Fetuin-A in Infants Born Small- or Large-for-Gestational-Age

Wen-Juan Wang1,2†, Shufan Wang2†, Meng-Nan Yang1,2†, Yu Dong1†, Hua He1†, Fang Fang1, Rong Huang2, Xiao-Gang Yu1, Guang-Hui Zhang3, Xia Zhao3, Tao Zheng4, Xiao-Yi Huang5, Jun Zhang1, Fengxiu Ouyang1* and Zhong-Cheng Luo1,2* for the Shanghai Birth Cohort

1 Ministry of Education-Shanghai Key Laboratory of Children’s Environmental Health, and Department of Pediatrics, Xinhua Hospital, Shanghai Jiao-Tong University School of Medicine, Shanghai, China, 2 Department of Obstetrics and Gynecology, Faculty of Medicine, Dalla Lana School of Public Health, Lunenfeld-Tanenbaum Research Institute, Prosserman Center for Population Health Research, Mount Sinai Hospital, and Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada, 3 Department of Clinical Assay Laboratory, Xinhua Hospital, Shanghai Jiao-Tong University School of Medicine, Shanghai, China, 4 Department of Obstetrics and Gynecology, Xinhua Hospital, Shanghai Jiao-Tong University School of Medicine, Shanghai, China, 5 Department of Pediatric, International Peace Maternity and Child Health Hospital, Shanghai Jiao-Tong University School of Medicine, Shanghai, China

Fetuin-A is a multifunctional glycoprotein that has been implicated in insulin resistance and bone metabolism. We assessed whether fetuin-A is associated with poor or excessive fetal growth. In the Shanghai Birth Cohort, we conducted a nested case-control study of 60 trios of small-for-gestational-age (SGA, birth weight <10th percentile), optimal-for-gestational-age (OGA, 25–75th, the reference) and large-for-gestational-age (LGA, >90th percentile) infants matched by sex and gestational age. Cord plasma concentrations of fetuin-A and fetal growth factors [insulin, proinsulin, insulin-like growth factor (IGF)-I and IGF-II] were measured. Cord plasma fetuin-A concentrations were higher in SGA (809.4 ± 306.9 µg/ml, P = 0.026) and LGA (924.2 ± 375.9 µg/ml, P < 0.001) relative to OGA (680.7 ± 262.1 µg/ml) newborns, and were not correlated to insulin, proinsulin, IGF-I and IGF-II (all P > 0.2). Higher fetuin-A concentrations were associated with increased risks of SGA [OR = 1.67 (1.08–2.58) per SD increment, P = 0.024] and LGA [OR = 2.36 (1.53–3.66), P < 0.001]. Adjusting for maternal and neonatal characteristics and fetal growth factors, the elevated risk changed little for LGA [adjusted OR = 2.28 (1.29–4.01), P = 0.005], but became non-significant for SGA (P = 0.202). Our study is the first to demonstrate that fetuin-A may be involved in excessive fetal growth. This association is independent of fetal growth factors.

Keywords: insulin-like growth factor, large-for-gestational-age, small-for-gestational-age, insulin, fetuin A

INTRODUCTION

Fetuin-A or α2-HS-glycoprotein (AHSG) is a liver-derived glycoprotein, and has been implicated in insulin resistance and metabolic syndrome related disorders (1–4). Fetuin-A inhibits insulin receptor signaling by binding to insulin receptor tyrosine kinase (5, 6). AHSG knockout mice manifest improved insulin sensitivity (3). Human studies have associated elevated circulating
fetuin-A concentrations with diabetes, obesity and non-alcoholic fatty liver disease in adults. Abnormal (poor or excessive) fetal growth is associated with elevated risks of metabolic syndrome related disorders in adulthood. A variety of maternal and fetal elements may contribute to abnormal fetal growth. Fetuin-A has been implicated in the regulation of bone growth. Animal studies showed that AHSG knockout mice had stunted femur growth. However, growth restricted pigs had higher plasma fetuin-A concentrations compared with normal sized littermate at birth, suggesting fetuin-A may have different implications for fetal growth across species.

