Original article

doi: 10.5385/jksn.2011.18.1.49

pISSN 1226-1513 • eISSN 2093-7849

Cord Blood Adiponectin and Insulin-like Growth Factor-I in Term Neonates of Gestational Diabetes Mellitus Mothers: Relationship to Fetal Growth

Jin A Sohn, M.D., Eun Ae Park, M.D., Su Jin Cho, M.D., Young Ju Kim, M.D.* and Hyesook Park, M.D.†

Departments of Pediatrics, Obstetrics*, and Preventive Medicine†, Ewha Womans University School of Medicine, Seoul, Korea

Purpose: The purpose of this study was to evaluate the relationship between cord blood adiponectin and insulin-like growth factor (IGF)-I and their effect on fetal growth and insulin resistance in mothers with gestational diabetes mellitus (GDM).

Methods: Cord blood adiponectin and IGF-I were compared between mothers with GDM (GDM group, N=53) and controls (non-GDM group, N=101). Neonates were classified into three groups of small for gestational age (SGA, N=26), appropriate for gestational age (AGA, N=97), and large for gestational age (LGA, N=31) by birth weight. The association between cord adiponectin and IGF-I levels was evaluated in relation to maternal and neonatal clinical data.

Results: Cord adiponectin was lower in the GDM group than in the non-GDM group ($P<0.001$). There was no significant difference in cord adiponectin among the SGA, AGA, and LGA groups in the GDM group ($P=0.228$). The cord adiponectin of AGA in the GDM group was significantly lower than that in the non-GDM group ($P<0.001$). The most powerful predictor affecting cord adiponectin was the result of maternal 75 g oral glucose tolerance test. The cord IGF-I values between the GDM group and the non-GDM group were not different ($P=0.834$). Neonates with the heavier birth weight had the higher cord IGF-I levels. The most powerful predictor affecting cord IGF-I was birth weight and the next was maternal parity.

Conclusion: Both cord blood adiponectin and IGF-I were associated with fetal growth, but IGF-I was a more general and direct factor affecting fetal body size, and adiponectin seemed to have more association with insulin sensitivity than growth.

Key Words: Adiponectin, Insulin-like growth factor-I, Cord blood, Gestational diabetes mellitus

Introduction

Gestational diabetes mellitus (GDM) is a common complication of pregnancy, affecting up to 7% of pregnant women and is associated with fetal macrosomia and insulin resistance¹⁾.

Adiponectin, a recently discovered adipocyte-secreted hormone, is postulated to play a role in the modulation of

glucose and lipid metabolism in insulin-sensitive tissues and is inversely associated with obesity, insulin resistance, and type II diabetes²⁾. The insulin-like growth factor (IGF) system is one of the essential endocrine regulators associated with both pre- and postnatal growth³⁾.

In contrast to IGF-I, the regulation of adiponectin in the fetus is still not known. There have been some studies about the effect of cord blood adiponectin on fetal growth⁴⁻⁷⁾, but

Received: 8 March 2011, Revised: 2 May 2011, Accepted: 7 May 2011

Correspondence to Eun Ae Park, M.D.

Department of Pediatrics, Ewha Womans University Mok-dong Hospital, 911-1 Mok-dong, Yangcheon-gu, Seoul 158-710, Korea

Tel: +82-2-2650-5574, Fax: +82-2-2653-3718, E-mail: pea8639@ewha.ac.kr

Poster presentation at PAS 2008 annual meeting.

the results were controversial. Also, there have been several studies about low adiponectin levels in women with GDM^{8,9)}, but no study about the relationship between fetus and the cord blood adiponectin or IGF-I of GDM mothers has been published.

The purposes of this study were to measure cord blood adiponectin and IGF-I levels and to evaluate the relationship between fetal growth and insulin resistance in mothers with GDM.

Materials and Methods

1. Subjects

One hundred fifty four term singleton infants born at Ewha Womans University Mok-dong Hospital from January 2003 to September 2008 were enrolled at mid-pregnancy with informed parental consent. The study protocol for sampling cord blood and using clinical data of mothers and babies was approved by Ewha Womans University Mok-dong Hospital Institutional Review Board. Patients with maternal thyroid disease, maternal chronic hypertension or preeclampsia, congenital anomaly, or inborn errors of metabolism were excluded.

Subjects were classified into two groups of mothers with gestational diabetes (GDM group, N=53) and control group (non-GDM group, N=101). The diagnosis of GDM was performed by a 2 hour 75 g oral glucose tolerance test (OGTT), which was modified as the more strict screening criteria from the American Diabetes Association criteria and the World Health Organization criteria¹⁾, because Koreans carry a high risk of GDM at 24–28 weeks of gestation. GDM was diagnosed if either the fasting glucose was >95 mg/dL or the 2 hour glucose was >140 mg/dL.

