Published in final edited form as:

J Pediatr Biochem. 2010 January 1; 1(3): 217–224.

Maternal obesity, diabetes mellitus and cord blood biomarkers in large-for-gestational age infants

Karen Mestan^{a,*}, Fengxiu Ouyang^b, Nana Matoba^a, Colleen Pearson^c, Katherin Ortiz^c, and Xiaobin Wang^b

^a Division of Neonatology, Children's Memorial Hospital, and Department of Pediatrics, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

^b Mary Ann and J. Milburn Smith Child Health Research Program, Children's Memorial Hospital and Children's Memorial Research Center, and Department of Pediatrics, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

^c Department of Pediatrics, Boston University School of Medicine and Boston Medical Center, Boston, MA, USA

Abstract

Infants born large-for-gestational age (LGA) are at risk for early childhood obesity. The aims of this study were to investigate factors associated with LGA status and their relationship to inflammatory biomarkers that have been implicated in the LGA infant at birth. Included were 364 mother-infant pairs enrolled as part of an ongoing longitudinal cohort study of infant birth weight being conducted at Boston Medical Center (BMC). LGA was defined as birth weight (BW) $\geq 90^{\text{th}}$ percentile of the reference population at BMC (N=45). Appropriate-for-gestational age (AGA) was defined as BW $< 90^{\text{th}}$ and $> 10^{\text{th}}$ percentile (N=319). Cord blood IL-6, IL-8, TNF-alpha and RANTES levels were analyzed from a larger panel of immune biomarkers measured using multiplex immunoassay. Multivariate regression models were used to determine the associations between LGA status, maternal BMI and diabetes (DM), which included either gestational or type 2 diabetes (T2DM), and cord blood biomarkers, with adjustment for important demographic and clinical variables. Maternal pre-pregnancy BMI within the obesity range ($\geq 30 \text{ kg/m}^2$), as well as DM, were each associated with increased risk of LGA (OR=2.64, 95% CI 1.31-6.20; OR=5.58, 95% CI 2.06-15.13, respectively). Among the 4 biomarkers, only RANTES (regulated on activation, normal T cell express and secreted upon uptake), which is a chemokine secreted by white adipose tissue, was significantly increased in LGA infants (beta-coefficient=0.37; 95% CI: 0.09, 0.65; $P < 0.01$). This association remained essentially unchanged after adjustment for maternal DM and BMI (beta-coefficient=0.37; 95% CI: 0.08, 0.65; $P = 0.01$). Ponderal index ($\text{PI} = \text{BW} \times 100 / \text{length}^3$) was also positively correlated with RANTES. Cord blood RANTES is selectively elevated with fetal macrosomia, independent of maternal factors. Further investigation of RANTES as a marker of LGA and future childhood health is warranted.

Keywords

Birth weight; large-for-gestational age; cord blood; inflammation; obesity; diabetes

* Correspondence: Assistant Professor of Pediatrics, Division of Neonatology, Children's Memorial Hospital, 2300 Children's Plaza, Box 45 Chicago, IL 60614, USA Tel: 773-880-4536; Fax: 773-880-3061; k-mestan@northwestern.edu .

1. Introduction

The incidence of fetal overgrowth ranges from 12 to 16 percent among high-risk pregnancies, and has been reported as high as 10.5 percent among non-diabetic, normal weight mothers (1). This is not only an important obstetric and neonatal clinical problem, but it is also linked to pediatric health. Infants born large-for-gestational age (LGA) are at risk for neonatal and early childhood problems. Among infants with fetal macrosomia and resultant LGA (defined as birth weight above the 90th percentile for gestational age), there is a higher rate of C-section delivery, birth trauma, neonatal hypoglycemia and respiratory distress syndrome (2). Long-term, infants born LGA are also at increased risk for future obesity, with a growing body of evidence suggesting that these outcomes may be a result of early fetal programming (3-5). This is of particular interest given the increasing rates of childhood obesity, and the risk of subsequent adulthood obesity, cardiovascular disease, and metabolic syndrome. Interestingly, high birth weight infants with early postnatal weight gain and childhood obesity may be at lower risk for future metabolic risk through mechanisms that remain unclear (6,7).