Both insulin resistance and bone growth are relevant for fetal growth, suggesting that fetuin-A may be implicated in abnormal fetal growth. A negative association has been observed between maternal circulating fetuin-A level and fetal growth. Data are scarce concerning whether cord blood fetuin-A is associated with fetal growth. A small study reported no significant differences in cord serum fetuin-A concentrations between newborns with growth restriction (n = 20) vs. normal birth weight (19), while another small study reported marked defects in the glycosylation of fetuin-A in small-for-gestation-age (n = 10) newborns. We are unaware of any study on cord blood fetuin-A concentration in excessive fetal growth. The aim of the present study was to evaluate whether cord blood fetuin-A concentration is associated with poor or excessive fetal growth.

**MATERIALS AND METHODS**

**Study Design, Population and Specimens**

We performed a nested matched case-control study based on the recently described Shanghai Birth Cohort (SBC). Briefly, the SBC is a prospective birth cohort study including 4,127 pregnant women in Shanghai, 2013–2016. Data on maternal, pregnancy and delivery characteristics were collected. Umbilical cord blood samples [in multiple tubes for serum (non-coagulant) and plasma (EDTA)] were collected in a standardized protocol by trained research staff immediately after delivery. Serum and plasma samples were obtained by centrifugation (centrifuge: BECKMAN COULTER Allegra X-15R, USA) at 4°C, 4,000 rpm for 10 min, and were stored in multiple aliquots at −80°C until assays. The study was approved by the research ethics committees of Xinhua Hospital (ref no. M2013-010) and all participating hospitals, Shanghai, China. Written informed consent was obtained from all study participants. The study adhered to the guidelines of the Declaration of Helsinki.

There were a total of 3,692 singleton live births with data available on birth weight and gestational age. Birth weight was measured by an electronic weighing device to the nearest gram. Gestational age (weeks) was calculated based on the date of last menstruation period (LMP) and confirmed by first trimester ultrasound dating. If the ultrasound dating was more than 2 weeks from the LMP-based estimate, the ultrasound dating-based gestational age was used. Infants were classified as small-for-gestational-age (SGA, <10th percentile), appropriate-for-gestational-age (AGA, between 10 and 90th percentile) and large-for-gestational-age (LGA, >90th percentile) according to the 2015 Chinese sex- and gestational age-specific birth weight standards. Among the AGA infants, we defined optimal-for-gestational-age (OGA) as birth weight between 25 and 75th percentiles, for the purpose of maximizing the contrasts to infants with poor (SGA) or excessive (LGA) fetal growth.

The present study is a random sample of 60 trios of SGA, OGA and LGA infants matched by sex (the same) and gestational age at birth (within 1 week). Eligible study subjects must meet all the following criteria: (1) Han ethnicity (the majority ethnic group); (2) maternal age 20–45 years; (3) natural conception; (4) singleton pregnancy; (5) free of maternal severe chronic disease or severe pregnancy complications (e.g., diabetes, heart disease, preeclampsia/eclampsia); (6) no birth defects; (7) 5-min Apgar score > = 7; (8) cord blood specimens available for biomarker assays. Therefore, the study sample included 180 singleton newborns (60 × 3). Their mothers were all non-smokers. **Figure 1** presents the flowchart in the selection of study subjects. The study had a power of 85% to detect a 0.6 SD or greater difference in cord plasma fetuin-A concentration between SGA vs. OGA, or LGA vs. OGA infants, accounting for multiple tests.

**Biochemical Assays**

Plasma fetuin-A (R&D system, Minnesota, USA), proinsulin (Mercodia, Uppsala, Sweden), and IGF-II (R&D system, MI, USA) were measured by enzyme-linked immunosorbent assay (ELISA) kits, and the absorbance was determined using a microplate spectrophotometer (Beckman CX7, USA). Serum insulin and insulin-like growth factor I (IGF-I) concentrations were detected by automated chemiluminescent assays (ADVIA Centaur and Immulite 2000, SIEMENS, Germany). The minimal detectable concentrations were 0.62 ng/ml for fetuin-A, 3.5 pmol/L for insulin, 1.7 pmol/L for proinsulin, 25 ng/ml for IGF-I and 1.88 pg/ml for IGF-II, respectively. The intra-assay and inter-assay coefficients of variation were in the range of 0.5–8.3% for fetuin-A, 2.0–6.5% for insulin and IGF-I, 0.34–5.0% for proinsulin, and 2.4–9.3% for IGF-II, respectively. We measured not only insulin but also proinsulin because both are positively associated with birth weight.

