

Rate and risk factors of hypoglycemia in large-for-gestational-age newborn infants of nondiabetic mothers

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OBJECTIVE: The purpose of this study was to investigate the rate of hypoglycemia in large-for-gestational-age infants of nondiabetic mothers in relation to maternal or neonatal risk factors.

STUDY DESIGN: Hospital charts of all term large-for-gestational-age infants born between 1994 and 1998 (n = 1136) were analyzed for the rate of neonatal hypoglycemia (capillary glucose level, ≤ 30 mg/dL) during the first 24 hours of life. Infants of women with preexisting or gestational diabetes mellitus were excluded (n = 180). Neonatal glucose testing was performed at 1 or 2 hours of life, with subsequent measurements every 4 to 6 hours. Maternal and neonatal parameters were compared between neonates with and without hypoglycemia, including recent oral glucose tolerance test values in those women who were tested (n = 358).

RESULTS: Of 956 infants, 69 infants (7.2%) were not tested for hypoglycemia. In the remaining 887 infants, hypoglycemia occurred in 142 infants (16%) within the first 24 hours of life. The incidence of hypoglycemia decreased sharply during the first few hours of life, from 9.2% within the first hour of life, to 3.5% between 2 to 5 hours (cumulative) of life, and 2.4% between 6 and 24 hours of life. Gestational age at delivery was the only neonatal parameter that differed significantly between infants with and without hypoglycemia (39.5 vs 39.3 weeks, $P = .01$). The antenatal 1-hour oral glucose tolerance test value was the only predictive maternal parameter (141.5 vs 163.0 mg/dL, $P < .006$). There was an incremental risk of hypoglycemia with increasing 1-hour oral glucose tolerance test values, with hypoglycemia rates of 2.5%, 9.3%, 22.0%, and 50.0% that were associated with maternal 1-hour glucose values of <120 , 120-179, 180-239, and ≥ 240 mg/dL, respectively ($P < .05$, for all comparisons).

CONCLUSION: Routine glucose testing is indicated in large-for-gestational-age newborn infants of nondiabetic mothers. The 1-hour glucose value of the maternal oral glucose tolerance test is a fairly good predictor of subsequent neonatal hypoglycemia. A single elevated 1-hour value of ≥ 180 mg/dL markedly increases the risk of neonatal hypoglycemia. (Am J Obstet Gynecol 2002;187:913-7.)

Key words: Newborn infant, large for gestational age, nondiabetic, hypoglycemia, oral glucose tolerance test

Excessive intrauterine growth may indicate fetal hyperinsulinism because of maternal hyperglycemia during pregnancy.¹ After the umbilical cord has been severed, delayed adaptation of neonatal insulin secretion to the sudden drop in glucose supply may pose the newborn infant at risk for hypoglycemia. If undiagnosed and untreated, hypoglycemia may cause subtle or overt brain damage in the newborn infant.^{2,3} Even in macrosomic newborns from nondiabetic mothers, insulin C-peptide concentrations in the cord blood have been

found to be elevated compared with normosomic infants.⁴ However, there is no consensus regarding the necessity to test large-for-gestational-age (LGA) neonates of nondiabetic mothers routinely.⁵⁻⁷ There is a remarkably small body of data that provides evidence as to the risk of neonatal hypoglycemia in these infants.⁸ Furthermore, there is no risk assessment for LGA infants of nondiabetic mothers that would allow an individualized approach based on neonatal conditions and pregnancy history. Universal testing of all LGA neonates of nondiabetic mothers followed by numerous repeat measurements might inflict pain unnecessarily on infants at no or low risk for hypoglycemia. Although missing significant hypoglycemia levels may have untoward long-term sequelae for the infant and the physician in charge. The aim of our study was therefore to determine the extent of neonatal hypoglycemia in the first 24 hours of life in a large population of LGA newborn infants of nondiabetic mothers and to identify possible maternal and neonatal predictors.