A growing body of evidence supports the interplay between inflammation, mother, and fetus in pregnancies at risk for LGA (8). We have previously reported that an inflammatory response in the fetus is associated with increased cord blood IL-6 and IL-8 (9). Others have reported distinct patterns of these and other proinflammatory cytokines at birth with maternal diabetes mellitus (DM) and obesity, two risk factors for LGA (10-13). We have also reported that intrauterine inflammation has a negative impact on neonatal growth in premature infants (14). However, the relationship between intrauterine inflammation and fetal overgrowth in term infants is not well-understood. It is possible that fetal inflammation may be secondary to maternal DM, maternal obesity, or both. Alternatively, cytokine production by the fetus may be a process independent of maternal factors.

In this study, we investigated the associations between fetal overgrowth, maternal clinical correlates of LGA, and cord blood biomarkers of fetal inflammation, as well as those associated with increased adiposity and insulin resistance. Identification of prenatal determinants and inflammatory biomarkers of LGA may enhance our understanding of the mechanisms surrounding fetal overgrowth and its impact on pediatric health.

2. Materials and methods

2.1. Study population

This study was conducted using a sample of patients from an ongoing molecular epidemiological study on environmental and genetic determinants of preterm birth and low birth weight conducted at Boston Medical Center (BMC), a large urban hospital serving a multi-ethnic, inner city population (15). This parent study is a case-control study in which cases are defined as either low birth weight (<2500 grams) or preterm (<37 weeks' gestation) births. Controls are defined as non-low birth weight and non-preterm births. Multiple gestation pregnancies and newborns with major birth defects were excluded. The patient population used in the study described below was drawn from the parent study's control group. This study was approved by the Institutional Review Boards at Boston University Medical Center and Children's Memorial Hospital.

2.2. Data Collection

After obtaining written informed consent, a questionnaire interview was conducted to obtain relevant information including demographic characteristics, medical and reproductive history. Maternal and infant medical records were reviewed to obtain clinical data including

prenatal care, clinical presentation, intrapartum management, pregnancy complications, and birth outcomes (infant gender, gestational age, birth weight and birth length).

2.3. Definition of maternal characteristics

Maternal variables examined included age at time of delivery, pre-pregnancy BMI, ethnicity, parity, cigarette smoking, drug and alcohol use either before or during pregnancy, and highest level of education achieved. Clinical variables included placental abruption, previa, clinical and histological chorioamnionitis, and mode of delivery and incidence of hypertensive disorders (pre-eclampsia, eclampsia, chronic hypertension, HELLP syndrome). Maternal obesity was defined as prepregnancy BMI ≥ 30 kg/m² according to the WHO and National Institutes of Health categories for weight status (16). Overweight was defined as BMI ≥ 25 to <30 kg/m²; normal weight as BMI ≥ 18.5 to <25 kg/m²; and underweight as BMI <18.5 kg/m². Since there were few patients with BMI in the underweight category (N=11), these patients were included in the normal category in the statistical analysis. DM was defined as having either gestational DM (any subtype) or pre-existing type 2 diseases (T2DM), and was based upon physician diagnosis and identified through medical record review.

2.4. Definition of the birth weight outcomes

LGA was defined as birth weight (BW) greater than or equal to the 90th percentile of the reference population at the same gestational week. Since 1995, the Department of Obstetrics and Gynecology at BMC has maintained a database of all pregnant women admitted to the labor and delivery service and their birth outcomes. The database now comprises more than 15,000 deliveries. In this study, we chose this internal population as a reference, using standardized birth weight (SBWT) as a continuous measure of fetal growth. SBWT was defined as birth weight standardized by the mean and variance in the corresponding ethnic group, sex, and gestational week in the reference population. We defined LGA as SBWT $\geq 90^{\text{th}}$ percentile of the SBWT in the reference population. Accordingly, the comparison group (AGA) was defined as SBWT above the 10th and below the 90th percentile of the SBWT in the reference population.

