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Cord blood insulin-like growth factor (IGF)-1, IGF-binding proteins and adiponectin, and birth size in offspring of women with mild gestational diabetes

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ABSTRACT

Objective: To clarify the impact of a mild form of gestational diabetes mellitus (GDM) on neonatal birth size, and on insulin-related hormones and adiponectin (AdipoQ) in cord blood.
Methods: Two hundred and sixteen Japanese pregnant women diagnosed as having normal glucose tolerance according to the JSOG criteria were enrolled. Of the 216 women, 38 women were reclassified into a mild GDM (mGDM) group according to the IADPSG criteria. Of the remaining 178 women, 135 women with normal 50-g glucose challenge test were reclassified into a normal glucose tolerance (NGT) group. Cord blood insulin-like growth factor (IGF)-1, IGF-binding proteins (IGFBPs) and AdipoQ were measured in the offspring of the two groups.
Results: Birth weight and its SD scores were larger in the mGDM group than in the NGT group. The incidence of large-for-gestational age (LGA) newborns was higher in the mGDM than in the NGT group. No differences in cord blood free IGF-1, IGFBP-1, IGFBP-2 or AdipoQ levels were observed between the mGDM and NGT groups.
Conclusions: Our study suggests that mild GDM reclassified according to the IADPSG criteria influences neonatal birth size, but neither the IGF-IGFBP axis nor AdipoQ can account for the changes of birth size in offspring of women with mild GDM.

1. Introduction

Gestational diabetes mellitus (GDM) is defined as a glucose intolerance with onset or first recognition during pregnancy [1]. It is well known that GDM is associated with increased risks of adverse perinatal outcomes [2]. Most of the previous diagnostic criteria for GDM were defined to identify pregnant women with a high risk of developing diabetes after pregnancy. In 2008, the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study demonstrated that maternal glucose levels during pregnancy were significantly associated with both birth weight and cord blood C-peptide levels [3]. On the basis of the HAPO study, the International Association of Diabetes and Pregnancy Study Group (IADPSG) established new diagnostic criteria for GDM in 2010 [4]. In Japan, the IADPSG criteria were adopted for the diagnosis of GDM in place of the Japan Society of Obstetrics and Gynecology (JSOG) criteria in 2010. Since the threshold values for a 75-g oral glucose tolerance test (OGTT) are lower by the IADPSG criteria than by the JSOG criteria, the number of pregnant women diagnosed with milder GDM is expected to increase after adoption of the IADPSG criteria. Macrosomia is a well-known complication of offspring born to women with GDM [2]. Based on the Pedersen hypothesis [5], fetal hyperglycemia and hyperinsulinemia caused by maternal GDM are expected to play a major role in fetal overgrowth. Previous studies have demonstrated that insulin mediates somatogenic actions through stimulating insulin-like growth factor (IGF)-1, and the bioactivity of the IGF-1 is controlled by IGF-binding proteins (IGFBPs) [6,7]. IGFBP-1 and -2 modulate IGF-1 activity and the secretion of these binding proteins is also regulated by insulin [8]. The IGF-IGFBP axis is thus an important regulator of fetal growth. On the other hand, adiponectin (AdipoQ), one of the most abundant adipocytokines, is considered to play a regulatory role in glucose metabolism as an insulin-sensitizer [9]. Recent studies have suggested a close association between cord blood AdipoQ concentrations and fetal growth [10–12]. Although both the IGF-IGFBP axis and AdipoQ are associated with fetal growth, little is known about the effects of these insulin-related hormones and AdipoQ on fetal growth in the offspring of women with mild GDM. In the present study, we first enrolled pregnant women with normal glucose tolerance

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according to the JSOG criteria and then reclassified the women fulfilling the IADPSG criteria among them into a mild GDM group. The study was undertaken in order to clarify the impact of the milder form of GDM on neonatal birth size and on insulin-related hormones and AdipoQ in cord blood.

2. Materials and methods

2.1. Study population and definitions

Japanese pregnant women who had a casual glucose value ≥95 mg/dl (5.3 mmol/L) or 1-h glucose value ≥140 mg/dl (7.8 mmol/L) by a 50-g glucose challenge test (GCT) for an initial screening of GDM were followed by a 75-g oral glucose tolerance test (OGTT) for the diagnosis of GDM. By the JSOG criteria, a patient was considered to have GDM when the plasma glucose measurements from at least two time points exceeded the following OGTT thresholds: fasting, 100 mg/dl (5.6 mmol/L); 1 h, 180 mg/dl (10.0 mmol/L); 2 h, 150 mg/dl (8.3 mmol/L). On the other hand, by the IADPSG criteria, a diagnosis of GDM was made when the plasma glucose measurements at only one or more time points exceeded the following OGTT thresholds: fasting, 92 mg/dl (5.1 mmol/L); 1 h, 180 mg/dl (10.0 mmol/L); 2 h, 153 mg/dl (8.5 mmol/L). The present study was conducted from 2009 to 2010 at Tsukuba University Hospital, and included 216 pregnant women diagnosed as having normal glucose tolerance on the basis of the JSOG criteria after undergoing a GCT and/or an OGTT at approximately 24 and 30 weeks of gestation. Gestational age was calculated according to the date of the mother's last menstrual period and was also determined by fetal ultrasonography. The women with multiple-fetus pregnancy, pre-gestational diabetes, pregnancy-induced hypertension, or chronic systematic disease, and those taking medication or with a smoking habit were excluded. The exclusion criteria regarding offspring were gestational age <35 weeks, abnormality requiring intensive care immediately after birth, life-threatening congenital malformation or chromosomal anomaly. Thirty-eight of the 216 women fulfilled the IADPSG criteria and were reclassified into a mild GDM (mGDM) group. Of the remaining 178 women, 135 women with normal GCT were reclassified into a normal glucose tolerance (NGT) group. Forty-three women with positive GCT were excluded from the study. All of the women received routine obstetrical care without any diet therapy during pregnancy. The SD scores of birth weight, length and chest circumference were calculated according to Japanese standards, in which gestational age, sex and parity are taken into account [13]. Large-for-gestational age (LGA) newborns were defined as birth weight being above the 90th percentile of the reference data. Macrosomia was defined as a birth weight at or above 4000 g. Jaundice was defined as hyperbilirubinemia requiring phototherapy. Cord blood samples were collected immediately after birth. Serum was separated by centrifugation and stored at −80 °C until analysis. The study was approved by the Tsukuba University Ethics Committee, and written informed consent was obtained from all participants.