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Table I. Maternal characteristics of nondiabetic women of LGA newborn infants with and without neonatal hypoglycemia*

Characteristic	Neonatal hypoglycemia		P value
	No (n = 745)	Yes (n = 142)	
Age (y)†	28.3 ± 5.4	29.1 ± 5.3	.5
Multipara (%)	70.4	63.7	.9
Prepregnancy body mass index (kg/m ²)†	25.8 ± 5.1	25.9 ± 5.6	.8
Weight gain during pregnancy (kg)†	14.0 ± 5.6	15.3 ± 6.0	.2
History of GDM (%)	3.3	5.6	.18
History of macrosomia of >4000 g (%)	16.9	14.0	.8
History of stillbirth (No.)	7 (0.9%)	3 (2.3%)	.2
OGTT (No.)	322	34	
Fasting glucose level (mg/dL)†	78.9 ± 15.02	72.7 ± 14.1	.1
1-hour postchallenge glucose level (mg/dL)†	141.5 ± 29.9	163.0 ± 36.7	<.006
2-hour postchallenge glucose level (mg/dL)†	107.8 ± 22.9	108.2 ± 17.4	.9

Newborn infants with <37 weeks of gestation were excluded.

*Defined as a glucose level <30 mg/dL

†Data are expressed as mean ± SD.

Methods

Study population and treatment of neonatal hypoglycemia. The study population consisted of all consecutive LGA infants who were born at the Department of Obstetrics of Vivantes Medical Center, during the 5-year period between 1994 and 1998. Current German birth weight percentiles were used to define LGA neonates (birth weight, >90th percentile).⁹ LGA newborns were identified in retrospect on the basis of a permanent institutional database that contains mandatory records of each delivery. Infants with major congenital anomalies were excluded.

A standardized protocol required early (within the first 60 minutes of life) oral feeding with colostrum or a 5% glucose solution in all LGA newborns. The first postnatal glucose testing was performed 30 to 60 minutes after the first feeding. Subsequent measurements of neonatal glucose were performed before feeding every 4 to 6 hours within the first 24 hours of life. Whenever blood glucose levels dropped to ≤40 mg/dL, a trial of oral feeding with a 12.5% glucose solution was undertaken. Testing of neonatal glucose was performed in capillary blood that was obtained by heel stick with a reflectance meter (Roche Diagnostics, Mannheim, Germany). Glucose values of ≤40 mg/dL were confirmed in laboratory measurements by the glucose oxidase method (Beckman Glucose Analyzer II, Beckman Instruments, Brea, Calif).

Management of gestational diabetes mellitus testing. Reflecting obstetric standards in Germany, testing for gestational diabetes mellitus (GDM) in the mothers of our study subjects was performed selectively by their community physicians on the basis of risk factors for GDM. The diagnosis of GDM was established by a 75-g oral glucose tolerance test (oGTT) with capillary blood glucose levels

measured by the glucose oxidase method. Diagnostic criteria for GDM that were used during the study period were adapted from the criteria of O'Sullivan and Mahan,¹⁰ which were originally based on a 100-g glucose load (fasting level, ≥90 mg/dL; 1-hour level, ≥165 mg/dL, 2-hour level, ≥145 mg/dL). Diagnosis of GDM required at least two abnormal values.

Data collection. Maternal and neonatal parameters were derived retrospectively from hospital charts (Tables I and II). The impact of asymmetric growth was investigated by the calculation of the ratio of birth weight/length and the neonatal body mass index. Then newborn infants were classified as to whether their data were below or above the 90th percentile, according to published German reference data.⁹

Major outcome variables were hypoglycemia (defined as a blood glucose concentration of ≤30 mg/dL)¹¹ and the hour of life when hypoglycemia was first diagnosed.

Statistical analysis. The first documented hypoglycemia was defined as an event in Kaplan-Meier analysis. At each hour of life, the fraction of infants who remained at risk of hypoglycemia decreased by the number of newly diagnosed cases at this time point.

