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Large-for-gestational-age newborns in women with insulin-treated gestational diabetes under strict metabolic control

Heinz Leipold[1], **Christof Worda**[1], **Christian J. Gruber**[2], **Alexandra Kautzky-Willer**[3], **Peter W. Husslein**[1], and **Dagmar Bancher-Todesca**[1]

[1] Department of Obstetrics and Gynecology, University of Vienna Medical School, Vienna, Austria
[2] Division of Gynecological Endocrinology and Reproductive Medicine, University of Vienna Medical School, Vienna, Austria
[3] Division of Endocrinology and Metabolism, Internal Medicine III, University of Vienna Medical School, Vienna, Austria

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Makrosomierate bei Frauen mit gut eingestelltem Gestationsdiabetes

Zusammenfassung. *Zielsetzung:* In dieser Studie wird der Einfluss einer strikten Blutzuckereinstellung bei Patientinnen mit insulinpflichtigen Gestationsdiabetes (GDM) auf das Auftreten von makrosomen Neugeborenen und geburtshilflichen Komplikationen untersucht.

Methode: In Rahmen dieser prospektiven Kohortenstudie wurden 875 schwangere Frauen mittels eines 75 g oralen Glukosetoleranztestes (OGTT) untersucht. Der OGTT wurde zwischen der 24. und 28. Schwangerschaftswoche durchgeführt. Die Studiengruppe (n = 162) bestand aus Frauen mit insulinpflichtigen GDM und die Vergleichsgruppe (n = 713) bestand aus Schwangeren mit physiologischem OGTT (NGT). Bei Patientinnen mit GDM wurde durch eine strenge Blutzuckereinstellung ein Nüchternblutzucker von 90 mg/dl und ein Postprandialblutzucker (1 Stunde postprandial) von 130 mg/dl angestrebt.

Resultat: Bei Frauen mit GDM und strikter Blutzuckereinstellung kann keine signifikant erhöhte Häufigkeit von makrosomen Neugeborenen beobachtet werden (16,7% vs. 12,3%; p = 0,1). Hauptrisikofaktoren für Makrosomie ist bei Patientinnen mit NGT der müttterliche BMI [27,2 kg/m^2 (5,0) vs. 24,4 kg/m^2 (5,6); p = 0,006], wobei der mütterliche BMI bei Frauen mit GDM keinen Einfluss auf die Häufigkeit von makrosomen Neugeborenen hat. Die Häufigkeit an kindlichen und mütterlichen Geburtskomplikationen, mit Ausnahme der Plexusparese, die in drei Fällen bei GDM Patientinnen und makrosomen Kindern aufgetreten ist, unterscheidet sich in den beiden Gruppen nicht signifikant voneinander.

Schlussfolgerung: Durch eine strikte Stoffwechselkontrolle und Überwachung von Patientinnen mit GDM ist die Anzahl an makrosomen Neugeborenen nicht höher als in der Normalpopulation, ebensowenig wie mütterliche Geburtskomplikationen.

Summary. *Objective:* To assess the influence of strict metabolic control in women with insulin-treated gestational diabetes on the risk of large-for-gestational-age (LGA) newborns, the frequency of obstetrical complications and fetal outcome.

Methods: In this prospective cohort study, 875 women were screened for gestational diabetes mellitus with a 75g oral glucose tolerance test (OGTT) between weeks 24 and 28 of gestation. The study group (n = 162) consisted of women with insulin-treated gestational diabetes mellitus (GDM) and the control group (n = 713) of women with normal glucose tolerance (NGT). In the women with diabetes, strict adjustments of fasting glucose levels to 90 mg/dl and 130 mg/dl postprandially were achieved with insulin administration.

Results: No increased risk for LGA newborns was observed in women with GDM and good metabolic control (16.7% vs. 12.3%; p = 0.1). In women with NGT, maternal prepregnancy BMI was significantly higher in those who delivered LGA newborns than in those who gave birth to newborns below the 90th percentile [27.2 kg/m^2 (5.0) vs. 24.4 kg/m^2 (5.6); p = 0.006], whereas there was no influence of maternal BMI on birth weight of newborns in women with GDM. There was no difference between the two groups with respect to maternal birth traumata and fetal outcome, except for plexus palsy which occurred in three GDM women with macrosomic newborns.

Conclusion: Strict metabolic control and surveillance in women with insulin-treated GDM seems to attenuate the risk for LGA newborns, diabetic fetopathia, and the influence of maternal BMI on fetal growth.

Key words: Macrosomia, gestational diabetes mellitus (GDM), large-for-gestational-age (LGA).

