide evidence that ICP is positively associated with SGA infants. Thus, it is suggested that the prevention and treatment of elevated serum TBA levels should be recommended in pregnant women.

Declarations

Abbreviations

ICP, Intrahepatic cholestasis of pregnancy; SGA, small for gestational age; FGR, fetal growth restriction; TBA, total bile acid; RR, relative risk; 95%CI, 95% confidence intervals.

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Authors' contributions

YHC and DXX designed research; LL, WC, XXQ, LM, ZBL, XL, XXG, HW and MZ conducted research. YYY and XLL provided obstetric expertise. YHC, LL and WC analyzed data and performed statistical analysis; YHC wrote paper; YHC had primary responsibility for final content.

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Availability of data and materials

The datasets used or analyzed in current study are available from the corresponding author on reasonable requests.

Ethics approval and consent to participate

The present study obtained ethics approval from the ethics committee of Anhui Medical University (No. 20160010). All participants signed a written informed consent for this study. All methods were carried out in accordance with the approved guidelines.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interest.

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Figures

Figure 1

Birth sizes among different groups. Means in birth sizes were compared among different groups. (A) birth weight. (B) birth length. (C) head circumference. (D) chest circumference. Left, all subjects; middle, boys; right, girls. Data were expressed as means $\pm$ SD. **P<0.01.

Figure 2

Association between maternal serum TBA levels and birth sizes based on linear regression analyses. Linear regression was used to explore the association between maternal serum TBA levels (independent variables) and birth sizes (dependent variables). (A) Birth weight. (B) Birth length. (C) Head circumference. (D) Chest circumference. Left, all subjects; middle, boys; right, girls. M-ICP, mild ICP; S-ICP, severe ICP. Adjusted for maternal age, pre-pregnancy BMI, maternal education, parity, gestational diabetes mellitus, gestational

hypertension and preeclampsia. Data are mean difference (95% CI) in birth sizes for each 1 μ mol/L increase in serum TBA levels. A 95%CI not including 0 was considered statistically significant.