Differences between groups with and without neonatal hypoglycemia were tested for statistical significance by analysis of variance (continuous variables) or χ^2 test (categorical variables). For the determination of a threshold for an increased rate of hypoglycemia, the cohort was divided according to the 1-hour glucose value of the oGTT (20-40 mg/dL grouping). Visual inspection was used to detect glucose concentrations above which the rate of hypoglycemia appeared to increase. Steps of significant increase were confirmed by χ^2 test. All calculations were performed by the statistics program Statview 4.5 (Abacus Concepts, Berkeley, Calif).

Table II. Newborn characteristics of LGA newborn infants with and without hypoglycemia*

	Neonatal hypoglycemia		P value
	No (n = 745)	Yes (n = 142)	
Gestational age at delivery (wk)†	39.5 ± 1.2	39.2 ± 1.3	.01
Cesarean delivery (%)	11.2	14.7	.2
Apgar score of <7 at 5 min (%)	1.0	1.4	.1
Umbilical artery pH†	7.2 ± 0.2	7.2 ± 0.1	.8
Neonatal anthropometry			
Birth weight ≥95th percentile (%)	50.8	55.9	.2
Birth weight/length ≥90th percentile (%)	96.6	95.0	.8
Body mass index ≥90th percentile (%)	79.9	75.7	.2
Birth injury % (No.)	26 (3.5%)	4 (2.9%)	.1
Transfer to neonatal care unit % (No.)	50 (6.7%)	24 (16.9%)	<.0001

Newborns of <37 weeks of gestation were excluded.

*Defined as a glucose level ≤30 mg/dL.

†Continuous data are expressed as mean ± SD.

Results

A total of 16,908 infants were born during the study period; 1210 infants (7.1%) were found to be LGA. Seventy-four infants were excluded because of prematurity, 180 infants were excluded because of known GDM or preexisting diabetes mellitus of the mothers, and 69 infants were excluded because of a missing measurement of neonatal glucose. Maternal and neonatal characteristics of infants who were excluded because of missing glucose measurements did not differ significantly from those of the infants included in the analysis (data not shown).

In the remaining 887 infants, neonatal hypoglycemia (≤30 mg/dL) occurred in 142 of the infants (16.0%) during the first 24 hours of life. Of these, 9 infants had blood glucose concentrations of ≤15 mg/dL. The rate of hypoglycemia was 5.9% in infants of mothers with normal oGTT glucose levels, 12.2% in infants of mothers with 1 elevated value, and 17.7% in infants of mothers without antenatal glucose testing.

The Kaplan-Meier plot (Fig 1) showed a steep decrease of the fraction of infants who remained at risk for hypoglycemia after 1 hour of life, which indicated that most cases were diagnosed within the first hour of life. Thus, the incidence of hypoglycemia at 1 hour was 9.3% (94/887 infants). Between 2 to 5 hours, a moderate stepwise decrease of infants at risk was observed, with an incidence of 3.5% newly diagnosed cases (n = 28 infants) of hypoglycemia during this period. In contrast, the number of infants who remained at risk stabilized after 5 hours; hypoglycemia was newly diagnosed in 2.4% of the infants (n = 20) between 5 and 24 hours.

Characteristics of mothers of newborn infants without and with neonatal hypoglycemia are displayed in Table I. In the subgroup of 358 women in whom the antenatal oGTT was performed, the 1-hour postchallenge glucose value was significantly higher in women with hypoglycemic infants compared to women with normoglycemic in-

fants (163.0 ± 36.7 mg/dL vs 141.5 ± 29.9 mg/dL, $P < .0006$).

Newborn infants with hypoglycemia were born with a slightly but statistically significant lower gestational age compared with normoglycemic infants (39.2 ± 1.3 weeks vs 39.5 ± 1.2 weeks, $P = .01$, Table II). None of the other delivery parameters or any neonatal indices of anthropometry showed a significant difference between the two groups.