Introduction

Alterations in glucose metabolism during pregnancy influence the birth weight of newborns and relate to fetal

outcome [1, 2]. In pregnant women with glucose intolerance, serum glucose levels are directly correlated with the incidence of fetal macrosomia [3], therefore the strategy to prevent fetal macrosomia is to maintain serum glucose levels within the physiological range during pregnancy [4, 5]. Fetal macrosomia can lead to serious obstetrical complications during delivery and to subsequent health hazards for both mothers and newborns [6]. In this context, perineal laceration, atone uterine bleeding, operative vaginal delivery and secondary cesarean section are all more frequent when the fetus is large [7]. Shoulder dystocia is often referred to as the most severe obstetrical complication and its likelihood is increased in macrosomic newborns of mothers with gestational diabetes mellitus (GDM) [8, 9].

The prognostic value of sonographic measurements of the fetus in order to diagnose LGA prior to delivery is limited [10]. The fetus of a diabetic woman often displays altered morphology, characterized by larger circumference of the shoulders and extremities, decreased head-to-shoulder ratio and greater abdominal circumference; however, these are weak predictors for obstetrical complications when estimated by ultrasound [11]. In this study we analyzed the frequency of LGA newborns in women with normal glucose tolerance (NGT) and in women with insulin-treated GDM. We attempted to determine (1) if women with GDM under strict metabolic control have a higher risk for LGA newborns than women with NGT, (2) the influence of maternal body-mass index (BMI) on the LGA rate of newborns, and (3) the frequency of obstetrical complications and the fetal outcome in both groups.

Patients, materials and methods

This study was conducted at the Department of Obstetrics and Gynecology of the University of Vienna Medical School, which is a tertiary care center serving high-risk pregnancies with risk factors for different pregnancy complications in cooperation with the Department of Endocrinology and Metabolism. We treat a disproportionately high rate of women with GDM in our hospital. Only women fulfilling the following criteria were included in the study: (1) normal ultrasound screening in week 21 of gestation, (2) no maternal chronic or infectious diseases, (3) no multiple pregnancy, and (4) no pre-existing diabetes mellitus. An oral glucose tolerance test (OGTT) was conducted in all women between weeks 24 and 28 of gestation. All women gave informed consent prior participating in the study. After an 8-hour period of fasting, a standardized 75 g glucose solution (Glucodrink®, Unipack, Wiener Neustadt, Austria) was ingested orally. Venous blood samples were drawn before glucose ingestion, and at one and two hours afterwards. $HbA1_c$ was measured on the same day. A precise medical and obstetrical history was obtained before the test and was entered into a computerized database. BMI was calculated from the pregravid weight and measured height. The guidelines of the German Society for Diabetes (DDG) were followed in evaluation of the OGTT. The upper normal limit was set at 95 mg/dl for fasting serum glucose, at 180 mg/dl one hour after glucose ingestion and at 155 mg/dl after two hours. If one or more values were exceeded, the woman was admitted to the gestational diabetes program [12], beginning with dietary instruction. After the instructions, these women were asked to measure their capillary blood glucose levels at home before and one hour after meals daily for a week. Upper limits of 90 mg/dl fasting glucose level and 130 mg/dl after meals were considered tolerable [13]. If a patient had five excess values per week in blood-glucose self-assessment, insulin therapy was started. Women with GDM who were on nutrition therapy only and women who did not deliver at our hospital were excluded from the final analysis. Every insulin-requiring patient with acceptable metabolic function and normal fetal biometric data was examined bi-weekly, and if necessary at weekly intervals. Acceptable metabolic function was defined as fewer than five excess values per week in blood-glucose self-assessment (capillary blood glucose concentrations were measured daily at home, before breakfast then one hour after breakfast, lunch and dinner). The study group consisted of women with insulin-treated GDM and the control group of women with NGT.

In women on insulin therapy, labor was induced at the estimated date of delivery, unless labor occurred spontaneously. Both vaginal deliveries and primary or secondary cesarean sections were included. All newborns were examined by neonatologists following the guidelines of the Austrian neonatal care system. We define large-for-gestational-age (LGA) as newborns whose birth weight is greater than the 90^{th} percentile for appropriate gestational age and sex. All maternal and fetal data at birth were collected and entered into a computerized database and an intention-to-treat analysis was used.

Table 1. Patient characteristics and differences between healthy women (control group) and women with gestational diabetes (GDM)

	Control group	GDM	p*
Number of patients	713	162	
Age (years)	30.1 (5.5)	32.9 (5.2)	< 0.001
Prepregnancy BMI (kg/m^2)	24.3 (5.2)	26.9 (6.2)	< 0.001
Partus	1.0 (1.0)	1.4 (1.3)	< 0.001
Abortus	0.3 (0.6)	0.6 (1.2)	< 0.001
Gestational age_OGTT (weeks)	26.0 (2.9)	25.8 (7.2)	0.63
Fasting value_OGTT (mg/dl)	76.5 (7.6)	96.1 (17.1)	< 0.001
One-hour value_OGTT (mg/dl)	126 (26.3)	186.7 (35.5)	< 0.001
Two-hour value_OGTT (mg/dl)	97.9 (21.4)	141.5 (34.4)	< 0.001
HbA1c (at the time of OGTT)	4.9 (0.4)	5.4 (0.8)	< 0.001
Gestational age at delivery	39.0 (1.7)	38.1 (2.2)	< 0.001
Birth weight (g)	3417 (512)	3276 (618)	0.02

Values are given as mean (SD). *GDM* gestational diabetes mellitus; *BMI* body mass index; *OGTT* oral glucose tolerance test; * t-test.