**Statistical Analysis**

Continuous variable data were presented as Mean ± SD. Categorical variable data were presented as n (%). Biomarker data were log-transformed for t-tests and correlation analyses. Paired Student's t-test and Chi-squared test were used to evaluate the differences between two groups (SGA vs. OGA; LGA vs. OGA). Pearson partial correlation coefficients were calculated to evaluate the associations of cord blood fetuin-A with fetal growth factors adjusted for gestational age at...
Wang et al. Fetuin-A in SGA or LGA

FIGURE 1 | Flowchart in the selection of study subjects in a nested matched case control study of SGA, LGA, and OGA newborns in the Shanghai Birth Cohort. SGA, small-for-gestational-age (birth weight <10th percentile); LGA, large-for-gestational-age (>90th percentile); OGA, optimal-for-gestational-age (25–75th percentiles).

Multinomial logistic regression models were fitted to assess the associations of cord blood fetuin-A with abnormal fetal growth (SGA, LGA) adjusted for maternal and neonatal characteristics. Z (standard deviation) scores of biomarker data were used in multinomial logistic regression models to facilitate the comparisons of effect sizes. There were no significant interactions between predictor variables affecting the primary effect estimates of interest. P < 0.025 was considered statistically significant in testing the primary hypothesis on the differences in fetuin-A concentrations between SGA vs. OGA, or LGA vs. OGA infants (Bonferroni correction for 2 tests).

Data analyses were performed using R, Version 3.5.1. Packages PPCOR and NNET were used in partial correlation and multinomial logistic regression analyses, respectively. The frequencies of missing values in co-variables were low (<7%). In the multinomial logistic regression analyses, multiple imputations were conducted using the MICE package in R. We created 25 datasets with imputations on missing data, and presented the results on the pooled regression coefficient statistics. We conducted sensitivity analysis to examine the multinomial logistic regression results without data imputations on missing values.

RESULTS

Maternal and neonatal characteristics are presented in Table 1. LGA newborns had higher maternal pre-pregnancy BMI, and were more frequently delivered by cesarean section than OGA newborns. As expected, mothers of LGA infants had higher blood glucose concentrations in the 75 g 2-h oral glucose tolerance tests (fasting, 1-h and 2-h) at 24–28 weeks of gestation. SGA infants had lower maternal pre-pregnancy BMI, but did not differ significantly from OGA infants in other characteristics.

Compared to OGA infants, cord plasma fetuin-A concentrations were significantly higher in both SGA (P = 0.024) and LGA (P < 0.001) infants (Table 2 and Figure 2). For all fetal growth factors (insulin, IGF-I, and IGF-II), cord blood
DISCUSSION

We observed elevated cord blood fetuin-A concentrations in infants with poor (SGA) or excessive (LGA) fetal growth relative to infants with optimal fetal growth (OGA). Higher cord blood fetuin-A concentrations were associated with an increased risk of LGA independent of fetal growth factors.

Our study is the first to report a strong positive association between cord blood fetuin-A and excessive fetal growth. The association is independent of IGF-I, IGF-II, proinsulin and insulin, suggesting it may be mediated by pathways other than fetal growth factors. Our data confirmed that cord blood IGF-I and IGF-II or maternal fasting blood glucose (all \( P > 0.2 \), Table 3).

Without any adjustment, higher cord plasma fetuin-A concentrations were associated with increased odds of both LGA and SGA (Table 4). Adjusted for maternal and neonatal characteristics, the OR for SGA became no longer statistically significant, while the OR remained highly significant for LGA (OR = 2.42, 95% CI 1.47–3.97). Among the fetal growth factors, higher cord blood IGF-I and proinsulin concentrations were strongly associated with a lower odds of SGA and a higher odds of LGA. Higher cord blood insulin concentrations were associated with a lower odds of SGA (OR = 0.45, 95% CI 0.25–0.81). Cord plasma IGF-II was not associated with SGA or LGA.