Neonates were classified into three groups by birth weight and gestational age according to the 2005 Korean percentile curves of birth weight by gestational age¹⁰⁾, small for gestational age (SGA, birth weight less than 10th percentile, N=26), appropriate for gestational age (AGA, birth weight between 10th and 90th percentile, N=97), and large for gestational age (LGA, birth weight more than 90th

Table 1. Distribution of Study Group by Birth Percentile and Maternal Gestational Diabetes Mellitus Status

	GDM (%)	Non-GDM (%)	Total (%)
SGA	5 (3.2)	21 (13.6)	26 (16.9)
AGA	39 (25.3)	58 (37.7)	97 (63.0)
LGA	9 (5.8)	22 (14.3)	31 (20.1)
Total	53 (34.4)	101 (65.6)	154 (100.0)

$\chi^2=4.5$, df=2, $P=0.106$.

Abbreviations: GDM, gestational diabetes mellitus; SGA, small for gestational age; AGA, appropriate for gestational age; LGA, large for gestational age.

percentile, N=31).

Distribution by birth percentile between the GDM group and the non-GDM group was not different (Table 1).

A standardized form was used to collect laboratory and anthropometrical data during pregnancy from the mother's medical record. Neonatal weight and length at birth were obtained from the delivery record.

2. Measurements of cord blood adiponectin and IGF-I

Cord blood samples were collected immediately after double clamping of the umbilical cord at birth. Cord blood sera were obtained by centrifugation and were kept at -70°C for subsequent assay.

Human adiponectin was measured by a sandwich enzyme-linked immunosorbent assay (ELISA) system (adiponectin ELISA kit, Bio Vender, Brno, Czech Republic). The total adiponectin level was measured, including low, middle, and high molecular weight adiponectin. The intra- and inter-assay coefficients of variations for adiponectin were 6.7% and 7.7%, respectively. Human IGF-I was measured by an ELISA system (Quantikine; Human IGF-I Immunoassay, R&D Systems Inc., Minneapolis, MN, USA). The intra- and inter-assay coefficients of variations for IGF-I were 4.0% and 7.9%, respectively.

3. Data analysis

Mean values of cord blood adiponectin and IGF-I were compared between the GDM group and the non-GDM group. Levels of cord blood adiponectin and IGF-I in SGA, AGA, and LGA subgroups were also compared. The association of cord blood adiponectin and IGF-I concentrations

Table 2. Clinical Characteristics of Study Group

		GDM (N=53)	Non-GDM (N=101)	P-value
Mother	Age (yr)	33.0±4.5	31.1±4.0	0.006
	Parity (N)	0.8±0.7	0.7±0.7	0.372
	Prepregnancy BMI (kg/m ²)	23.0±3.9	20.7±2.6	0.002
	Fasting glucose (mg/dL)	91.5±23.5	81.6±5.5	0.010
	75 g OGTT, 2 hr (mg/dL)	174.3±49.5	112.2±15.0	<0.001
	Weight gain during pregnancy (kg)	12.5±4.3	14.0±4.5	0.158
	Feto-placental weight ratio	5.7±1.8	5.40±0.8	0.279
Baby	Gestational age at birth (day)	274.8±7.4	276.2±7.5	0.272
	Male : Female	29 : 24	44 : 57	0.190
	Birth weight (kg)	3.3±0.5	3.3±0.7	0.778
	Birth height (cm)	49.5±2.0	49.4±2.8	0.765

Abbreviations: GDM, gestational diabetes mellitus; BMI, body mass index; OGTT, oral glucose tolerance test.

Fig. 1. Cord blood adiponectin and insulin-like growth factor (IGF)-I were compared between the gestational diabetes mellitus (GDM) group and the non-GDM group. (A) The levels of cord blood adiponectin were significantly lower in the GDM group than the non-GDM group. (B) There was no difference in the levels of cord blood IGF-I between the GDM group and the non-GDM group.

was evaluated in relation to maternal age, parity, pre-pregnancy body mass index (BMI), fasting glucose, 2 hour 75 g OGTT, weight gain during pregnancy, feto-placental weight ratio, gestational age at birth, neonatal gender, birth weight, and birth height.

Statistical analysis was processed by SPSS 12.0 (SPSS Inc., Chicago, IL, USA). The differences between the GDM group and the non-GDM group were assessed with Student t-test and χ^2 -test. The differences among SGA, AGA, and LGA were assessed with one-way analysis of variance (ANOVA). The relationships among cord blood adiponectin, IGF-I, and other parameters were performed by simple and multiple linear regression analysis. $P \leq 0.05$ was considered statistically significant.

Results

1. Clinical characteristics of the GDM group and the non-GDM group

Mothers of the GDM group were older ($P=0.006$) and had higher prepregnancy BMI ($P=0.002$) than that of the non-GDM group. Both fasting glucose level ($P=0.010$) and glucose level of 75 g OGTT in 2 hours ($P<0.001$) were higher in the GDM group than in the non-GDM group. However, maternal parity, weight gain during pregnancy, and feto-placenta weight ratio were not different in both groups. The basic clinical data of neonates were not significantly different between the GDM group and the non-GDM group (Table 2).