Table 2. Fetal outcome and birth complications in women with normal OGTT (Control group) and women with GDM

	Control group	GDM	p*
Number of patients	713	162	
LGA newborns	88 (12.3%)	27 (16.7%)	0.14
Brachial plexus palsy	0	3 (1.8%)	< 0.01
Perineal laceration	228 (32%)	41 (25.3%)	0.10
Cesarean section	178 (25%)	51 (31.5%)	0.09
Transferal to neonatal intensive care	43 (6%)	12 (7.4%)	0.51
Fetal death	0	0	

OGTT oral glucose tolerance test; *GDM* gestational diabetes mellitus; *LGA* large for gestational age; * chi-squared test.

Statistical data were evaluated using SPSS 10.0 (SPSS Inc., Chicago, IL.). Our calculation has a power of 0.86 to show a difference in LGA proportions of 10% with alpha equal to 0.05. The Kolmogorov-Smirnov test was used to verify tests for normal distributed variables. Values are given as mean plus standard deviation (SD). Binominal logistic regression analysis, t-test and the chi-squared test were used accordingly. All tests were two-tailed and a statistical value of $p < 0.05$ was considered significant.

Results

Complete data sets of 875 women were available and included in the study: 713 women (81.5%) showed a normal OGTT and 162 women (18.5%) were diagnosed as having GDM. The high rate of women with GDM may be because our clinic is a tertiary care center. In women with GDM, insulin therapy was started at week 28 of gestation (± 3 weeks) and was continued until delivery. As expected, women with GDM had significantly elevated serum glucose levels in the OGTT, elevated levels of $HbA1_c$, a higher BMI and were significantly older than controls (Table 1). There were comparable rates of infant macrosomia in the two groups, but newborns of mothers with diabetes were more likely to have shoulder dystocia resulting in pareses of the brachial plexus (3 vs. 0). All newborns with pareses of the brachial plexus had a birth weight of more than 4250 g. There were no significant differences between the two groups with respect to perineal laceration and the rate of transferal of the neonate to the intensive care unit (Table 2). In total (women with GDM and NGT), 13.1% of the newborns were classified as LGA. There was a 4.3% difference in numbers of LGA babies between women with NGT and women with well treated GDM (95% confidence interval: –1.9%; 10.6%), not reaching statistical significance (Table 2). When newborns in the control group surpassed the 90th percentile of birth weight, their mothers had significantly higher BMI than women who gave birth to newborns below the 90th percentile; however, there was no significant difference in the glucose levels in OGTT or in HbA1c (Table 3). In contrast, the women with diabetes who gave birth to LGA newborns had significantly higher fasting glucose levels in the OGTT than women with newborns below the 90th percentile of birth weight. There were no significant differences in the one- and two-hour values of the OGTT or, notably, in the prepregnancy maternal BMI (Table 4).

In order to assess the compound influence on LGA of maternal age, parity, gestational week of delivery, fasting, one- and two-hour glucose concentration of the OGTT, HbA1c and BMI, we used binominal logistic regression analysis with backstep selection for women with GDM and NGT separately. In women with GDM, none of the parameters influenced LGA; whereas in women with NGT, BMI was significantly associated with LGA ($r = 0.009$, $p = 0.02$).

Discussion

In our study, women with GDM under strict metabolic control did not bear a higher risk for LGA newborns. A wide range of risk factors for LGA newborns is given in previous literature, and maternal BMI is often cited as being the most important factor [14, 15]. Further studies are thus warranted to clarify the exact relationship between maternal BMI and risk of obstetrical complications in women with NGT [16]. Maternal BMI is known to constitute a major risk factor for the development of GDM [17, 18].