In the fully adjusted model including maternal, neonatal characteristics and fetal growth factors (Table 5), the OR for fetuin-A in association with LGA or SGA changed little compared to the OR adjusted for maternal and neonatal characteristics only (Table 4). The elevated risk after the adjustment remained significant for OR = 2.28, \( P = 0.005 \), and became not statistically significant for SGA (OR = 1.41, \( P = 0.202 \)). Similar findings were observed in the multinomial logistic regression analyses without imputations for missing data (results not shown).

**TABLE 1 | Cord blood concentrations of fetuin-A and fetal growth factors in SGA, OGA, and LGA infants.**

| Biomarker          | SGA       | OGA       | LGA       | \( P^a \)  | \( P^b \)  |
|--------------------|-----------|-----------|-----------|-----------|-----------|
| Insulin (pmol/L)   | 35.3 ± 34.9 | 21.7 ± 16.3 | 20.9 ± 18.1 | 0.027     | 0.404     |
| Proinsulin (pmol/L)| 19.9 ± 16.6 | 12.3 ± 6.3  | 12.2 ± 6.2  | 0.075     | 0.119     |
| IGF-I (ng/mL)      | 29.0 ± 0.311| 29.0 ± 1.41 | 28.8 ± 1.4  | 0.080     | 0.210     |
| IGF-II (ng/mL)     | 0.311 ± 0.010| 0.311 ± 0.010| 0.311 ± 0.010| 0.100     | 0.210     |

Data presented are Mean ± SD, SGA, small-for-gestational-age (birth weight <10th percentile); OGA, optimal-for-gestational-age (25–75th h percentiles); LGA, large-for-gestational-age (>90th percentile). \( P^a \) values comparing SGA and OGA groups; \( P^b \) values comparing LGA and OGA groups in paired t-tests of log-transformed biomarker data. P values in bold, \( p < 0.025 \).

**TABLE 2 | Maternal and neonatal characteristics in a matched study of SGA, OGA, and LGA singleton newborns in Shanghai Birth Cohort.**

| Characteristic                      | OGA       | SGA       | LGA       | \( P^a \)  | \( P^b \)  |
|-------------------------------------|-----------|-----------|-----------|-----------|-----------|
| N                                   | 60        | 60        | 60        |           |           |
| **Maternal characteristics**        |           |           |           |           |           |
| Age, years                          | 30.0 ± 3.5| 29.4 ± 3.3| 28.9 ± 3.5| 0.324     | 0.080     |
| >35                                 | 6 (10)    | 4 (6.7)   | 3 (5.0)   | 0.741     | 0.488     |
| Education (university)              | 39 (65)   | 36 (60)   | 38 (63)   | 0.491     | 0.752     |
| Drinking alcohol                    | 8 (13)    | 1 (1.7)   | 2 (3.3)   | 0.037     | 0.180     |
| Family history of diabetes          | 6 (10)    | 7 (12)    | 5 (8.3)   | 0.617     | 0.901     |
| Pre-pregnancy BMI (kg/m²)           |           |           |           |           |           |
| BMI group                           |           |           |           |           |           |
| Underweight (<18.5)                 | 8 (13)    | 15 (23)   | 1 (2)     |           |           |
| Normal weight (18.5–24.0)           | 45 (75)   | 31 (52)   | 36 (60)   |           |           |
| Overweight (>24.0)                  | 6 (10)    | 4 (6.7)   | 12 (20)   |           |           |
| Primiparity                         | 47 (78)   | 55 (92)   | 49 (82)   | 0.074     | 0.820     |
| **Neonatal characteristics**        |           |           |           |           |           |
| C-section delivery                  | 12 (20)   | 17 (28)   | 35 (58)   | 0.333     | <0.001    |
| Sex                                 | 33 (55)   | 33 (55)   | 33 (55)   | 1.00      | 1.00      |
| Gestational age (weeks)             | 39.6 ± 1.1| 39.5 ± 1.2| 39.6 ± 1.2| 0.130     | 0.825     |
| Birth weight (g)                    | 3,572 ± 264| 2,674 ± 293| 4,162 ± 351| <0.001   | <0.001   |
| z score                             | 0.13 ± 0.65| 1.63 ± 0.68| 2.10 ± 0.76| <0.001   | <0.001   |
| Birth length (cm)                   | 49.8 ± 1.2 | 48.7 ± 1.5 | 51.2 ± 1.1 | <0.001   | <0.001   |
| z score                             | -0.15 ± 0.98| -1.08 ± 1.30| 1.21 ± 1.00| <0.001   | <0.001   |