Table 3. Cord Blood Adiponectin and Insulin-like Growth Factor-I according to Neonatal Gender

Group (Male:Female)	Adiponectin (ug/mL)		<i>P</i> -value	IGF-I (ng/mL)		<i>P</i> -value
	Male	Female		Male	Female	
GDM (29:24)	18.8±6.9	20.8±5.3	0.243	48.2±22.7	58.0±26.9	0.156
Non-GDM (44:57)	23.3±8.0	29.3±11.4	0.002	49.6±28.0	53.2±29.4	0.545
Total (73:80)	21.5±7.8	26.9±10.7	< 0.001	49.0±25.8	54.7±28.6	0.209

Abbreviations: IGF, insulin-like growth factor; GDM, gestational diabetes mellitus.

Fig. 2. Cord blood adiponectin was analyzed according to maternal gestational diabetes mellitus (GDM) status and birth weight groups. (A) There was no difference in the adiponectin levels between the GDM group and the non-GDM group in small for gestational age (SGA) and large for gestational age (LGA) neonates. The levels of adiponectin of the GDM group were significantly lower than that of the non-GDM group in appropriate for gestational age (AGA) neonates. (B) There was no difference in the adiponectin levels according to birth weight in the GDM group. The levels of adiponectin of AGA neonates were significantly higher than that of SGA and LGA neonates in the non-GDM group.

2. Cord blood adiponectin level

The cord blood adiponectin was lower in the GDM group (19.7 ± 6.3 $\mu\text{g/mL}$) than in the non-GDM group (26.7 ± 10.5 $\mu\text{g/mL}$) ($P < 0.001$, Fig. 1A). Even after adjustment for maternal age and prepregnancy BMI, the cord blood adiponectin was lower in the GDM group (20.8 ± 6.5 $\mu\text{g/mL}$) than the non-GDM group (27.0 ± 10.2 $\mu\text{g/mL}$) ($P = 0.050$).

The cord blood adiponectin levels of girls were significantly higher than that of boys in the non-GDM group ($P = 0.002$), but adiponectin levels of both genders decreased and did not become different in the GDM group (Table 3).

The cord blood adiponectin of the GDM group was lower than that of the non-GDM group in all SGA, AGA, and LGA groups, but there was a statistical significance only in the AGA group ($P < 0.001$, Fig. 2A). There was no significant difference in cord blood adiponectin among the SGA, AGA,

and LGA groups in the GDM group. The cord blood adiponectin of the AGA group was significantly higher than that of the SGA and LGA groups in the non-GDM group ($P = 0.003$, Fig. 2B).

The cord blood adiponectin was inversely related to maternal prepregnancy BMI, fasting glucose, and 75 g OGTT glucose level but was positively correlated with gestational age at birth, birth weight, and cord blood IGF-I (Table 4).

In multiple linear regression analysis, the most powerful predictor affecting cord blood adiponectin was the result of the maternal 75 g OGTT at mid-pregnancy. After adjustment of other factors, the following equation could be obtained:

$$Y = -0.15X + 45.5 \quad (P < 0.001)$$

Y : Cord blood adiponectin (ug/mL)

X : Glucose level of 75 g OGTT in 2 hours (mg/dL)

Table 4. Simple Linear Regression of Cord Blood Adiponectin and Insulin-like Growth Factor-I with Other Parameters

	Adiponectin (ug/mL)			IGF-I (ng/mL)		
	β	Std. Error	P-value	β	Std. Error	P-value
Maternal age (yr)	-0.314	0.186	0.093	1.112	0.521	0.035
Maternal parity (N)	-0.422	1.118	0.706	10.885	3.035	<0.001
Maternal prepregnancy BMI (kg/m ²)	-0.952	0.317	0.004	0.933	0.920	0.314
Maternal fasting glucose (mg/dL)	-0.145	0.059	0.016	0.014	0.166	0.935
Maternal 75 g OGTT, 2 hr (mg/dL)	-0.080	0.020	< 0.001	-0.052	0.059	0.376
Maternal weight gain during pregnancy (kg)	0.063	0.239	0.792	-0.269	0.668	0.688
Feto-placental weight ratio	0.356	0.906	0.696	0.244	2.613	0.926
Gestational age at birth (day)	0.264	0.104	0.012	-0.132	0.303	0.665
Birth weight (kg)	2.655	1.232	0.033	29.406	2.694	<0.001
Birth height (cm)	0.353	0.311	0.257	4.969	0.792	<0.001
Cord blood IGF-I (ng/mL)	0.066	0.029	0.025			
Cord blood adiponectin (ug/mL)				0.515	0.227	0.025

Abbreviations: IGF, insulin-like growth factor; BMI, body mass index; OGTT, oral glucose tolerance test.

Fig. 3. Cord blood insulin-like growth factor (IGF)-I was analyzed according to maternal gestational diabetes mellitus (GDM) status and birth weight groups. (A) There was no difference in the IGF-I levels between the GDM group and the non-GDM group in all of small for gestational age (SGA), appropriate for gestational age (AGA), and large for gestational age (LGA) neonates. (B) Neonates with the heavier birth weight had higher concentrations of IGF-I in both the GDM group and the non-GDM group.