In order to take into account both body weight and length when assessing infant size at birth, we calculated ponderal index (PI) for each infant, defined as BW (g) $\times$ 100/Birth length³ (cm³). This measure has been recognized as an important complementary index of body proportionality that may provide better understanding of long-term outcomes related to birth weight (17).

2.5. Biomarker assays

Umbilical cord blood was collected at delivery, kept on ice and subsequently centrifuged for 10 minutes in a tabletop refrigerated centrifuge at 2500 rpm. Plasma was separated and stored at -80°C until assay. As part of the larger parent study, panels of 27 immune markers were assayed simultaneously using multiplex immunoassay (Luminex, Austin, TX). The methods for conduction and validation of the biomarker assays have been described in detail previously (9,18,19). For the present study, the following four biomarkers were selected: Interleukin (IL)-6, IL-8, TNF-alpha, and RANTES (regulated on activation, normal T cell expressed and secreted upon uptake), which is a chemokine released by white adipose tissue. These biomarkers were selected based upon previous studies implicating their roles as markers of fetal inflammation (9,20,21), obesity (10,22) and gestational DM (12,13,23,24).

2.6. Statistical Analyses

Patient demographics and characteristics were compared using F-test for continuous variables and Chi-squared tests for categorical data between AGA and LGA groups. Logistic regression was used to determine the associations between potential maternal determinants of LGA (maternal DM and pre-pregnancy BMI) on the outcome of LGA status (yes/no), adjusting for maternal age, race, parity, maternal education and infant gender.

Biomarker levels were natural log-transformed to approximate normal distribution. We used multiple linear regressions to determine the associations between each biomarker level (the dependent variable) with LGA status, using AGA as the reference. Therefore, the beta-coefficient represents the correlation between biomarker levels of LGA versus AGA infants. Models were adjusted for known clinical covariates of fetal growth, including maternal age, ethnicity, parity, level of education, substance abuse during pregnancy, type of delivery, and infant gender (Model 1). We further adjusted for maternal DM (yes/no) and the three categories of BMI (normal, overweight, and obese) (Model 2) to determine if associations of biomarkers with LGA were independent of maternal DM and BMI.

All p-values were from two-sided tests and all statistical analyses were performed using SAS v.9.1 (SAS Institute Inc., Cary, NC, USA). To account for multiple comparisons of 4 biomarkers, a bonferroni corrected p-value <0.0125 was used as the threshold for statistical significance.

3. Results

A total of 364 full-term births were studied. Of these, 45 infants were LGA and 319 were AGA. Table 1 shows the mother and infant demographics and clinical characteristics, according to LGA and AGA status. As expected, mean birth weight, SBWT, and PI were all significantly higher in the LGA group. There were no differences in maternal race, parity, level of education, or other reported pregnancy complications, infant gender or gestational age. There was a higher percentage of DM (either gestational or pre-existing) and of obese mothers (BMI >30 kg/m²) in the LGA group. The groups also differed with respect to mode of delivery, with a higher rate of C-section in the LGA group.

3.1. Maternal determinants of infant LGA status

As shown in Table 2, there was a significant increase in the risk of LGA with maternal obesity but not with maternal overweight (BMI ≥25 to <30kg/m²), and the highest odds ratio was in births with any DM. Subgroup analysis of DM and non-DM groups revealed that the associations between maternal DM (OR=4.57, 95% CI 1.37-15.25) and obesity (OR=2.65, 95% CI 1.13-6.21) were independently associated with LGA status. Furthermore, the association was strongest when maternal DM and obesity were both present (OR=7.67, 95% CI 1.83-32.09, P=0.005).