Thus, gestational age at delivery and the 1-hour glucose value of the oGTT were found to be the only predictors for neonatal hypoglycemia. For the determination of a threshold of the gestational age at delivery for an increased risk of hypoglycemia, we calculated the rate of hypoglycemia in subgroups of infants who were categorized by completed gestational weeks. No threshold was identifiable. Similarly, we investigated whether there was a threshold for the 1-hour glucose concentration of the maternal oGTT and divided the cohort according to the 1-hour glucose values. Strata of 20-mg/dL intervals were used for glucose ranges with large numbers of subjects, and strata of 40-mg/dL intervals for glucose ranges with small numbers of subjects (<10 infants). Visual inspection revealed increments in the rate of hypoglycemia at glucose levels of 120, 180, and 240 mg/dL (Fig 2). A χ^2 analysis confirmed statistically significant increases of the rate of hypoglycemia at these three cutoff points. There were only two cases of hypoglycemia with maternal glucose values of <120 mg/dL, which resulted in a rate of 2.5% (2/80 cases). The rate was 9.3% (22/236 cases) for glucose values of ≥120 and ≤179 mg/dL ($P = .02$, compared with <120 mg/dL) and increased further to 22% (8/36 cases) for values of ≥180 and ≤239 mg/dL ($P < .001$, compared with ≥120 and ≤179 mg/dL). If the maternal glucose value exceeded 240 mg/dL, neonatal hypoglycemia was diagnosed in 50% of the infants (2/4 infants).

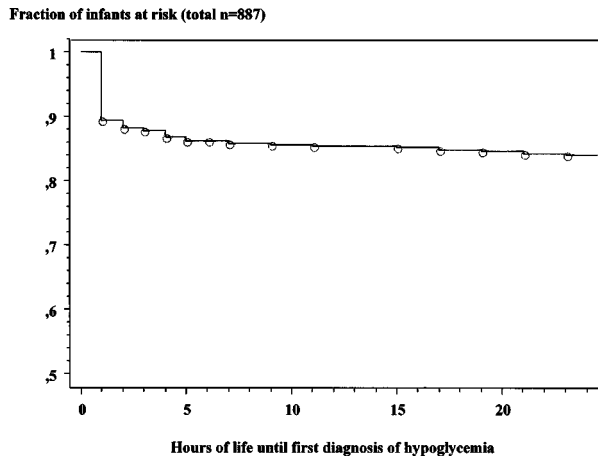


Fig 1. Kaplan-Meier analysis displays the fraction of infants that remain at risk for severe neonatal hypoglycemia plotted against the age when neonatal hypoglycemia was diagnosed first. Within the first hour of life, 9.3% were diagnosed; 3.5% were diagnosed during the next 4 hours, and 2.4% were diagnosed in the remaining 19 hours.

Comment

To our knowledge, this is the largest published study that specifically investigated the incidence and risk factors of hypoglycemia in LGA newborn infants from nondiabetic mothers. Our study has three major findings. First, hypoglycemia occurred in 16% of these infants. Second, most infants were diagnosed within the first 5 hours of life. Third, the 1-hour postchallenge glucose value of the maternal oGTT was found to be the only useful predictor for neonatal hypoglycemia. A single abnormal oGTT value already conferred a substantially increased risk for hypoglycemia to the newborn infant.

LGA infants whose mothers do not have diabetes mellitus have been claimed to be at risk for transient hypoglycemia,⁷ despite the lack of studies that support this assumption. The present investigation demonstrates that substantial numbers of infants of nondiabetic mothers experience hypoglycemic episodes. Thus, routine testing of these infants is indicated clearly.