Adjusted for maternal age, maternal prepregnancy BMI, maternal GDM status, maternal fasting glucose, gestational age at birth, neonatal gender, birth weight, and cord blood IGF-I

3. Cord blood IGF-I level

The cord blood IGF-I between the GDM group (52.7 ± 25.0 ng/mL) and the non-GDM group (51.7 ± 28.8 ng/mL) were not different (Fig. 1B). Also, there was no significant difference in cord blood IGF-I according to neonatal gender (Table 3).

There was no difference in cord blood IGF-I between the GDM group and the non-GDM group in all SGA, AGA, and LGA neonates (Fig. 3A). The SGA group had the lowest level of cord blood IGF-I, and the LGA group had the highest level of cord blood IGF-I in both the GDM group and the non-GDM group ($P < 0.001$, Fig. 3B). Neonates with the heavier birth weight had the higher cord blood IGF-I levels.

Cord blood IGF-I was positively correlated to maternal age, maternal parity, birth weight, birth height, and cord blood adiponectin (Table 4).

In multiple linear regression analysis, the most powerful

Fig. 4. Cord blood adiponectin and insulin-like growth factor (IGF)-I had positive correlation.

predictor affecting cord blood IGF-I was birth weight and the next was maternal parity. After adjustment of other factors, the following equation could be obtained:

$$Y = 27.64 X_1 + 5.98 X_2 - 43.0 \quad (P < 0.001)$$

Y : Cord blood IGF-I (ng/mL)

X₁ : Birth weight (kg)

X₂ : Maternal parity (N)

Adjusted for maternal age, birth height, and cord blood adiponectin

4. Relationship between cord blood adiponectin and IGF-I

The cord blood adiponectin was positively correlated with the cord blood IGF-I (Fig. 4).

Discussion

The cord blood adiponectin was lower in the GDM mother. Both cord blood adiponectin and IGF-I were associated with fetal growth, but IGF-I was a more general and direct factor affecting fetal body size, and adiponectin seemed to have more association with insulin sensitivity than growth.

GDM is defined as glucose intolerance that begins or is first detected during pregnancy¹⁾. Maternal complications associated with GDM include hypertension, preeclampsia,

and an increased risk of Cesarean delivery. In addition, women with a history of GDM have an increased risk of developing diabetes compared to the general population after pregnancy^{11, 12)}. Fetal complications associated with GDM include macrosomia, neonatal hypoglycemia, perinatal mortality, congenital malformations, hyperbilirubinemia, polycythemia, hypocalcemia, and respiratory distress syndrome^{1, 11, 13)}. Long-term complications to the offspring include an increased risk of impaired glucose tolerance, type II diabetes, and obesity^{1, 14)}.

Normal pregnancy is a diabetogenic condition characterized by insulin resistance with a compensatory increase in pancreatic β -cell response and hyperinsulinemia. Insulin resistance usually begins in mid-pregnancy and progresses through the third trimester of pregnancy. Insulin resistance appears to result from a combination of increased maternal adiposity and the insulin-desensitizing effects of placental hormones¹⁵⁾. Mothers with GDM have a greater severity of insulin resistance compared to that seen in normal pregnancies and an impairment of the compensatory increase in insulin secretion of β -cells¹²⁾. Working together, those factors reduce insulin stimulation of glucose uptake by skeletal muscle, inhibition of glucose release by liver, and insulin suppression of lipolysis and amino acid turnover¹⁶⁾.

It is important to understand the mechanisms promoting obesity and insulin resistance associated with obesity, because women with GDM tend to be obese. Some studies have reported increased circulating levels of leptin¹⁷⁾, tumor necrosis factor (TNF)- α ¹⁸⁾, and C-reactive protein¹⁹⁾, and decreased levels of adiponectin^{8, 9)} in women with GDM. Also, women with GDM have increased levels of fat in liver²⁰⁾ and muscle²¹⁾. We can deduce some potential causes of obesity-related insulin resistance from all of those findings.

Adiponectin secreted by the adipocyte is down-regulated in obesity and increased by weight reduction, in contrast to other adipokines like leptin, TNF- α , and Interleukin-6^{22, 23)}. Adiponectin is postulated to play a role in the modulation of glucose and lipid metabolism in insulin-sensitive tissues. Recent studies have reported that adiponectin has atheroprotective properties and anti-inflammatory effects²⁴⁾.

²⁵⁾. Therefore, high concentrations of adiponectin may be related to a lower incidence of type II diabetes and coronary heart disease.

The mechanisms of regulating adiponectin levels in the fetus are still not known. Adiponectin seems to be produced and secreted exclusively by adipocytes. However, an increase in fat mass leads to down-regulation of adiponectin²²⁾, whereas body weight reduction in obese²³⁾ as well as in normal-weight subjects results in elevation of adiponectin concentrations, suggesting that fat mass may exert a negative feedback on adiponectin production. In our study, the GDM group had lower cord blood adiponectin than that of the non-GDM group (Fig. 1A), and the cord blood adiponectin was negatively correlated to maternal BMI (Table 4). That might be because obese GDM mothers have hypertrophic adipocytes, which causes a decrease in the production and secretion of insulin-sensitizing hormones and an increase in insulin-resistant hormones, and insulin resistance and a hyperinsulinemic state aggravate hypo-adiponectinemia²⁶⁾.