\( P^a \) values comparing SGA vs. OGA groups. \( P^b \) values comparing SGA vs. OGA groups matched by sex and gestational age (weeks) at delivery; all mothers were non-smokers. SGA, small-for-gestational-age (birth weight <10th percentile); OGA, optimal-for-gestational-age (25–75th h percentiles); LGA, large-for-gestational-age (>90th percentile).
and proinsulin concentrations are strongly associated with fetal growth (23, 24).

We observed higher cord blood fetuin-A concentrations in SGA vs. OGA infants, but the adjusted OR became not statistically significant, suggesting that the association may be an artifact of confounding factors. Similarly, a small study reported that fetuin-A concentrations were not different in infants with fetal growth restriction (n = 20) compared to normal birth weight infants (19). It should be cautioned that both our and previous studies were not powered to detect relatively small differences. It is unclear whether the higher cord blood fetuin-A concentrations in SGA infants are related to their increased insulin resistance in childhood (25). Long-term follow-up studies are required to address this question.

We are unaware of any research data on cord blood fetuin-A concentration in excessive fetal growth. We observed that LGA - an indicator of excessive fetal growth, was associated with substantially elevated cord blood fetuin-A concentrations. Interestingly, a study in prepubertal children observed higher fetuin-A concentrations in overweight/obese relative to underweight/normal weight children (4), consistent with our finding to some extent but at a different life stage. Moreover, studies in children and adults have associated elevated circulating fetuin-A concentrations with obesity and other metabolic disorders (26, 27). We might speculate that elevated fetuin-A concentrations in LGA infants may play a role in early life development of the vulnerability to metabolic syndrome related disorders.

We could not determine whether the elevated fetuin-A concentration in LGA infants is a cause or consequence of excessive fetal growth. A previous study using bidirectional Mendelian randomization analysis suggests that AHSG (the gene coding fetuin-A) is casually related to BMI (28), lending some support in fetuin-A’s role in the development of fetal overgrowth. The pathways relating fetuin-A to fetal growth are unknown. Studies have linked fetuin-A with insulin resistance (4). The production of pro-inflammatory cytokines as well as the mobilization of free fatty acids via toll-like-receptor-4 (1, 29). Some nutrients such as curcumin and niacin have been associated with decreased serum fetuin-A concentrations (30, 31). It remains to be explored whether these nutrients may be related to the association between fetuin-A and LGA.

The matched study is a powerful design to detect differences in cord blood biomarkers between groups. All study subjects are Chinese Han ethnicity, eliminating the potential confounding effect of ethnic difference in fetal growth. We used OGA (25–75th percentiles) rather than AGA (10–90th percentiles) infants as the comparison (control) group. This study approach may be more powerful in identifying the differences between infants with extreme (poor or excessive) vs. normal fetal growth due to stronger contrasts than a study using AGA as the comparison group (24). A main limitation is the lack of data on fetuin-A isoforms. We did not have the data on glycosylation and/or phosphorylation isoforms of fetuin-A. Future studies may further explore whether there are elevations in specific isoforms of cord blood fetuin-A in LGA infants. Our study was powered to
detect moderate to large differences (>0.6 SD), but not powered to detect small differences. This is an observational study, and causality could not be affirmed. Reverse causality could not be ruled out. The study sample was restricted to Chinese infants. More studies in other ethnic groups/populations are required to confirm the generalizability of the study findings.

In conclusion, cord blood fetuin-A concentrations were elevated in SGA and LGA infants. Fetuin-A may be involved in excessive fetal growth independent of fetal growth factors (insulin, IGF-I and IGF-II).