The hypoglycemia rate in this study was twice as high as that of a previous report in a smaller population of LGA infants, although the authors of that study had used a blood glucose concentration of <35 or 40 mg/dL to define hypoglycemia, depending on the hour of life.⁸

The importance of the antenatal oGTT was supported by our failure to identify any other clinically useful predictor for hypoglycemia in infants of nondiabetic mothers. Moreover, there was a stepwise increase of neonatal hypoglycemia rates with increasing maternal glucose levels. With a 1-hour oGTT glucose value of <120 mg/dL, there was a minimal risk of hypoglycemia. Only 2 of 80 infants had asymptomatic hypoglycemia within the first hour of life, which resolved after feeding. Thus, neonatal

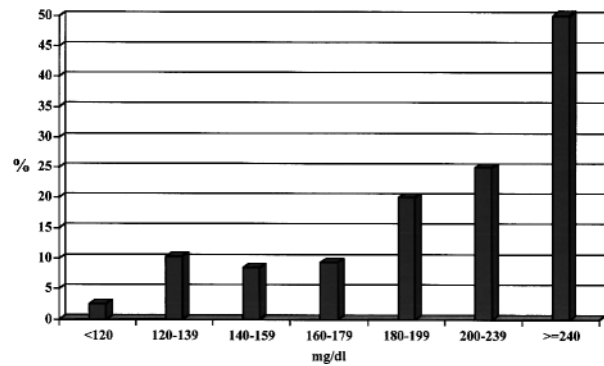


Fig 2. Rate of severe hypoglycemia within the first 24 hours of life according to the 1-hour postchallenge glucose value of the maternal antenatal oGTT. There was a significant stepwise increase in the rate of hypoglycemia at 120, 180, and 240 mg/dL.

glucose testing beyond the first hour of life may not be warranted in LGA infants whose mothers have 1-hour oGTT values of <120 mg/dL. In contrast, when the maternal glucose value exceeded a threshold level of 180 mg/dL, hypoglycemia occurred in 25% of the infants. Interestingly, the glucose level of 180 mg/dL corresponds to the threshold for an abnormal 1-hour glucose value of the oGTT, according to the Carpenter and Coustan¹² criteria, which have recently been adopted by the American Diabetes Association.¹³ In Germany, as in most European countries, the oGTT in pregnancy is traditionally performed with a 75-g glucose load. There are no studies so far that compare 75-g and 100-g oGTT, and the Fourth Workshop Conference on GDM (1997) recommended the use of the Carpenter and Coustan criteria for both the 100-g and the 75-g oGTT.¹⁴ However, we cannot exclude the possibility that the threshold that was identified in this study indicating an increased risk for neonatal hypoglycemia might have been slightly higher when a 100-g oGTT was applied.

Because the diagnosis of GDM requires two abnormal values, mothers with 1-hour oGTT glucose concentrations of ≥ 180 mg/dL, but normal fasting or 2-hour concentrations, did not receive diet education and glucose control that were applied to women with GDM. This investigation adds to the increasing body of evidence that demonstrated that mild glucose intolerance below the threshold that defines GDM is already associated with substantially increased neonatal and maternal morbidity rates.¹⁵⁻¹⁷

Central obesity has been reported to be a hallmark of diabetes mellitus-associated neonatal macrosomia because of an increase of the insulin-sensitive tissue caused by fetal hyperinsulinism.¹⁸ Therefore, we tested several different growth indicators that consider asymmetric or excessive growth for their ability to predict hypoglycemia. Disappointingly, none of the anthropometric

neonatal parameters was found to be useful for hypoglycemia risk assessment. The poor accuracy of body length measurements of newborn infant might limit the use of body mass index and birth weight/ length ratios.

In conclusion, routine glucose testing is indicated in LGA newborn infants of nondiabetic mothers. The 1-hour postchallenge oGTT glucose concentration appears to be the only clinical predictor that is apt to discriminate between LGA neonates at low, intermediate, and high risk for hypoglycemia. The frequency of neonatal glucose testing may be adjusted to the infant's individual risk based on maternal antenatal oGTT values. The general availability of oGTT values may help to reduce costs and amount of pain that is inflicted on LGA infants. The hypoglycemia risk of LGA newborns from mothers with an elevated 1-hour glucose concentration, but otherwise normal oGTT values, may exceed that of infants from mothers with treated GDM. Whether the increased risk of hypoglycemia after a single pathologic oGTT glucose concentration that is observed in LGA infants also extends to non-LGA infants remains to be investigated.

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