In both adults and children, women have higher adiponectin levels than men²⁷⁾. In accordance with other studies, girls had higher cord blood adiponectin than boys in the non-GDM group in our study (Table 3). However, girls in the GDM group had a greater decrease in cord blood adiponectin than boys, and such gender difference was not apparent in the GDM group. Our study supports the finding of Ong et al.²⁷⁾ that girls showed a steeper decline in adiponectin levels and steeper change in lipid levels with increasing BMI compared to boys. That might be because girls with a larger central fat mass than boys withstand a larger effect of negative feedback.

Several reports have that there is no inverse relationship between birth size and adiponectin in neonates^{4, 5)} in contrast to adults^{22, 23)}. However, other studies have found a positive relationship between cord blood adiponectin and birth weight or height^{6, 7)}. We found a positive relationship among cord blood adiponectin, gestational age at birth, and birth weight in single linear regression analysis (Table 4). However, the relationship between cord blood adiponectin

and birth weight was not significant after adjusting for GDM status (GDM vs. non-GDM), because cord blood adiponectin according to maternal GDM status had a different condition ($P=0.403$).

In our study, there was no difference between the GDM group and the non-GDM group in the adiponectin levels of the SGA and LGA groups, but the adiponectin level of the GDM group was lower than that of the non-GDM group in the AGA group (Fig. 2A). Considering that SGA and LGA are pathologic conditions related to insulin resistance affected by multi-factors, the difference in the AGA group would reveal the effect of maternal GDM. The adiponectin levels of all three groups in the GDM group were similarly low (Fig. 2B). Maternal GDM lowered cord blood adiponectin independent from the obesity status of neonates, especially in the AGA group.

A recent study reported that young adults who had been born SGA had lower levels of adiponectin²⁸⁾. It will be important to determine if normalized adiponectin levels in cord blood after treatment is related to improved insulin sensitivity or glucose tolerance later in life of the low adiponectin group, because SGA and LGA are predisposing factors for type II diabetes in adults²⁹⁾. Recently, administration of adiponectin to normal or obese mice improved glucose tolerance and insulin sensitivity³⁰⁾. A potential treatment might be administration of adiponectin to GDM mothers to prevent insulin resistance or obesity of offspring.

The IGF system is one of the essential endocrine regulators associated with both pre- and postnatal growth³⁾. IGFs are part of a complex system comprising IGF-I and II, types 1 and 2 IGF receptors, six different IGF-binding proteins (IGFBPs-1 to -6), specific IGFBP proteases, and inhibitors of IGFBP proteolytic activity³¹⁾. Studies of null mutant mice have demonstrated that whereas IGF-I is the dominant growth promoting factor during the rapid phase of somatic growth in late gestation³²⁾, IGF-II is important in fetal growth during early gestation only³³⁾. Therefore, IGF-I cord levels tend to correlate well with birth weight³⁴⁾, but IGF-II levels do poorly with birth weight³⁵⁾. Some studies have described the endocrine profile of an intrauterine

growth retardation fetus as hypoinsulinemic, hypothyrotropic, hypoglycemic, hypoalbuminemic, and hypomagnesemic, with lower IGF-I and higher growth hormone compared to a normal group³⁶. This confirms the crucial role played by those hormones as a mediator in the regulation of intrauterine growth.

In agreement with previous studies^{3, 34}, we found that cord blood levels of IGF-I positively correlate to birth weight and birth height (Table 4). However, there was no difference between the GDM group and the non-GDM group in cord blood IGF-I levels (Fig. 1B). Therefore, we can suppose that IGF-I is the main endocrine regulator associated with fetal growth, but it seems to not directly affect the manner in which neonates from GDM mothers become SGA or LGA. Also, cord blood IGF-I was positively related to maternal age and parity (Table 4); therefore, older or multipara mothers appeared to have larger babies.

It would be important to document whether adiponectin, which has a known role not only in improving insulin and IGF sensitivity, but also in promoting cell proliferation and inhibiting apoptosis^{37, 38}, could interact with or influence the production and tissue effects of those regulators on fetal growth. Another study suggests that the association between adiponectin and length is probably mediated by alterations of the IGF system³⁹. In our study, both cord blood adiponectin and IGF-I were positively correlated to birth weight (Table 4), and cord blood adiponectin was also positively correlated to cord blood IGF-I (Fig. 4). However, in contrast to IGF-I, cord blood adiponectin was not related to birth weight after adjustment of other factors; therefore, further study about the relationship between cord blood adiponectin and fetal growth is needed.

