Original article

Are the neonatal outcomes similar in large-for-gestational age infants delivered by women with or without gestational diabetes mellitus?

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Background: **Infants are considered large for gestational age (LGA) if their birth weight is greater than the 90th percentile for gestational age and they have an increased risk for adverse perinatal outcomes. Maternal diabetes is one of the factors affecting birthweight. However there are limited data on the perinatal outcomes of infants of gestational diabetic mothers. The aim of the present study was to compare the neonatal outcomes of LGA infants delivered by women with and without gestational diabetes mellitus.**

Methods: **This was a retrospective study of LGA infants of ≥36 weeks of gestation born at the Gazi University Medical School Hospital during the period of 2006-2009. Neonatal outcomes included hypoglycemia and polycythemia in the early neonatal period and hospital admissions. The Chi-square and Student's *t* test were used for comparing variables.**

Results: **Seven hundred eligible infant-mother pairs were enrolled in the study. Eighty-seven of them (12.4%) were infants of gestational diabetic mothers and 613 (87.6%) were infants of non-diabetic mothers. The incidence of hypoglycemia at the first hour was higher in infants of diabetic mothers (12.8%) than in infants of non-diabetic mothers (5.3%) (*P*=0.014). Polycythemia was also more frequently observed in infants of the gestational diabetic mothers (9.3%) than in infants of the non-diabetic mothers (3.0%) (*P*=0.010). Although overall hospital admission rates were not different between the two groups, infants of diabetic mothers were more likely to be admitted because of resistant hypoglycemia (*P*=0.045).**

Conclusions: **The results of this study suggested that LGA infants of mothers with gestational diabetes mellitus were at a greater risk for hypoglycemia and polycythemia in the early neonatal period than LGA infants of non-diabetic mothers.**

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Key words: **gestational diabetes; large-for-gestational age infants; neonatal hypoglycemia; polycythemia**

Introduction

Infants are considered large for gestational age (LGA) if their birth weight is greater than the 90th percentile. Birth weight is influenced by several extrinsic factors, including maternal smoking, viral infections and diseases such as maternal diabetes and hypertension. Maternal height and body mass index (BMI) as well as weight gain during pregnancy are known to be positively associated with infant size at birth.[1-3] Excessive fetal growth can occur because of genetic factors or increased supply of nutrients. Fetal hyperglycemia and hyperinsulinemia enhance growth in infants of diabetic mothers.[4]

One subgroup of LGA infants of particular interest consists of offspring of mothers with gestational diabetes mellitus. Such mothers have increased risk of giving birth to LGA infants than those without gestational diabetes mellitus. Adverse perinatal outcome of those pregnancies are well known, and diabetic mothers are at risk for metabolic dearrangements such as hypoglycemia and hypocalcemia in the early neonatal period.[5,6] Chronic fetal hyperinsulinemia results in an elevated metabolic rate, leading to increased oxygen consumption and fetal hypoxemia.

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One of the effects of fetal hypoxemia is increased synthesis of erythropoietin which can result in polycythemia.[7]

Hypoglycemia is a common problem in neonates and it has been recognized as a cause of serious long-term neurological morbidity. As LGA newborns have an increased risk of hypoglycemia even when they are not the products of diabetic pregnancies, the screening of LGA babies for hypoglycemia is recommended.[8] However, there are conflicting approaches according to the report of the World Health Organization (WHO) screening, and supplementary feeding is inappropiate for infants who are healthy but LGA, unless known to be born from diabetic mothers.[9] Paucity of the supporting evidence evolves different follow-up protocols for LGA infants of diabetic or nondiabetic mothers in different hospital nurseries.

The objective of this study was to compare the neonatal outcomes of LGA infants of diabetic and non-diabetic mothers.

Methods

LGA infants of ≥36 weeks of gestation born at the Gazi University Medical School Hospital between 2006-2009 were enrolled in the study. Infants of mothers with preexisting diabetes, pregnancy-induced hypertension and preeclampsia, and other systemic illness or history of smoking during gestation were excluded. Premature infants with a gestational age of less than 36 weeks, infants with congenital malformations, infants with known metabolic disorders, and those delivered from multiple pregnancies were also excluded.

Medical charts of infants and mothers were reviewed retrospectively for clinical and demographic information. Infants whose birth weight was above the 90th percentile were defined as LGA. Because national intrauterine growth curves are not available, Lubchenco curves were used.[10] Gestational age was determined by the last menstrual period or fetal ultrasonography performed before 12 weeks of gestation. A 100-g glucose loading test (GLT) was used for diagnosing gestational diabetes mellitus. The National Diabetes Data Group[11] and the Carpenter and Coustan[12] criteria which are frequently used for the diagnosis with a 100-g GLT are qualitative diagnostic criteria for gestational diabetes mellitus when two or more of the four measured values exceed the criteria.

