

**ASSOCIATION BETWEEN FOETAL GROWTH AND DIFFERENT
MATERNAL METABOLIC CHARACTERISTICS IN WOMEN
WITH GESTATIONAL *DIABETES MELLITUS***

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Abstract: *Objective:* The aim of the study was to investigate the association between foetal growth and different maternal metabolic characteristics in women with gestational *diabetes mellitus* (GDM).

Methods: The study group included 200 consecutive pregnant women who attended the Endocrinology, Diabetes and Metabolic Disorders Outpatient Department in the period from 02.2006 to 02.2009 with singleton pregnancy and GDM diagnosed following ADA criteria. The following parameters were studied: pre-pregnancy maternal body mass index (BMI), 3-hours 100g oral glucose tolerance test (OGTT) results, glycosylated haemoglobin (HbA1c), total lipids (TL), total cholesterol (TH), triglycerides (TG), HDL- and LDL-cholesterol levels at admission. Neonatal birth weight and the prevalence of being large for gestational age (LGA) was an end-point.

Results: We found a significant association between birth weight and pre-pregnancy BMI, HDL-C and birth weight of a large child born previously. Birth weight of a large child born previously was the strongest independent predictor for LGA. The prevalence of LGA (from 27% to 80%) was related to a number of altered maternal characteristics.

Conclusion: Pre-pregnancy BMI, HDL-C and birth weight of a large child born previously are the independent predictors for LGA, but results of glucose levels during OGTT are not useful in the prediction of LGA in GDM pregnancies. Probably more

factors and other maternal metabolic parameters than glucose levels during OGTT are responsible for the risk of LGA.

Key words: gestational diabetes, LGA, macrosomia, maternal characteristics, OGTT.

Introduction

Foetal growth is affected by genetic, demographic and metabolic factors of the mother [1]. In particular, disturbances of maternal glucose metabolism are known to favour foetal overgrowth and macrosomia, a major complication of GDM [2, 3].

GDM is defined as a carbohydrate intolerance that begins or is first diagnosed during pregnancy [4]. GDM, also known as glucose intolerance of pregnancy, affects about 100,000 women every year. Pregnancies complicated with GDM are at increased risk of neonatal mortality and morbidity, mainly as a result of foetal macrosomia as well as operative and instrumental deliveries, birth trauma and metabolic abnormalities in the newborn [5, 6].

The major reason for poor perinatal outcome is foetal macrosomia (defined as large for gestational age, with a birth weight above the 90th percentile; LGA). Foetal overgrowth induced by foetal hyperinsulinaemia can develop as a response to increased placental glucose transfer to the foetus which is secondary to maternal hyperglycaemia [7]. Therefore, normalization of foetal growth is a principle in the management of pregnancies with diabetes.

In recent decades, significant improvements in perinatal care, diagnosis and treatment of GDM complicated pregnancies have been made. Despite this, macrosomia still remains a serious problem, which may complicate up to 30% of diabetic pregnancies [1, 8]. Interestingly, a certain percentage of newborns with macrosomia remains high even in women with proper carbohydrate controls, measured using commonly available parameters (fasting and 2-hrs postprandial glycemia, HbA1c concentration) [9]. Therefore, further studies are necessary to investigate other factors contributing to foetal overgrowth in diabetic pregnancy [7].

There is no doubt from the literature that maternal glycaemia in women with GDM is involved in determining birth weight, but whether there is any influence of maternal glycaemia during OGTT on foetal macrosomia is unknown [10]. In recent studies foetal growth and development is considered a complex process where maternal characteristics, foetal potential and the intrauterine environment play an important role [9]. The list of factors influencing foetal growth both in normal and in diabetic pregnancy is expanding and is still far from being complete. Results of different studies are often conflicting and new areas for research are emerging [11]. Recently, a great deal of data has accumulated on lipid metabolism in normal and diabetic pregnancies, maternal

obesity and gestational insulin resistance; however, data concerning their impact on foetal growth are limited [12–15]. Pregnancy is commonly described as a condition characterized by a rapid increase in all lipids; however, evidence concerning the relationship between lipid metabolism and hormonal changes during foetal gestation is conflicting [16].

In our study we aim to investigate different maternal metabolic characteristics and their compounding influence on foetal growth and the incidence of LGA in pregnant women with GDM.

Material and methods

The study was conducted from 02.2006 to 02.2009, at the Endocrinology, Diabetes and Metabolic Disorders Outpatient Department in Skopje, R. Macedonia. Two hundred consecutive pregnant women in whom gestational diabetes was diagnosed were included in this study. According to the guidelines of the ADA [17] we used the 2 steps system. A glucose challenge test (GCT) was performed between the 24th and 28th weeks of gestation in high and middle risk groups of pregnant patients. In GCT, the pregnant women underwent a standard 50-g glucose load and a 1-h plasma glucose concentration was measured. A plasma glucose ≥ 7.8 mmol/l was considered positive according to these recommendations. All women with positive GCT performed a diagnostic 3-h 100-g oral glucose tolerance test (OGTT). After an overnight fast and at least 3 days of unrestricted diet (≥ 150 g carbohydrate per day) and unlimited physical activity, blood was taken to determinate plasma glucose levels. According to Carpenter and Coustan's criteria [18] the cut-off values were the following: fasting glycaemia: 5.3 mmol/l, 1 h: 10.0 mmol/l, 2 h: 8.6 mmol/l, 3 h: 7.8 mmol/l. Two or more of the cut-off values must be met or exceeded for a diagnosis of GDM. Capillary blood glucose levels were measured by glucose oxidase (Glucose Analyzer; Beckman, Brea, CA).