**TABLE 3** | Pearson partial correlation coefficients * of cord blood fetuin-A with fetal growth factors and maternal fasting glucose (24–28 weeks of gestation).

|       | r   | P   |
|-------|-----|-----|
| IGF-I | 0.023 | 0.772 |
| IGF-II| 0.090 | 0.237 |
| Insulin| 0.021 | 0.779 |
| Proinsulin| −0.006 | 0.939 |
| Maternal fasting glucose| 0.045 | 0.572 |

*IGF, insulin-like growth factor.

*Data presented are Pearson partial correlations in log-transformed data adjusting for gestational age at birth/blood sampling. The correlations were similar for small-for-gestational-age, optimal-for-gestational-age, and large-for-gestational-age infants; therefore, the results for the total sample were presented.

**TABLE 4** | Associations of cord blood fetuin-A and fetal growth factors (insulin, proinsulin, IGF-I, IGF-II) with the risks of SGA and LGA.

|       | Crude OR (95% CI) | P     | *Adjusted OR (95% CI) | P     |
|-------|-------------------|-------|----------------------|-------|
| Fetuin-A |                    |       |                      |       |
| SGA    | 1.67 (1.08–2.58)  | 0.024 | 1.46 (0.92–2.32)     | 0.110 |
| LGA    | 2.36 (1.53–3.66)  | <0.001| 2.42 (1.47–3.97)     | <0.001|
| IGF-I  |                    |       |                      |       |
| SGA    | 0.30 (0.16–0.55)  | <0.001| 0.34 (0.17–0.68)     | 0.003 |
| LGA    | 2.34 (1.50–3.85)  | <0.001| 2.49 (1.45–4.27)     | 0.001 |
| IGF-II |                    |       |                      |       |
| SGA    | 0.77 (0.52–1.14)  | 0.197 | 0.83 (0.54–1.28)     | 0.406 |
| LGA    | 1.25 (0.87–1.80)  | 0.224 | 1.43 (0.91–2.23)     | 0.120 |
| Insulin|                    |       |                      |       |
| SGA    | 0.48 (0.28–0.82)  | 0.008 | 0.45 (0.25–0.81)     | 0.009 |
| LGA    | 1.10 (0.79–1.52)  | 0.578 | 0.92 (0.63–1.35)     | 0.677 |
| Proinsulin |                |       |                      |       |
| SGA    | 0.12 (0.04–0.42)  | 0.001 | 0.15 (0.04–0.51)     | 0.003 |
| LGA    | 1.84 (1.15–2.93)  | 0.011 | 1.66 (1.05–2.62)     | 0.033 |

*Data presented are the effect estimates (OR) in the final models adjusting for maternal fasting glucose, pre-pregnancy BMI, primiparity, C-section and cord blood fetuin-A, IGF-I, IGF-II, insulin and proinsulin; other maternal and neonatal characteristic variables were excluded since they were not associated with SGA or LGA (p > 0.2) and did not affect the comparisons. The effect estimates are for per SD increase in each biomarker. P values in bold, p < 0.05.

**DATA AVAILABILITY STATEMENT**

The datasets presented in this article are not readily available because Access to the de-identified participant research data must be approved by the research ethics board on a case-by-case basis, please contact the corresponding author for assistance in data access request. Requests to access the datasets should be directed to Zhong-Cheng Luo, zcluo@lunenfeld.ca; Fengxiu Ouyang, ouyangfengxiu@xinhuaamed.com.cn.

**ETHICS STATEMENT**

The Institutional Review Board of Xinhua Hospital, Shanghai Jiao-Tong University School of Medicine approved this study (ref no. M2013-010, date of approval: August 23, 2013). The patients/participants provided their written informed consent to participate in this study.

**AUTHOR CONTRIBUTIONS**

Z-CL, JZ, and FO conceived the study with inputs from all co-authors. W-JW, M-NY, YD, HH, FF, RH, X-GY, G-HZ, XZ, TZ, X-YH, JZ, FO, and Z-CL contributed to the acquisition of research data. W-JW and SW conducted the literature review, data analysis, and drafted the manuscript. Z-CL is the guarantor of this work, has full access to all the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed in revising the article critically for
important intellectual content and approved the final version for publication.