All LGA infants were routinely evaluated for hypoglycemia by heel-stick at the first and fourth hour. Also these infants are evaluated for polycythemia by venous blood sampling at the fourth hour of life according to our institutional protocol. Further blood glucose measurements were done if an infant was symptomatic. Feeding patterns and postnatal weight loss were also examined and recorded routinely in the first few days or longer if needed.

Blood glucose measurement was done by a glucometer (GlucoDr®) routinely. Serum glucose level was checked by a hexokinase method using commercially available kits (Abbott, USA) if it was below 46 mg/dL or the infant was symptomatic.

Primary neonatal outcomes included hypoglycemia, polycythemia and hospital admissions due to hyperbilirubinemia, respiratory distress or other causes during the first week of life. Postnatal weight loss during the first 72 hours of life and need of supplementary feeding were also evaluated. Although the definition of hypoglycemia remains one of the most confused issues in neonatology, hypoglycemia was defined as blood glucose <46 mg/dL (2.6 mmol/L) irrespective of gestational or postnatal age in this study.[13] Peripheral venous hemotocrit value ≥65% was defined for polycythemia.

Infants with resistant hypoglycemia were admitted to the hospital for intravenous infusion of dextrose, and resistant hypoglycemia was recognized when the blood glucose level persisted below 46 mg/dL in spite of two separate feedings at 30-minute intervals.

The Chi-square test was used to compare nominal variables between the two groups and Student's *t* test was used to determine numeric variables. Values were expressed as mean ± standard deviation. All statistical calculations were performed using SPSS 11.0 for Windows. A P value of <0.05 was considered statistically significant.

This study was approved by the institutional ethics committee of Gazi University School of Medicine.

Results

Seven hundred eligible infant-mother pairs were included in the study. Of the 700 LGA infants, 87 (12.4%) were infants of gestational diabetic mothers and 613 (87.6%) were infants of non-diabetic mothers. The birth weight of infants of the gestational diabetic mothers were significantly higher than that of the non-diabetic mothers, whereas the gestational age of the gestational diabetic mothers was lower than that of the non-diabetic mothers. Gestational diabetic mothers were older and had higher BMI than non-diabetic mothers. Gestational diabetic mothers were more likely to deliver by cesarean section than non-diabetic mothers (Table 1).

The incidence of hypoglycemia at the first hour was higher in the gestational diabetic mothers than in the non-diabetic mothers (P=0.014), whereas a similar incidence was seen (P=0.840) at the fourth hour following delivery. Polycythemia was more frequently

Table 1. Demographic and anthropometric characteristics of the study groups

Characteristics	non-IDM (n=613)	IGDM (n=87)	P value
Gestational age (wk)	39.3 ± 1.2	38.9 ± 1.1	0.001
Birth weight (g)	3987 ± 220	4067 ± 299	0.003
Birth length (cm)	51.3 ± 1.6	51.4 ± 1.6	0.442
Infants' BMI (kg/m^2)	15.2 ± 1.1	15.4 ± 1.1	0.127
Sex (female/male)	223/390	35/52	0.479
Mothers' age (y)	30.0 ± 4.8	32.9 ± 4.9	0.000
Maternal weight gain	15.9 ± 5.7	14.6 ± 5.2	0.074
Maternal BMI (kg/m^2)	29.2 ± 4.0	30.6 ± 4.8	0.006
Maternal BMI ≥30 kg/m^2, n (%)	238 (38.9%)	48 (55.2%)	0.009
Delivery route (vaginal/ cesarean section), n (%)	196 (32.0%)/ 417(68.0%)	16 (18.4%)/ 71(81.6%)	0.009

Values are mean ± SD. non-IDM: infants of non-diabetic mothers; IGDM: infants of gestational diabetic mothers; BMI: body mass index.

Table 2. Primary neonatal outcomes of the study groups

Characteristics	non-IDM n (%)	IGDM n (%)	P value
Hypoglycemia on 1st hour	32/606 (5.3)	11/86 (12.8)	0.014
Hypoglycemia on 4th hour	53/602 (8.8)	8/86 (9.3)	0.840
Polycythemia	18/602 (3.0)	8/86 (9.3)	0.010
Hospital admissions	44/613 (7.2)	11/87 (12.6)	0.087

non-IDM: infants of non-diabetic mothers; IGDM: infants of gestational diabetic mothers.

Table 3. The reasons for hospital admissions according to causes of infants with diabetic and non-diabetic mothers

	non-IDM (n=613)	IGDM (n=87)	P value
Hypoglycemia	4 (0.7%)	3 (3.5%)	0.045
Hyperbilirubinemia	20 (3.3%)	5 (5.7%)	0.227
Other causes*	20 (3.3%)	3 (3.5%)	0.361
Total hospital admissions	44 (7.2%)	11 (12.6%)	0.087

*: Other causes include respiratory distress, polycythemia, etc. non-IDM: infants of non-diabetic mothers; IGDM: infants of gestational diabetic mothers.

