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Original Article

Amniotic fluid, maternal, and neonatal serum C-peptide as predictors of macrosomia: A pilot study

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Abstract

Background: Fetal macrosomia is associated with increased maternal and fetal complications. Various factors may predispose a fetus to macrosomia. The aim of the present study was to evaluate the association between serum and amniotic fluid (AF) insulin, C-peptide, and glucose and macrosomia.
Methods: Thirty-eight neonates were enrolled in this case-control study. Ten macrosomic neonates were considered as the case group, and 28 normal weight neonates were designated as the control group. AF C-peptide, insulin, and glucose were measured in both groups; also maternal and neonatal serum C-peptide, insulin, and glucose were simultaneously measured during delivery.
Results: There was a significant correlation between neonatal (P=0.01) and maternal (P=0.006) serum C-peptide levels and macrosomia. The serum glucose levels of the mothers in the macrosomic group were also significantly higher than those of the control group. The AF insulin and C-peptide levels in the macrosomic group were higher than those of the control group; however, the difference was not significant. There was no significant correlation between macrosomia and the other factors such as placental weight, gender, neonatal Apgar score, and gestational age.
Conclusion: The results demonstrated that AF C-peptide and also maternal and neonatal serum C-peptide were factors that could influence fetal weight and predict macrosomia.

Keywords: Macrosomia, Amniotic fluid, Insulin, C-peptide

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Introduction

Fetal macrosomia, defined as a birth weight≥ 4000g, is associated with increased maternal and neonatal complications including perinatal mortality, asphyxial injuries, meconium aspiration, and prolonged labor [1, 2]. The causes of macrosomia, in addition to diabetes, are race, maternal obesity, maternal age, post-term pregnancy, multiparity, and history of macrosomia.

Fetal hyperinsulinemia has been shown to be a predictor of diabetic fetopathy [3,4] and can be determined indirectly by amniotic fluid (AF) insulin levels, which reflects urinary excretion of fetal insulin [5,6].

It is believed that maternal hyperglycemia results in fetal hyperglycemia, fetal hyperinsulinemia, and consequently an increased birth weight [7-9]. Hyperinsulinemia causes macrosomia, and insulin elevation in AF increases the risk of macrosomia [10].

Gestational diabetes is the most common metabolic disorder during pregnancy [11, 12] and macrosomia accompanied by gestational diabetes causes neonatal hypoglycemia in 50-60% of cases and increases neonatal intensive care unit admission rates [13].

Some studies have shown higher levels of AF C-peptide in macrosomic neonates than those in control groups [13, 14]. There are reported studies in humans that have found a positive correlation between umbilical cord C-peptide levels and insulin concentrations and neonate birth weight [15, 16]; nonetheless, there is a dearth of data on the relation between AF C-peptide and macrosomia. It is, therefore, important to determine factors which may predict macrosomia.

The aim of this study was to compare some important maternal and fetal characteristics such as serum and AF C-peptide, insulin, and glucose levels between macrosomic neonates and normal weight control group. Also, some factors that may be affected by macrosomia such as the placental weight and Apgar score were evaluated.

Methods

Pregnant women who were admitted to Dr. Shariati, an educational university hospital in Tehran, between July and September 2005 and delivered newborns with normal or over 4000 gr weights were recruited. All the participants were healthy, normotensive, and non-diabetic (including gestational diabetes); furthermore, had singleton alive and full-term fetuses. Sample selection was based on a ratio of 1:3.

The case group was consisted of 10 consecutively recruited macrosomic term newborns (body weight ≥4000g), and the control group was consisted of 28 consecutively selected newborns with a birth weight appropriate for the gestational age. Two women were excluded because of inadequate blood samples.

The exclusion criteria included: multiparity, severe Rh-isoimmunization, history of rupture of membrane, cervix insufficiency, and history of neonatal malformations like omphalocele, spina bifida, and anencephaly.