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**REFERENCES**

1. Pal D, Dasgupta S, Kundu R, Maitra S, Das G, Mukhopadhyay S, et al. Fetuin-A acts as an endogenous ligand of TLR4 to promote lipop-induced insulin resistance. *Nat Med.* (2012) 18:1279–85. doi: 10.1038/nm.2851

2. Stefan N, Hennige AM, Staiger H, Machann J, Schick F, Krober SM, et al. Alpha2-Heremans-Schmid glycoprotein/fetuin-A is associated with insulin resistance and fat accumulation in the liver in humans. *Diabetes Care.* (2006) 29:853–7. doi: 10.2337/diacare.29.04.06.di05-1938

3. Mathews ST, Singh GP, Ranalletta M, Cintron VJ, Qiang X, Goustian AS, et al. Improved insulin sensitivity and resistance to weight gain in mice null for the Ahsg gene. *Diabetes.* (2002) 51:2450–8. doi: 10.2337/diabetes.51.8.2450

4. Shim YS, Kang MJ, Oh YJ, Baek JW, Yang S, Hwang IT. Fetuin-A as an alternative marker for insulin resistance and cardiovascular risk in prepubertal children. *J Atheroscler Thromb.* (2017) 24:1031–8. doi: 10.5551/jat.38323

5. Mathews ST, Chellam N, Srinivas PR, Cintron VJ, Leon MA, Goustian AS, et al. Alpha2-HSG, a specific inhibitor of insulin receptor autophosphorylation, interacts with the insulin receptor. *Mol Cell Endocrinol.* (2000) 186:47–98. doi: 10.1016/S0303-7207(00)00237-9

6. Auberger P, Falquerho L, Contreres JO, Pages G, Le Cam G, Rossi B, et al. Characterization of a natural inhibitor of the insulin receptor tyrosine kinase: cDNA cloning, purification, and anti-mitogenic activity. *Cell.* (1989) 58:631–40. doi: 10.1016/0092-8674(89)90098-6

7. Meex RCR, Watt MJ. Hepatokines: linking nonalcoholic fatty liver disease and insulin resistance. *Nat Rev Endocrinol.* (2017) 13:509–20. doi: 10.1038/nrendo.2017.36

8. Jaddoe VW, de Jonge LL, Hofman A, Franco OH, Steegers EA, Goustián AS, et al. Association of gestational weight gain with maternal and infant phenotypes: a pQCT study of GH-deficient and small-for-gestational-age (SGA) children. *Bone.* (2007) 41:875–81. doi: 10.1016/j.bone.2007.06.028

9. Zbucka-Kretowska M, Kuzmicki M, Telejko B, Goscić J, Ciborowski M, Lipinska D, et al. First-trimester irisin and fetuin-A concentration in predicting macrosomia. *J Matern Fetal Neonatal Med.* (2019) 32:2868–73. doi: 10.1080/14767058.2018.1450859

10. McGrath RT, Glastras SJ, Hocking SL, Fulcher GR. Large-for-gestational-age (LGA) birth weight curve for different gestational age. *Zhonghua Er Ke Za Zhi.* (2015) 31:93–107. doi: 10.15337/bbk.2015.0019

11. Goldstein RF, Abell SK, Ranasinha S, Misso M, Boyle JA, Black MH, et al. Similar effects of long-term exogenous growth hormone (GH) on bone and muscle parameters: a pQCT study of GH-deficient and small-for-gestational-age (SGA) children. *Bone.* (2007) 41:875–81. doi: 10.1016/j.bone.2007.06.028

12. Goldstein RF, Abell SK, Ranasinha S, Misso M, Boyle JA, Black MH, et al. Similar effects of long-term exogenous growth hormone (GH) on bone and muscle parameters: a pQCT study of GH-deficient and small-for-gestational-age (SGA) children. *Bone.* (2007) 41:875–81. doi: 10.1016/j.bone.2007.06.028

13. Mathews ST, Singh GP, Ranalletta M, Cintron VJ, Qiang X, Goustian AS, et al. Alpha2-HSG, a specific inhibitor of insulin receptor autophosphorylation, interacts with the insulin receptor. *Mol Cell Endocrinol.* (2000) 186:47–98. doi: 10.1016/S0303-7207(00)00237-9