Table 4. Postnatal weight loss of the study infants (Infants who were admitted to the newborn ward were excluded)

Weight loss (%)	non-IDM (n=563)	IGDM (n=76)	P value
24th hour	4.5 ± 1.8	4.5 ± 1.8	0.728
48th hour	6.8 ± 2.3	6.9 ± 2.1	0.883
72nd hour	6.3 ± 3.0	6.1 ± 3.4	0.599

Values are mean ± SD. non-IDM: infants of non-diabetic mothers; IGDM: infants of gestational diabetic mothers.

observed in the gestational diabetic mothers than in the non-diabetic mothers (P=0.010). Although the overall hospital admission rates were not different between the two groups, the gestational diabetic mothers were more likely to be admitted due to resistant hypoglycemia (Tables 2 and 3).

The rates of exclusively breast-feeding were not different between the two groups (81% *vs* 84%, P=0.902). No significant difference was seen between the two groups in terms of weight loss percentage after excluding the infants who were admitted to the level 2 neonatal intensive care unit (Table 4).

Mothers were defined as obese if their BMIs were ≥30 kg/m^2, and there was no significant difference in neonatal outcomes between infants delivered by obese and non-obese mothers in both groups (data not shown).

Discussion

The screening of LGA babies for hypoglycemia is controversial because of conflicting reports about the risk of hypoglycemia in non-diabetic mothers.[9,10,14,15] In a study of LGA infants excluding infants of mothers with gestational diabetes, blood glucose levels suggested that the otherwise healthy LGA infants of 36 to 42 weeks of gestation should be monitored for blood glucose level in the same manner as appropiate for the gestational age infant.[14] A recent study showed that the incidence of hypoglycemia in macrosomic infants was lower in non-diabetic mothers than in diabetic mothers.[16] Our results are consistent with those findings.

Esakoff et al[16] retrospectively examined perinatal outcomes of a large cohort of mothers with or without gestational diabetes. They found that birthweight of 4000 g or greater was associated with a higher incidence of adverse perinatal outcomes including hypoglycemia in mothers with or without gestational diabetes mellitus, and gestational diabetes mellitus increased the risk further. Macrosomia indicates excessive growth regardless of gestational age. This condition is defined as birth weight greater than 4000 g or 4500 g. Because macrosomia is already a well known risk factor for many perinatal adverse outcomes,[17,18] we studied not only macrosomic babies but all LGA infants according to their gestational age.

Excessive fetal growth may occur because of genetic factors and it could be hypothesized that if a fetus is genetically meant to be large, it is less likely to exhibit abnormal metabolic dearangements such as hypoglycemia that is frequently associated with intrauterine hyperglycemia. There were significantly higher rates of hypoglycemia and polycythemia in LGA infants of mothers with gestational diabetes irrespective of whether they were macrosomic or not, therefore we suggested that LGA infants of diabetic mothers should be followed up closely for hypoglycemia and polycythemia, whereas routine observations are sufficient for large infants of non-diabetic mothers.

The incidence of polycythemia ranges 1%-5% of healthy newborns screened for this disorder.[19] In our study we found similar rates of polycythemia in non-diabetic mothers. However, polycythemia is thought to be due to increased erythropoiesis, which occurs in

13%-33% of infants of diabetic mothers. Although the long-term complications and treatment strategies of polycythemia are controversial, we thought increased hemotocrit values might be a marker of unfavorable intrauterine conditions of infants of diabetic mothers.

This is a retrospective study, but we investigated a relatively large cohort. We also investigated feeding patterns and postnatal weight losses of infants, which indicates that the results were not influenced by those extrauterine factors. As another limitation, we did not investigate mechanical complications such as shoulder dystocia and brachial plexus injury. However, diabetic mothers had a significantly higher rate of cesarean deliveries, similar to the results of other studies.[15,20] In such case, comparing mechanical complications would not be proper.

Another significant difference in this study is that diabetic mothers delivered at an earlier gestational age than non-diabetic mothers. This finding is consistent with the report by Das et al[15] who suggested that intense antenatal testing and monitoring of diabetic women and the difficulty in clinical identification of a macrosomic infant led to delivery at an earlier gestational age. We did not include infants whose gestational age was lower than 36 weeks. Primary neonatal outcomes investigated were hypoglycemia, polycythemia and hospital admissions due to hyperbilirubinemia, respiratory distress or other causes during the first week of life. These events could also be affected by prematurity, and thus it would be difficult to differ this from any perinatal adverse outcome caused by maternal gastational diabetes or prematurity.

In conclusion, the results of this study suggest that LGA infants of mothers with gestational diabetes mellitus are more likely to suffer from hypoglycemia and polycythemia in the early neonatal period than LGA infants of non-diabetic mothers.

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