The research protocol was approved by the Ethics Committee of the Endocrinology and Metabolism Research Center of Tehran University of Medical Sciences, and written informed consent was obtained from all the participants.

The following parameters were analyzed: neonatal birth weight, pre-pregnancy body mass index (BMI), gestational age, AF and serum insulin; C-peptide, and glucose in the mothers and neonates, placental weight, Apgar scores, and the blood pressure of the mothers.

During the early stages of the pregnancy, the blood pressure of the mothers was measured in supine and sitting positions with the sphygmomanometer.

During parturition, a sample of AF (10 ^{cc}) was drawn and transfered to the laboratory of Endocrinology and Metabolism Research

Center of Tehran University of Medical Sciences for assessment of insulin and C-peptide levels.

Cord blood samples were collected during delivery from the neonates. Maternal blood samples were also taken during delivery. The samples were centrifuged, and serum was separated and stored at -20°C before assay. Glucose, insulin, and C-peptide levels were measured in the maternal and neonatal samples. Insulin and C-peptide levels were determined via the radioimmunoassay method using Immunokit and gamma counter. The coefficient of variation (CV) of insulin with 95% sensitivity was 4.5% (Monobind kit). Glucose was measured using the Auto-analyzer (Hitachi 902). Newborn birth weights were recorded after delivery. Apgar scores in the first 5 minutes were determined in the delivery room, furthermore, placental weight was measured after delivery.

All the newborns were evaluated for the presence hypoglycemia every 6 hours within the first 48 hours after delivery.

Gestational age at delivery was calculated according to the recorded last menstrual period.

Statistical analysis

SPSS software version 11.5 was used for data analysis. Two-tail t-test or proper non-parametric tests such as the Mann-Whitney U-test and Chi- square were used and P-values≤0.05 were considered as significant.

Results

In this study, 10 newborns were macrosomic and 28 had normal weights. Tables 1 and 2 reveal baseline characteristics of newborns.

The serum C-peptide levels of the mothers and neonates in the macrosomic group were approximately twice as those of the control group (Table 3). The serum glucose levels of the mothers in the macrosomic group were also significantly higher than those of the control group (P=0.05).

Table 1. Baseline characteristics of mothers in control and macrosomic groups

characteristics	Macrosomia n=10	Control group n=28
Mother age (years)	27±3	30±5
Gravidity	1.60±0.52	2.14±1.24
Weight before pregnancy (kg)	64.5±10.1	61.5±11.3
Weight during labor (kg)	77.2±8.3	73.4±10.9
Gestational age (weeks)	39.1±0.6	39.2±0.9
Systolic blood pressure(mm Hg)	108.5±10.0	111.2±11.8
Diastolic blood pressure(mm Hg)	68.1±8.8	71.4±9.2
Family history of macrosomia n (%)	2 (20)	4 (14.3)
Prepregnancy BMI (kg/m^2)	30.9±4.4	29.7±4.9

Data are means± SD, BMI : Body Mass Index, ∗ differences were not significant (P>0.05), statistical method: 2-tail t-test

Table 2. Baseline characteristics of neonates in both control and macrosomic groups

characteristics	Macrosomia n=10	Control group n=28
Neonatal Weight (gr)∗	4080.1±120.6	3137.5±323.4
Placental weight (gr)	668/7±157.4	552.2±230.4
Apgar score	9.5±0.5	9.7±0.6
Male Sex n (%)	6 (60)	12 (42.9)

Data are means± SD, statistical method: 2-tail t-test, ∗P-values were significant (<0.05)

Table 3. Insulin and C-peptide of amniotic fluid and mothers' and neonates' blood sample for insulin, glucose, and C-peptide

characteristics	Macrosomia n=10	Control group n=28
AF insulin (ng/ml)	0.093±0.075	0.084±0.068
AF glucose (mg/dl)	20. 50± 10	22.07±12
AF C-peptide (ng/ml)	1.88±0.946	1.34±0.726
Mother insulin levels (ng/ml)	0.88±1.571	0.31±0.702
Neonate insulin levels (ng/ml)	0.15±0.128	0.13±0.145
Mother serum C-peptide levels (ng/ml) ∗	4.21±2.82	2.05±1.608
Neonate serum C-peptide levels (ng/ml) ∗	1.82±1.133	0.99±0.686
Mother serum glucose levels (mg/dl) ∗	106.30±63.568	77.78±24.284
Neonate serum glucose levels (mg/dl)	68.30±18.862	57.17±30.241