3.2. Associations between cord blood biomarkers and LGA status

Table 3 shows the associations from the linear regression analyses of cord blood IL-6, IL-8, TNF-alpha, and RANTES. When adjusted for maternal age, race, parity, maternal education, substance abuse, mode of delivery and infant gender (Model 1), only RANTES was increased with LGA (P<0.01). After adjustment for maternal BMI and DM (Model 2), RANTES remained significantly associated with LGA status (P=0.01). Cord blood IL-6, IL-8, and TNF-alpha were neither increased nor decreased with LGA status in either model.

3.3. Relative influence of fetal versus maternal size on cord blood RANTES

A large proportion of LGA infants were either born to mothers with normal BMI and no history of DM (31.8%) or to obese mothers without DM (27.7%). Therefore, we studied the patterns of association between RANTES and fetal size (ponderal index, or PI) according to maternal size, independent of DM. Figure 1 shows the plot of RANTES levels against infant PI and SBWT. Among infants born to mothers with normal BMI and no DM, the association between infant growth indices and RANTES was roughly linear and positive, with the strongest, most consistent linear association seen among non-overweight, non-obese mothers. A similar, yet less consistent pattern was seen when RANTES was plotted against SBWT (Figure 1).

4. Discussion

In this study, we confirmed previous observations that maternal obesity and DM are important, independent determinants of infant LGA status. We found that RANTES was selectively elevated in cord blood of LGA infants, while IL-6, IL-8, and TNF-alpha were not. This association persisted after adjustment for maternal BMI and DM, and was linearly correlated with increasing fetal size (ponderal index). Our findings demonstrate that maternal health status plays an important role in LGA status at birth. Moreover, the mechanisms for fetal overgrowth in pregnancies not complicated by maternal weight and DM may be distinct from those that are complicated by these risk factors. A new role for cord blood RANTES is suggested.

The associations between maternal obesity, DM, and fetal macrosomia have been reported in large-scale epidemiologic studies (1,25), and are confirmed in our predominantly African American inner-city population, for which LGA status is defined according to standardized birth weight curves generated by the reference population. Elevated insulin resistance in DM is a known mechanism of fetal overgrowth (26), in which higher than normal circulating glucose stores result in increased fat deposition as well as altered insulin kinetics in the developing fetus. There is compelling evidence that inflammatory processes during diabetic pregnancy have direct and indirect impact on the developing fetus (12). The link to maternal obesity, particularly in the absence of accompanying DM, is less well understood but may involve a less severe degree or early evolving insulin resistance (10).

In a previous study by Ategbro and colleagues, IL-6 and TNF-alpha are up-regulated in mothers with gestational DM (23). In cord blood of their macrosomic offspring, there are decreased levels of these adipocytokines which could be explained by a fetal down-regulation response to maternal inflammation, a lack of production by fetal adipocytes, or both. Our study supports the former of these two mechanisms, as IL-6 and TNF-alpha were neither increased nor decreased. In contrast to Ategbro's study, our LGA infants had a higher proportion of normal weight, non-DM mothers, allowing us to study the influence of LGA independent of maternal DM. In the absence of maternal inflammation secondary to DM, IL-6 and TNF-alpha in macrosomic infants were not significantly different from their AGA counterparts. Also in our study, TNF-alpha, which is perhaps the strongest predictor of insulin resistance in pregnancy (13), was significantly decreased in DM pregnancies as compared to non-DM pregnancies (beta-coefficient= -0.37 ± 0.14 ; 95%CI= $-0.65, -0.08$; $P=0.01$), supporting Ategbro's finding of down-regulation in the fetus with maternal DM.

This is the first report to identify RANTES as a potential marker of LGA status at birth. RANTES is a chemokine with IgG heavy chain moieties that has recently been reported to be increased in white adipose tissue in the setting of human obesity (27). This biomarker has been proposed as a mediator of obesity-related pathologies in adults (22). Activated macrophages and T-cells within adipose tissue may produce increased levels of cytokines

and chemokines, which in turn act as mediators of inflammation and impact organs involved in metabolic syndrome through paracrine or endocrine crosstalk. In individuals with type 2 DM, serum RANTES is elevated, but CCL5 gene polymorphisms are not associated with disease (24). This would suggest that increased RANTES levels may be a direct result of adiposity. Since our sample of mothers bearing LGA infants were predominantly of normal weight and non-diabetic, this might explain the selective elevation of RANTES that was not seen with IL-6, IL-8, or TNF-alpha. Moreover, the direct relationship between cord blood RANTES and fetal size was most consistently seen in non-obese, non-DM mothers (Figure 1) further supporting the role of RANTES as a marker of fetal macrosomia, independent of maternal disease.