In multiple regression analysis, the most powerful predictors were the results from the 75 g OGTT in cord blood adiponectin and birth weight in cord blood IGF-I after the adjustment for other confounding factors. In addition, there was no difference in IGF-I levels between the GDM group and the non-GDM group, but was difference in adiponectin levels. We can conclude that IGF-I is a more general and direct factor affecting fetal body size, and

adiponectin has more association with insulin sensitivity than growth. The relation between adiponectin and IGF-I needs to be explored further in future in vitro and in vivo studies.

Intrauterine and postnatal programming of adiponectin dynamics may play a role in the state of insulin sensitivity and body-fat acquisition of later life. LGA infants and prepubertal children who were SGA as in the infants and went through a catch-up growth period have low serum adiponectin levels. Both SGA and LGA infants are at increased risk for development of insulin resistance that is often accompanied by obesity^{40, 41}. According to our data, even though neonates belong to the AGA group, they tend to have low adiponectin levels of cord blood if they have mothers with GDM. Therefore, it is important to follow up the change of the adipoinular axis and growth of neonates born to mothers with GDM despite a baby having normal birth weight.

Our study has several limitations. First is the small numbers of the SGA and LGA groups, especially in the GDM group. Second, we could not investigate several factors affecting GDM and adiponectin levels such as previous history of macrosomic infants and the smoking history of the mother.

In our study, the cord blood adiponectin was lower in the GDM mothers, but IGF-I was not. Adiponectin, a novel product of adipocytes, is potentially important to the later development of metabolic disease. Maternal GDM, maternal obesity, or being large or small at birth may predict an increased risk of glucose intolerance or diabetes in childhood, adolescence, and adulthood. Therefore, the offspring of women with GDM, even AGA neonates, should be followed closely for a change in the adipoinular axis and the development of obesity and/or abnormalities of glucose tolerance during both the prenatal and postnatal periods.

한글요약

목적: 임신성 당뇨병은 임신의 흔한 합병증 중의 하나이며 임신성 당뇨병 산모의 아기는 정상 산모의 아기에게 비해서 체지방률이

높다. Adiponectin은 인슐린 민감성 조직에서 당과 지방 대사를 조절하는 중요한 물질이며, insulin-like growth factor (IGF)-I은 출생 전후기에 성장을 조절하는 중요한 내분비 조절 물질로 알려져 있다. 본 연구에서는 임신성 당뇨 산모의 아기에 서 제대혈 adiponectin과 IGF-I 수치와 태아 성장과의 관계 및 인슐린 저항성에 대해서 알아보하고자 하였다.

방법: 임신성 당뇨 이외에 임신과 관련된 기타 합병증이 동반되지 않은 산모에서 태어난 아기(임신성 당뇨군, N=53)와 정상 산모에서 태어난 아기(대조군, N=101)의 제대혈 adiponectin과 IGF-I 수치를 비교하였다. 신생아는 출생 체중에 따라 부당경량아(N=26), 적정체중아(N=97), 부당중량아(N=31)로 세분화하였다. 제대혈 adiponectin, IGF-I 농도와 산모의 나이, 분만력, 임신 전 체질량지수, 공복 혈당 및 75 g 경구당부하검사, 임신 중 산모 체중 증가, 태아-태반 무게비, 출생시 재태연령, 아기의 성별, 출생체중, 출생신장과의 관계를 비교하였다.

결과: 대조군보다 임신성 당뇨군에서 제대혈 adiponectin의 평균이 의미 있게 낮았다($P<0.001$). 임신성 당뇨군에서는 부당경량아군, 적정체중아군, 부당중량아군 사이의 제대혈 adiponectin 수치에 유의한 차이를 보이지 않았으나($P=0.228$), 적정체중아군은 대조군의 적정체중아군에 비해 의미 있게 낮은 adiponectin 수치를 보였다($P<0.001$). 제대혈 adiponectin은 산모의 임신 전 체질량지수, 공복혈당, 75 g 경구당부하검사와 음의 상관관계를 가졌고, 출생시 재태연령, 출생체중, 제대혈 IGF-I과 양의 상관관계를 가졌다. 다중선형회귀분석에서 75 g 경구당부하검사가 가장 강력한 예측인자로 나왔다. 임신성 당뇨군과 대조군 사이의 제대혈 IGF-I은 의미 있는 차이를 보이지 않았다($P=0.834$). 제대혈 IGF-I은 출생체중이 높은 군일수록 의미 있게 높았다($P<0.001$). 제대혈 IGF-I은 산모의 연령, 분만력, 출생체중, 출생신장, 제대혈 adiponectin과 유의한 양의 상관관계를 보였고, 이 중에서 출생체중과 분만력이 가장 강력한 예측인자였다.

결론: 산모의 임신성 당뇨는 제대혈 adiponectin을 낮춘다. 제대혈 adiponectin과 IGF-I 모두 출생체중과 연관성을 보였지만 IGF-I이 태아의 성장에 좀 더 직접적인 영향을 미치며, adiponectin은 성장보다는 인슐린 저항성과 더 연관이 있는 것으로 생각된다. 그러므로 임신성 당뇨를 가진 산모에서 태어난 아기는 적정체중아일지라도 생후 성장과 인슐린 저항성의 변화를 추적 관찰하는 것이 중요할 것이다.