14. Mathews ST, Singh GP, Ranalletta M, Cintron VJ, Qiang X, Goustian AS, et al. Alpha2-HSG, a specific inhibitor of insulin receptor autophosphorylation, interacts with the insulin receptor. *Mol Cell Endocrinol.* (2000) 186:47–98. doi: 10.1016/S0303-7207(00)00237-9

15. Pal D, Dasgupta S, Kundu R, Maitra S, Das G, Mukhopadhyay S, et al. Fetuin-A acts as an endogenous ligand of TLR4 to promote lipop-induced insulin resistance. *Nat Med.* (2012) 18:1279–85. doi: 10.1038/nm.2851

16. Stefan N, Hennige AM, Staiger H, Machann J, Schick F, Krober SM, et al. Alpha2-Heremans-Schmid glycoprotein/fetuin-A is associated with insulin resistance and fat accumulation in the liver in humans. *Diabetes Care.* (2006) 29:853–7. doi: 10.2337/diacare.29.04.06.di05-1938

17. Mathews ST, Chellam N, Srinivas PR, Cintron VJ, Leon MA, Goustian AS, et al. Alpha2-HSG, a specific inhibitor of insulin receptor autophosphorylation, interacts with the insulin receptor. *Mol Cell Endocrinol.* (2000) 186:47–98. doi: 10.1016/S0303-7207(00)00237-9

18. Meex RCR, Watt MJ. Hepatokines: linking nonalcoholic fatty liver disease and insulin resistance. *Nat Rev Endocrinol.* (2017) 13:509–20. doi: 10.1038/nrendo.2017.36

19. Jaddoe VW, de Jonge LL, Hofman A, Franco OH, Steegers EA, Goustian AS, et al. Association of gestational weight gain with maternal and infant phenotypes: a pQCT study of GH-deficient and small-for-gestational-age (SGA) children. *Bone.* (2007) 41:875–81. doi: 10.1016/j.bone.2007.06.028

20. Karamessinis PM, Malamitsi-Puchner A, Boutsikou T, Makridakis M, Vougas R. First trimester fetal growth restriction and cardiovascular risk factors in normal pregnancy and gestational diabetes. *Eur J Endocrinol.* (2002) 147:243–8. doi: 10.1530/eje.0.1470243

21. Zhang J, Tian Y, Wang W, Ouyang F, Xu J, Yu X, et al. Cohort profile: the shanghai birth cohort. *PLoS ONE.* (2011) 216:180–6. doi: 10.1016/j.atherosclerosis.2011.01.020

22. Zhu L, Zhang R, Zhang S, Shi W, Yan W, Wang X, et al. Chinese neonatal birth weight curve for different gestational age. *Zhonghua Er Ke Za Zhi.* (2015) 31:93–107. doi: 10.15337/bbk.2015.0019
Thakkinstian A, Chailurkit L, Warodomwichit D, Ratanachaiwong W, Yamwong S, Chanprasertyothin S, et al. Causal relationship between body mass index and fetuin-A level in the Asian population: a bidirectional mendelian randomization study. *Clin Endocrinol.* (2014) 81:197–203. doi: 10.1111/cen.12303

Hennige AM, Staiger H, Wicke C, Machicao F, Fritsche A, Haring HU, et al. Fetuin-A induces cytokine expression and suppresses adiponectin production. *PLoS ONE.* (2008) 3:e1765. doi: 10.1371/journal.pone.0001765

Oner-Iyidogan Y, Kocak H, Seyidhanoglu M, Gurdol F, Gulcubuk A, Yildirim F, et al. Curcumin prevents liver fat accumulation and serum fetuin-A increase in rats fed a high-fat diet. *J Physiol Biochem.* (2013) 69:677–86. doi: 10.1007/s13105-013-0244-9

Kaushik SV, Plaisance EP, Kim T, Huang EY, Mahurin AJ, Grandjean PW, et al. Extended-release niacin decreases serum fetuin-A concentrations in individuals with metabolic syndrome. *Diabetes Metab Res Rev.* (2009) 25:427–34. doi: 10.1002/dmrr.967

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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