Elevated RANTES in cord blood could be of fetal origin, maternal origin, or both, given that some evidence exists that the RANTES molecule is capable of crossing the placental barrier (28,29). Cord blood RANTES was less consistently associated with fetal size when the mother was overweight or obese (Figure 1). Furthermore, the positive correlation appeared to be more consistent with PI than SBWT. Since PI is comparatively a better measure of adiposity (17), our findings suggest that elevated RANTES is a marker of increased adiposity in LGA infants. We speculate that the fetus is producing higher than normal levels of RANTES in response to its own increased adiposity.

Certain limitations of our study include that we were not able to evaluate other related metabolic factors such as maternal or postnatal infant blood glucose or insulin status, or maternal cytokine levels. Whether increased cord blood RANTES at birth could be predictive of future childhood morbidity is a topic of future investigation. Unlike leptin and adiponectin (30), there is less evidence of the extent to which circulating RANTES may contribute to human disease related to obesity (31,32). In a preliminary review of our follow-up data, 15% of the LGA infants had a BMI within the obesity range (BMI>95th percentile for child age and gender) at 3-5 years of age. Among these LGA infants, mean maternal BMI was significantly higher in children who developed obesity, and highest among former LGA infants born to mothers with DM (Figure 2). Therefore, maternal risk factors appear to be a strong predictor of childhood obesity in LGA infants.

In conclusion, cord blood RANTES is selectively elevated in LGA births, independent of maternal DM and BMI. The role of cord blood biomarkers such as RANTES in understanding and predicting future childhood health warrants further investigation.

References

1. Ehrenberg HM, Mercer BM, Catalano PM. The influence of obesity and diabetes on the prevalence of macrosomia. *Am J Obstet Gynecol.* 2004; 191:964–968. [PubMed: 15467573]
2. Yogev Y, Visser GH. Obesity, gestational diabetes and pregnancy outcome. *Semin Fetal Neonatal Med.* 2009; 14:77–84. [PubMed: 18926784]
3. Barker DJ, Gluckman PD, Godfrey KM, Harding JE, Owens JA, Robinson JS. Fetal nutrition and cardiovascular disease in adult life. *Lancet.* 1993; 341:938–941. [PubMed: 8096277]
4. Garn SM, Clark DC. Trends in fatness and the origins of obesity Ad Hoc Committee to Review the Ten-State Nutrition Survey. *Pediatrics.* 1976; 57:443–456. [PubMed: 1264536]
5. Martorell R, Stein AD, Schroeder DG. Early nutrition and later adiposity. *J Nutr.* 2001; 131:874–880.
6. Bouhours-Nouet N, Dufresne S, de Casson FB, et al. High birth weight and early postnatal weight gain protect obese children and adolescents from truncal adiposity and insulin resistance: metabolically healthy but obese subjects? *Diabetes Care.* 2008; 31:1031–1036. [PubMed: 18223033]