References

- 1) American Diabetes Association. Gestational diabetes mellitus. *Diabetes Care* 2003;26 Suppl 1:S103-5.
- 2) Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE, et al. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. *J Clin Endocrinol Metab* 2001;86:1930-5.
- 3) Christou H, Connors JM, Ziotopoulou M, Hatzidakis V, Papanthassoglou E, Ringer SA, et al. Cord blood leptin and insulin-like growth factor levels are independent predictors of fetal growth. *J Clin Endocrinol Metab* 2001;86:935-8.
- 4) Corbetta S, Bulfamante G, Cortelazzi D, Barresi V, Cetin I, Mantovani G, et al. Adiponectin expression in human fetal tissues during mid- and late gestation. *J Clin Endocrinol Metab* 2005;90:2397-402.
- 5) Mazaki-Tovi S, Kanety H, Sivan E. Adiponectin and human pregnancy. *Curr Diab Rep* 2005;5:278-81.
- 6) Sivan E, Mazaki-Tovi S, Pariente C, Efraty Y, Schiff E, Hemi R, et al. Adiponectin in human cord blood: relation to fetal birth weight and gender. *J Clin Endocrinol Metab* 2003;88:5656-60.
- 7) Tsai PJ, Yu CH, Hsu SP, Lee YH, Chiou CH, Hsu YW, et al. Cord plasma concentrations of adiponectin and leptin in healthy term neonates: positive correlation with birthweight and neonatal adiposity. *Clin Endocrinol (Oxf)* 2004;61:88-93.
- 8) Retnakaran R, Hanley AJ, Raif N, Connelly PW, Sermer M, Zinman B. Reduced adiponectin concentration in women with gestational diabetes: a potential factor in progression to type 2 diabetes. *Diabetes Care* 2004;27:799-800.
- 9) Williams MA, Qiu C, Muy-Rivera M, Vadachkoria S, Song T, Luthy DA. Plasma adiponectin concentrations in early pregnancy and subsequent risk of gestational diabetes mellitus. *J Clin Endocrinol Metab* 2004;89:2306-11.
- 10) Lee JJ, Park CG, Lee KS. Birth weight distribution by gestational age in Korean population: using finite mixture model. *Korean J Pediatr* 2005;48:1179-86.
- 11) Casey BM, Lucas MJ, McIntire DD, Leveno KJ. Pregnancy outcomes in women with gestational diabetes compared with the general obstetric population. *Obstet Gynecol* 1997;90:869-73.
- 12) Di Cianni G, Miccoli R, Volpe L, Lencioni C, Del Prato S. Intermediate metabolism in normal pregnancy and in gestational diabetes. *Diabetes Metab Res Rev* 2003;19:259-70.
- 13) Dang K, Homko C, Reece EA. Factors associated with fetal macrosomia in offspring of gestational diabetic women. *J Matern Fetal Med* 2000;9:114-7.
- 14) Weiss PA, Scholz HS, Haas J, Tamussino KF, Seissler J, Borkenstein MH. Long-term follow-up of infants of mothers with type 1 diabetes: evidence for hereditary and nonhereditary transmission of diabetes and precursors. *Diabetes Care* 2000;23:905-11.
- 15) Buchanan TA, Xiang AH. Gestational diabetes mellitus. *J Clin Invest* 2005;115:485-91.