In agreement with previous observations, women with GDM in our study had higher BMIs than healthy pregnant women [19, 20]. Limited information is currently available about the benefit of insulin treatment with respect to fetal outcome, but nutrition therapy alone does not seem to be associated with improved outcome [21]. We demonstrated that proper adjustment of glucose levels in women with GDM seems to attenuate the increased risk of LGA newborns and plays an even more important role

Table 3. Comparison of LGA (≥ 90th Percentile) vs. non LGA (< 90th Percentile) newborns from mothers with normal OGTT (control group)

	≥ 90th Percentile		< 90th Percentile		p*
Number of patients	88	(12.4%)	625	(87.6%)	
Prepregnancy BMI	27.2	(5.0)	24.4	(5.6)	< 0.01
Fasting value_OGTT (mg/dl)	78	(7.8)	76.2	(7.5)	0.19
One-hour value_OGTT (mg/dl)	128	(29.5)	126.3	(25.7)	0.73
Two-hour value_OGTT (mg/dl)	100.1	(25.6)	98.2	(20.2)	0.6
HbA1c	5.0	(0.5)	4.9	(0.5)	0.42

Values are given as mean (SD). *GDM* gestational diabetes mellitus; *BMI* body mass index; *OGTT* oral glucose tolerance test; *LGA* large for gestational age; * t-test.

Table 4. Comparison of LGA (≥ 90th Percentile) vs. non LGA (< 90th Percentile) newborns from mothers with GDM

	≥ 90th Percentile		< 90th Percentile		p*
Number of patients	27	(16.7%)	135	(83.3%)	
Prepregnancy BMI	29.1	(6.2)	26.8	(6.5)	0.13
Fasting value_OGTT (mg/dl)	107.4	(27.0)	92.6	(12.6)	0.02
One-hour value_OGTT (mg/dl)	191.6	(28.4)	182.6	(32.8)	0.26
Two-hour value_OGTT (mg/dl)	138.5	(30.2)	136.4	(32.5)	0.8
HbA1c	5.6	(0.7)	5.3	(0.8)	0.3

Values are given as mean (SD). *GDM* gestational diabetes mellitus; *LGA* large-for-gestational-age; *OGTT* oral glucose tolerance test; * t-test.

than the degree of obesity. Other parameters, such as maternal age, parity, gestational week of delivery, fasting, HbA1c and one- or two-hour glucose concentration in the OGTT, did not influence LGA. We believe that in women with well treated GDM and weight control starting from diagnosis at the late second/early third trimester until delivery, maternal BMI per se does not constitute an additional independent risk factor for LGA newborns. Nevertheless, our study does not rule out the possibility that there might be no difference in the prevalence of LGA per se, although this seems unlikely. The only way to exclude such possibility would be to deny treatment in women with GDM. Therefore, for ethical reasons, this might be a limitation of our study, in that we could not investigate untreated hyperglycemic women to demonstrate the influence of maternal hyperglycemia on fetal growth. On the other hand, we could study differences in the rates of LGA newborns in women with NGT or GDM on insulin treatment and strict metabolic control. Of note, we confirmed that women with GDM on insulin therapy indeed had a comparable rate of LGA newborns, the hallmark of GDM. Nevertheless, in a future study it might be of interest to compare different treatment regimes in relation to fetal outcome and LGA rate.

Schaefer et al. found that in women with GDM maternal obesity appeared to be a strong risk factor for macrosomia [14]. We observed such association only in women with NGT, whose BMI continued to exert significant influence on fetal weight. It should be noted that a small decrease of < 10% difference in LGA proportions due to glucose intolerance might be masked in our series because of the sample size.

We measured $HbA1_c$ levels at the time of the OGTT (weeks 24 to 28 of gestation) and found significantly higher levels in the women with diabetes. However, $HbA1_c$ was not related to the birth weight of newborns in women with GDM or in women with NGT. A likely explanation is the assumption that women diagnosed with GDM at the end of the second trimester received therapy which prevented excessive weight gain of the fetus and masked any potential impact of the degree of hyperglycemia at time of diagnosis. However, Rust et al. did not find an association between the degree of hyperglycemia and macrosomia [22].

If women with GDM manage to maintain their glucose levels within the normal range during pregnancy, there appears to be no increased risk of maternal birth traumata compared with controls. Notably, we observed three cases of shoulder dystocia resulting in pareses of the brachial plexus in the GDM group, and all three occurred in diabetic women with newborn weights exceeding the 90th percentile. These three newborns had birth weights of more than 4250 g. The most likely explanation is that the risk of shoulder dystocia with consecutive pareses of the brachial plexus is significantly higher in newborns whose macrosomia is caused by maternal GDM than in macrosomia of different origin. This might be due to increased abdominal circumference in a fetus with diabetic fetopathia, as shown in other studies [23].

In conclusion, according to our data, maternal BMI constitutes an important risk factor for GDM but does not have significant influence on neonatal birth weight if glucose levels in women with GDM are kept within or close to the normal glycemic range. When compared with women with NGT, women with GDM on insulin therapy under strict metabolic control do not carry an excess risk for LGA newborns.

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Correspondence: Dr. Christof Worda, Department of Obstetrics and Gynecology, University of Vienna Medical School, Währinger Gürtel 18–20, 1090 Vienna, Austria,
E-mail: christof.worda@meduniwien.ac.at