7. Brufani C, Grossi A, Fintini D, et al. Obese children with low birth weight demonstrate impaired beta-cell function during oral glucose tolerance test. *J Clin Endocrinol Metab.* 2009; 94:4448–4452. [PubMed: 19820011]
8. Schmatz M, Madan J, Marino T, Davis J. Maternal obesity: the interplay between inflammation, mother and fetus. *J Perinatol.* 2010; 30:441–446. [PubMed: 19907427]
9. Mestan K, Yu Y, Thorsen P, et al. Cord blood biomarkers of the fetal inflammatory response. *J Matern Fetal Neonatal Med.* 2009; 22:379–387. [PubMed: 19529994]
10. Challier JC, Basu S, Bintein T, et al. Obesity in pregnancy stimulates macrophage accumulation and inflammation in the placenta. *Placenta.* 2008; 29:274–281. [PubMed: 18262644]
11. Nelson SM, Sattar N, Freeman DJ, Walker JD, Lindsay RS. Inflammation and endothelial activation is evident at birth in offspring of mothers with type 1 diabetes. *Diabetes.* 2007; 56:2697–2704. [PubMed: 17704300]
12. Radaelli T, Varastehpour A, Catalano P, Hauguel-de Mouzon S. Gestational diabetes induces placental genes for chronic stress and inflammatory pathways. *Diabetes.* 2003; 52:2951–2958. [PubMed: 14633856]
13. Richardson AC, Carpenter MW. Inflammatory mediators in gestational diabetes mellitus. *Obstet Gynecol Clin North Am.* 2007; 34:213–224. [PubMed: 17572268]
14. Mestan K, Yu Y, Matoba N, et al. Placental inflammatory response is associated with poor neonatal growth: preterm birth cohort study. *Pediatrics.* 2010; 125:891–898.
15. Wang X, Zuckerman B, Pearson C, et al. Maternal cigarette smoking, metabolic gene polymorphism, and infant birth weight. *JAMA.* 2002; 287:195–202. [PubMed: 11779261]
16. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser.* 2000; 894:1–253. [No authors listed].
17. Olsen IE, Lawson ML, Meinzen-Derr J, et al. Use of a body proportionality index for growth assessment of preterm infants. *J Pediatr.* 2009; 154:486–491. [PubMed: 19041096]
18. Matoba N, Yu Y, Mestan K, et al. Differential patterns of 27 cord blood immune biomarkers across gestational age. *Pediatrics.* 2009; 123:1320–1328. [PubMed: 19403498]
19. Skogstrand K, Thorsen P, Nørgaard-Pedersen B, Schendel DE, Sørensen LC, Hougaard DM. Simultaneous measurement of 25 inflammatory markers and neurotrophins in neonatal dried blood spots by immunoassay with xMAP technology. *Clin Chem.* 2005; 51:1854–1866. [PubMed: 16081507]
20. Hung TH, Chen SF, Hsu JJ, Hsieh CC, Hsueh S, Hsieh TT. Tumour necrosis factor- α converting enzyme in human gestational tissues from pregnancies complicated by chorioamnionitis. *Placenta.* 2006; 27:996–1006. [PubMed: 16376986]
21. Tasci Y, Dilbaz B, Onal B, Uzmez, et al. The value of cord blood interleukin-6 levels for predicting chorioamnionitis, funisitis and neonatal infection in term premature rupture of membranes. *Eur J Obstet Gynecol Reprod Biol.* 2006; 128:34–39. [PubMed: 16459014]
22. Matter CM, Handschin C. RANTES (regulated on activation, normal T cell expressed and secreted), inflammation, obesity, and the metabolic syndrome. *Circulation.* 2007; 115:946–948. [PubMed: 17325252]
23. Atègbo JM, Grissa O, Yessoufou A, et al. Modulation of adipokines and cytokines in gestational diabetes and macrosomia. *J Clin Endocrinol Metab.* 2006; 91:4137–4143. [PubMed: 16849405]
24. Herder C, Illig T, Baumert J, et al. RANTES/CCL5 gene polymorphisms, serum concentrations, and incident type 2 diabetes: results from the MONICA/KORA Augsburg case-cohort study, 1984-2002. *Eur J Endocrinol.* 2008; 158:1–5.
25. Boney CM, Verma A, Tucker R, Vohr BR. Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. *Pediatrics.* 2005; 115:290–296.
26. Catalano PM, Huston L, Amini SB, Kalhan SC. Longitudinal changes in glucose metabolism during pregnancy in obese women with normal glucose tolerance and gestational diabetes mellitus. *Am J Obstet Gynecol.* 1999; 180:903–916. [PubMed: 10203659]
27. Wu H, Ghosh S, Perrard XD, et al. T-cell accumulation and regulated on activation, normal T cell expressed and secreted upregulation in adipose tissue in obesity. *Circulation.* 2007; 115:1029–1038. [PubMed: 17296858]