2.2. Laboratory analyses

The serum levels of free IGF-1 were determined with an ELISA kit (R&D Systems, Inc., Minneapolis, MN, USA). The lower limit of detection was 0.015 ng/ml, and the inter- and intra-assay coefficients of variation were 6.2% to 11.1% and 3.6% to 5.0%, respectively. The serum levels of total IGFBP-1 were determined with an ELISA kit (BioVendor Laboratories, Ltd., Asheville, NC, USA). The lower limit of detection was 0.02 ng/ml, and the inter- and intra-assay coefficients of variation were 5.2% to 7.4% and 5.9% to 6.8%, respectively. The serum levels of total IGFBP-2 were determined with an ELISA kit (BioVendor Laboratories, Ltd., Asheville, NC, USA). The lower limit of detection was 0.2 ng/ml, and the inter- and intra-assay coefficients of variation were 1.7% to 7.4% and 4.5% to 6.6%, respectively. The serum AdipoQ concentrations were assayed with an ELISA kit (Linco Research, Inc., Missouri, USA). The sensitivity of the assay was 1 μg/ml and the limit of linearity was 250 μg/ml. The inter- and intra-assay coefficients of variation were 6.9% to 9.3% and 1.8% to 6.2%, respectively.

2.3. Statistical methods

The results are expressed as the mean ± SD or as median and interquartile ranges when the data were not normally distributed. The differences in categorical variables between groups were assessed by chi-square test or the Fisher's exact test. The Student's unpaired *t*-test, Mann–Whitney *U*-test or Welch's test was used to determine statistical significance. Differences in subject characteristics were determined by analysis of covariance, with neonatal sex or maternal pre-gestational body mass index (BMI) as a class variable. Relationships between parameters were evaluated by simple linear regression analysis. To investigate independent predictors of birth weight SD scores, a multiple regression analysis was performed considering variables maternal age, pre-pregnancy BMI, placental weight and cord blood biochemical parameters. All analyses were performed using SPSS software (SPSS for Windows, Version 22; SPSS Inc., Chicago, IL, USA). A level of $p < 0.05$ was accepted as statistically significant.

3. Results

3.1. Basal characteristics of mothers and neonates

The clinical characteristics of mothers and their offspring included in the study are shown in Table 1. There was no significant difference in the rate of parous women or pre-gestational BMI between the mGDM and NGT groups. Maternal age in the mGDM group was higher than in the NGT group. No differences were found in the gestational age, sex ratio, Apgar score or rate of jaundice in neonates between the two groups. Umbilical artery pH was lower in the mGDM group than in the NGT group.

3.2. Anthropometric measurements of neonates (Table 1)

Birth weight, length, head circumference and chest circumference were larger in the mGDM group than in the NGT group. SD scores of birth weight, length and head circumference were also higher in the mGDM group. The differences between groups persisted after adjustment for maternal pre-gestational BMI or neonatal sex. Multiple regression analysis revealed that maternal glucose intolerance was a significant and independent determinant for birth weight SD scores ($\beta = 0.18$, $p < 0.05$). Although there was no significant difference in the incidence of macrosomia between the mGDM and NGT groups, the incidence of LGA was higher in the mGDM than in the NGT group. In contrast, no low-birth weight infants were found in the mGDM group. The ponderal index, an indicator of fatness in infants, was similar between the two groups.

3.3. Free IGF-1, IGFBP-1, IGFBP-2 and adiponectin in cord blood (Tables 2 and 3)

No differences in cord blood free IGF-1, IGFBP-1, IGFBP-2 or AdipoQ levels were observed between the mGDM and NGT groups. The free IGF-1 levels were significantly and positively correlated with birth weight SD scores in both the mGDM and NGT groups ($r = 0.401$, $p = 0.017$ and $r = 0.255$, $p = 0.004$, respectively). There were no significant relationships between IGFBP-1, IGFBP-2 or AdipoQ levels and birth weight SD scores in the mGDM group, while AdipoQ levels were significantly correlated with birth weight SD scores in the NGT group ($r = 0.360$, $p < 0.001$).