Data are means± SD, statistical method: 2-tail t-test, ∗P-values were significant (<0.05)

Although serum glucose levels in the newborns of the macrosomic group were higher than that of the control group, the difference was not significant (P=0.2).

The AF insulin and C-peptide levels in the macrosomic group were higher than those of the control group, but the difference was not significant; however, the P-values showed a trend toward significance, especially with regard to AF C-peptide levels.

Maternal and neonatal serum insulin in the macrosomic group was higher than that of the control group, but did not reach a statistical significance.

There was no significant difference in the serum glucose levels of the newborns present in both two groups. The correlation between the mothers' BMI, newborns' Apgar scores and placental weight, and macrosomia was not significant.

We found no significant correlation between macrosomia and such other variables as the systolic and diastolic blood pressure of the mothers, gender of the newborns, and gestational age. No evidences of hypoglycemia were observed in participated newborns.

Discussion

According to the findings of the present study, the maternal and neonatal serum C-peptide of the macrosomic group was significantly higher than those of the control group, a finding consistent with previously reported studies [13, 14].

Positive correlations between at birth C-peptide levels of cord blood samples and insulin concentrations and fetal weight have been previously reported [15, 17-21].

Our study confirmed the hypothesis that insulin and C-peptide are major anabolic factors influencing the intrauterine growth. Also, maternal blood glucose in the macrosomic group was significantly higher than that of the control group. Clinical studies support the concept that maternal hyperglycemia leads to fetal hyperinsulinemia and probably induces macrosomia.

Apart from maternal hyperglycemia, there may be an additional explanation for the increase in fetal insulin secretion and anabolism, which warrants further investigations [22].

Fetal hyperinsulinemia is a strong predictor of excessive growth and fetopathy in diabetic pregnancies [3, 4] and can be indirectly determined by AF insulin levels secondary to the urinary excretion of fetal insulin [5, 6]. Moreover, it may increase neonatal morbidity, not only by increasing the risk of neonatal hypoglycemia, but also through macrosomia. An association between at birth macrosomia and elevated AF insulin at third trimester as well as at

the time of delivery has been well documented [23-25].

As mentioned, the correlation between AF insulin, glucose, and C-peptide and macrosomia was not significant, which may due to insulin degradation by placental insulinase and probably, our small sample size.

Weiss et al. demonstrated that neonatal morbidity was largely related to AF insulin levels, which were increased two- to threefold above normal [26].

Although, in the present study, the serum insulin levels of the mothers and newborns of the macrosomic group were higher than that of the control group, the correlation was not significant. The suggested explanation may be the small sample size of our study. Recent studies have shown that maternal BMI is a strong predictor of the birth-weight of the offspring [27-30]; and, could be a predictor of fetal cord insulin concentration. Our results did not confirm this observation, and there was no significant correlation between maternal BMI and fetal insulin and macrosomia, which may be due to the small sample size of our study.

In the present study, there was no correlation between placental weight and birth-weight. The placenta plays an important role in feto-maternal nutrients and metabolites transfer, and its precise function warrants further research.

There are some shortcomings in the present study which small sample size is one of the most observable ones. However, as a pilot study, we have recruited a small sample and therefore, further surveys with greater sample size are warranted.

In conclusion, the results of the present study show that neonatal weight is related to the serum C-peptide levels of mother and newborn. In addition, these factors may be related to the hyperinsulinemia and insulin resistance observed in mothers. Further studies are required to demonstrate the effect of insulin resistance treatment on neonatal birth weight.

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