28. Challita-Eid PM, Klimatcheva E, Day BT, et al. Inhibition of HIV type 1 infection with a RANTES-IgG3 fusion protein. *AIDS Res Hum Retroviruses*. 1998; 14:1617–1624. [PubMed: 9870314]
29. Derrien M, Faye A, Dolcini G, Chaouat G, Barré-Sinoussi F, Menu E. Impact of the placental cytokine-chemokine balance on regulation of cell-cell contact-induced human immunodeficiency virus type 1 translocation across a trophoblastic barrier in vitro. *J Virol*. 2005; 79:12304–12310. [PubMed: 16160157]
30. Díez JJ, Iglesias P. The role of the novel adipocyte-derived hormone adiponectin in human disease. *Eur J Endocrinol*. 2003; 148:293–300. [PubMed: 12611609]
31. Skopková M, Penesová A, Sell H, et al. Protein array reveals differentially expressed proteins in subcutaneous adipose tissue in obesity. *Obesity*. 2007; 15:2396–2406. [PubMed: 17925465]
32. Fain JN, Tague BM, Cheema P, Madan AK, Tichansky DS. Release of 12 adipokines by adipose tissue, nonfat cells, and fat cells from obese women. *Obesity*. 2010; 18:890–896. [PubMed: 19834460]

Figure 1.

Smoothing plot of infant ponderal index (PI) and standardized birth weight (SBWT) against RANTES among babies born to non-DM mothers

Ponderal Index (PI)= Birth weight (g) *100/birth length³ (cm³). Data adjusted for infant gender and maternal race (black/others) in the plot of PI vs. RANTES.

Standardized birth weight (SBWT) is defined as birth weight standardized by mean and variance in the stratum of corresponding ethnic group, sex, and gestational week in the reference population using around 15,000 births born at BMC during 1998-2003.

Figure 2.

Weight outcomes of LGA infants at 3-5 years of age

Childhood obesity at 3-5y is defined as any BMI >95th percentile for age and gender.

*P<0.05 for maternal pre-pregnancy BMI in the obese vs. non-obese LGA groups.

Table 1

Patient demographics and clinical characteristics

Variables	Large-for-gestational age (LGA) ¹	Appropriate-for-gestational age (AGA) ²	P ³
	N=45	N=319	
Birth weight, g (mean ± SD)	4152.0 ± 361.8	3292.4 ± 359.7	<0.0001
Ponderal Index, 10mg/cm ³	2.89 ± 0.26	2.58 ± 0.29	<0.0001
Standardized birth weight	1.86 ± 0.65	-0.05 ± 0.63	<0.0001
Gestational age, wks	39.44 ± 1.24	39.48 ± 1.26	0.8197
Infant gender, male n(%)	25 (55.6)	164 (51.4)	0.7176
Maternal age, year (mean ± SD)	30.36 ± 6.31	28.78 ± 6.64	0.1330
Pre-pregnancy BMI n(%)			
<18.5 kg/m ²	1 (2.2)	10 (3.1)	0.0092*
≥18.5 to <25	14 (31.1)	144 (45.1)	
≥25 to <30	13 (28.9)	112 (35.1)	
≥30	17 (37.8)	53 (16.6)	
Race			
Black	30 (66.7)	235 (73.7)	0.4185
Other	15 (33.3)	84 (26.3)	
Parity (1+)	32 (71.1)	175 (54.9)	0.0574
Smoking before and during pregnancy ⁴	4 (8.9)	43 (13.5)	0.5338
Illicit drug use during pregnancy	1 (2.2)	26 (8.2)	0.2641
Smoking or drug use during pregnancy	4 (8.9)	54 (16.9)	0.2453
Alcohol use during pregnancy	2 (4.4)	7 (2.2)	0.6965
Mode of delivery (vaginal)	21 (47.7)	229 (72.7)	0.0014*
Level of education			
Elementary/secondary school	14 (31.1)	106 (33.2)	0.5064
High school/GED	17 (37.8)	94 (29.5)	
College and above	14 (31.1)	119 (37.3)	
Maternal hypertensive disorders ⁵	4 (9.1)	22 (7.0)	0.8547
Placental inflammatory response, histological ⁶	5 (22.7)	24 (24.7)	1.0000
Chorioamnionitis, clinical	3 (7.9)	6 (2.0)	1.0000
Diabetes			
Gestational diabetes	5 (11.4)	15 (4.7)	<0.0001
Pre-existing	5 (11.4)	1 (0.3)	
Placental abruption	0 (0.0)	1 (0.3)	1.0000
Placental previa	1 (2.2)	4 (1.3)	1.0000