- 16) Catalano PM, Kirwan JP, Haugel-de Mouzon S, King J. Gestational diabetes and insulin resistance: role in short- and long-term implications for mother and fetus. *J Nutr* 2003;133:1674S-83S.
- 17) Qiu C, Williams MA, Vadachkoria S, Frederick IO, Luthy DA. Increased maternal plasma leptin in early pregnancy and risk of gestational diabetes mellitus. *Obstet Gynecol* 2004;103:519-25.
- 18) Winkler G, Cseh K, Baranyi E, Melczer Z, Speer G, Hajós P, et al. Tumor necrosis factor system in insulin resistance in gestational diabetes. *Diabetes Res Clin Pract* 2002;56:93-9.
- 19) Retnakaran R, Hanley AJ, Raif N, Connelly PW, Sermer M, Zinman B. C-reactive protein and gestational diabetes: the central role of maternal obesity. *J Clin Endocrinol Metab* 2003;88:3507-12.
- 20) Tiikkainen M, Tamminen M, Häkkinen AM, Bergholm R, Vehkavaara S, Halavaara J, et al. Liver-fat accumulation and insulin resistance in obese women with previous gestational diabetes. *Obes Res* 2002;10:859-67.
- 21) Kautzky-Willer A, Krssak M, Winzer C, Pacini G, Tura A, Farhan S, et al. Increased intramyocellular lipid concentration identifies impaired glucose metabolism in women with previous gestational diabetes. *Diabetes* 2003;52:244-51.
- 22) Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, et al. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochem Biophys Res Commun* 1999;257:79-83.
- 23) Yang WS, Lee WJ, Funahashi T, Tanaka S, Matsuzawa Y, Chao CL, et al. Weight reduction increases plasma levels of an adipose-derived anti-inflammatory protein, adiponectin. *J Clin Endocrinol Metab* 2001;86:3815-9.
- 24) Ouchi N, Kihara S, Arita Y, Nishida M, Matsuyama A, Okamoto Y, et al. Adipocyte-derived plasma protein, adiponectin, suppresses lipid accumulation and class A scavenger receptor expression in human monocyte-derived macrophages. *Circulation* 2001;103:1057-63.
- 25) Haluzik M. Adiponectin and its potential in the treatment of obesity, diabetes and insulin resistance. *Curr Opin Investig Drugs* 2005;6:988-93.
- 26) Meier U, Gressner AM. Endocrine regulation of energy metabolism: review of pathobiochemical and clinical chemical aspects of leptin, ghrelin, adiponectin, and resistin. *Clin Chem* 2004;50:1511-25.
- 27) Ong KK, Frystyk J, Flyvbjerg A, Petry CJ, Ness A, Dunger DB. Sex-discordant associations with adiponectin levels and lipid profiles in children. *Diabetes* 2006;55:1337-41.
- 28) Jaquet D, Deghmoun S, Chevenne D, Czernichow P, Levy-Marchal C. Low serum adiponectin levels in subjects born small for gestational age: impact on insulin sensitivity. *Int J Obes (Lond)* 2006;30:83-7.
- 29) Newsome CA, Shiell AW, Fall CH, Phillips DI, Shier R, Law CM. Is birth weight related to later glucose and insulin metabolism?--A systematic review. *Diabet Med* 2003;20:339-48.
- 30) Fruebis J, Tsao TS, Javorschi S, Ebbets-Reed D, Erickson MR, Yen FT, et al. Proteolytic cleavage product of 30-kDa adipocyte complement-related protein increases fatty acid oxidation in muscle and causes weight loss in mice. *Proc Natl Acad Sci U S A* 2001;98:2005-10.
- 31) Giudice LC. Insulin-like growth factors and ovarian follicular development. *Endocr Rev* 1992;13:641-69.
- 32) Liu JP, Baker J, Perkins AS, Robertson EJ, Efstratiadis A. Mice carrying null mutations of the genes encoding insulin-like growth factor I (IGF-I) and type 1 IGF receptor (IGF1R). *Cell* 1993;75:59-72.
- 33) DeChiara TM, Efstratiadis A, Robertson EJ. A growth-deficiency phenotype in heterozygous mice carrying an insulin-like growth factor II gene disrupted by targeting. *Nature* 1990;345:78-80.
- 34) Giudice LC, de Zegher F, Gargosky SE, Dsupin BA, de las Fuentes L, Crystal RA, et al. Insulin-like growth factors and their binding proteins in the term and preterm human fetus and neonate with normal and extremes of intrauterine growth. *J Clin Endocrinol Metab* 1995;80:1548-55.
- 35) Wiznitzer A, Reece EA, Homko C, Furman B, Mazor M, Levy J. Insulin-like growth factors, their binding proteins, and fetal macrosomia in offspring of nondiabetic pregnant women. *Am J Perinatol* 1998;15:23-8.
- 36) Nieto-Díaz A, Villar J, Matorras-Weinig R, Valenzuela-Ruiz P. Intrauterine growth retardation at term: association between anthropometric and endocrine parameters. *Acta Obstet Gynecol Scand* 1996;75:127-31.
- 37) Stefan N, Vozarova B, Funahashi T, Matsuzawa Y, Weyer C, Lindsay RS, et al. Plasma adiponectin concentration is associated with skeletal muscle insulin receptor tyrosine phosphorylation, and low plasma concentration precedes a decrease in whole-body insulin sensitivity in humans. *Diabetes* 2002;51:1884-8.
- 38) Bräkenhielm E, Veitonmäki N, Cao R, Kihara S, Matsuzawa Y, Zhivotovsky B, et al. Adiponectin-induced antiangiogenesis and antitumor activity involve caspase-mediated endothelial cell apoptosis. *Proc Natl Acad Sci U S A* 2004;101:2476-81.
- 39) Mantzoros C, Petridou E, Alexe DM, Skalkidou A, Dessypris N, Papathoma E, et al. Serum adiponectin concentrations in relation to maternal and perinatal characteristics in newborns. *Eur J Endocrinol* 2004;151:741-6.
- 40) Cianfarani S, Martinez C, Maiorana A, Scirè G, Spadoni GL, Boemi S. Adiponectin levels are reduced in children born small for gestational age and are inversely related to postnatal catch-up growth. *J Clin Endocrinol Metab* 2004;89:1346-51.
- 41) Mazaki-Tovi S, Kanety H, Pariente C, Hemi R, Schiff E, Sivan E. Cord blood adiponectin in large-for-gestational age newborns. *Am J Obstet Gynecol* 2005;193:1238-42.