¹ LGA defined as infant birth weight ≥90th percentile of the reference population at Boston Medical Center. AGA defined as infant birth weight between the 10th and 90th percentile.

³ P-value is based upon F-test for continuous variables and chi-square for categorical variables.

⁴Includes ever smoking 3 months before pregnancy and during pregnancy.

⁵Includes pre-eclampsia, eclampsia, chronic hypertension, HELLP syndrome.

⁶Includes either maternal or fetal inflammatory response.

Table 2

Associations between maternal DM and pre-pregnancy body mass index (BMI) and LGA status at birth

		LGA at birth				
DM	BMI	N	Case(n)	Case(%)	OR	95%CI P
No	<25	164	14	8.5	1.00	
	≥25 to <30	114	8	7.0	0.77	0.30,1.94 0.58
	≥30	59	12	20.3	2.64	1.13,6.20 0.03
Yes	Any	26	10	38.5	5.58	2.06,15.13 <0.001
	<30	16	6	37.5	4.57	1.37,15.25 0.01
	≥30	10	4	40.0	7.67	1.83,32.09 <0.01

All logistic regression models were adjusted for maternal age, race (black/others), parity (0,≥=1), maternal education (<high school, high school, >high school), and infant gender.

Table 3

Significant associations of cord blood biomarkers and LGA status at birth*

LGA status	Mean $\pm$ SD	Beta $\pm$ se	95%CI	P	Beta $\pm$ se	95%CI	P
Model 1							
IL-6							
No	3.65 $\pm$ 1.25	Ref.			Ref.		
Yes	3.77 $\pm$ 1.52	0.26 $\pm$ 0.21	-0.15, 0.67	0.21	0.24 $\pm$ 0.21	-0.18, 0.66	0.26
IL-8							
No	3.31 $\pm$ 1.60	Ref.			Ref.		
Yes	3.32 $\pm$ 1.59	0.07 $\pm$ 0.26	-0.44, 0.58	0.78	0.06 $\pm$ 0.27	-0.47, 0.58	0.83
TNF-alpha							
No	2.77 $\pm$ 0.66	Ref.			Ref.		
Yes	2.76 $\pm$ 0.74	-0.4 $\pm$ 0.11	-0.26, 0.17	0.71	0.01 $\pm$ 0.11	-0.21, 0.23	0.91
RANTES							
No	4.02 $\pm$ 0.8	Ref.			Ref.		
Yes	4.43 $\pm$ 1.27	0.37 $\pm$ 0.14	0.09, 0.65	<0.01	0.37 $\pm$ 0.15	0.08, 0.65	0.01

* All values are log-transformed to approximate normal distribution.

Model 1: adjusted for maternal age, race (black/others), parity (0, $\geq$ 1), maternal education (<high school, high school, >high school), substance use (smoking or drug) during pregnancy (yes/no), type of delivery (vaginal/c-section) and infant gender.

Model 2: model 1 + maternal DM (yes, no) and pre-pregnancy BMI (<25, > 25 to <30, > 30).