Further inclusion criteria were: singleton pregnancy, live birth and no foetal malformation suspected during gestation or detected postpartum. All patients gave informed consent to participate in the study.

In our research, we investigated the following parameters: the patient's age, pre-pregnancy body mass index (BMI), gestational age when GDM was diagnosed, glycaemia levels of 100g OGTT (fasting, 2-h and 3-h post-load glycaemia), TL, TH, HDL-C, LDL-C, TG, HbA1c concentration and arterial blood pressure at booking. We also recorded the birth weight of the largest child born in a previous pregnancy (if applicable). Birth weight and the proportion of LGA (defined as a birth weight of > 90 th percentile for local population after adjusting for gestational age and sex) were studied at the end-point.

Blood samples for HbA1c and lipid assessment were taken after overnight fasting. The blood samples for lipoproteins were analyzed using Cobas Integra 700, according to standard methods. TH and triglycerides were determined by full enzymatic methods (TH-CHOD-POD-PAP and triglycerides-GPO; Cobas Integra 700, Hoffmann-La Roche, Basel, Switzerland). HDL-C was measured by the polyanion precipitation method, while LDL-C was calculated using the Friedewald formula. LDL-C were fractionated using ultracentrifugation in cases of triglycerides exceeding 4mmol/l. HbA1c was measured by an ion-exchange HPLC instrument (DS5; Drew, USA) with a reference range of 4.2–6%. Blood pressure was measured twice in a supine position. In a case of hypertension (> 145/90 mmHg) the measurement was repeated after five minutes. The patients were weighed wearing clothes without shoes in the morning of the first visit with an electronic scale. Height was measured to the nearest 1 cm with a stadiometer.

For the purposes of this study, we initially investigated bivariate correlations between the maternal parameters and birth weight, while features that correlated significantly with a birth weight were chosen for further calculations. We analysed the distribution of the following covariates: fasting, 2-h and 3-h post-load glycaemia in 100g OGTT, HbA1c level, pre-pregnancy BMI, TL, TH, LDL-C, HDL-C, TG concentration and birth weight of the largest child born in a previous pregnancy. Then, we defined values above the 75th percentile as altered, except for HDL, which was described as altered if below the 25th percentile. As a next step, we retrospectively divided the study group into three subgroups according to the number of altered parameters found in each participant: from 0 if all of the following: BMI, HDL-C concentration and birth weight of the largest child born in a previous pregnancy were within interquartile range (i.e. between 25th and 75th percentile) to 3 if all of them were altered. Then the birth weight and prevalence of LGA were studied across the subgroups.

Statistical analysis

Statistical analysis was performed using the Statistics for Windows programme, version 5, 0. Associations between birth weight and maternal metabolic parameters were analysed using Spearman rank correlation coefficients. Linear regression analysis was performed to find independent predictors for birth weight in the study group. The significance of the differences between study groups was tested using the Kruskal-Wallis test. Differences in categorical variables were tested using a chi-square statistic. $P < 0.05$ was considered statistically significant.

Results

Basic characteristics of the patients enrolled in the study are given in Table 1. Hypertension was diagnosed in 7% of individuals.

Table 1 – Табела 1

Characteristics of study group
Карактеристике на испитиванујућа група

Number of patients studied	N = 200
Age (years)	31 (18–47)
Proportion of individuals > 30 years	55%
Pre-pregnancy BMI (kg/m ²)	26.64 (17–46)
Gestational age at diagnosis (week of gestation)	28 (6–40)
Fasting glycaemia in 100g OGTT (mmol/l)	5.8 (4.2–11.7)
2h post-load glycaemia in 100g OGTT (mmol/l)	9.4 (4.3–17.6)
3h post-load glycaemia in 100g OGTT (mmol/l)	6.7 (3–13.5)
HbA1c at booking (%)	5.7 (3.8–11)
Proportion of patients with Hb1c at booking 6.0%	36.17
Gestational age at delivery (week of gestation)	39 (30–42)
Birth weight (g)	3500 (1450–5410)
Proportion of LGA (%)	31.5
insulin/ diet treated GDM	51/200
Hypertensive/ normotensive individuals	14/200

Data given as median (minimum-maximum value)

Податоците се прикажани како медијана (минимална-максимална вредност)

We found a positive significant correlation between birth weight and pre-pregnancy BMI ($r = 0.18$, $p = 0.01$), birth weight of the largest child born before ($r = 0.32$, $p = 0.02$) and HDL-C ($r = -0.22$, $p = 0.001$) at booking. No correlation was found for maternal age, gestational age when GDM was diagnosed, HbA1c, TL, TG, TH, LDL-C, fasting, 2-h or 3h post-load glycaemia in 100g OGTT.

To determine independent predictors of birth weight in our study group, we used linear multiple regression analysis with birth weight as a dependent variable and maternal characteristics as independent variables. Results of the regression analysis are given in Table 2.

Table 2 – Табела 2

Independent predictors of birth weight in study group
Независни предиктори на родилната тежина во испитуваната група

Covariates	R ²	p
Pre-pregnancy BMI	0.062	< 0.001
Birth weight-largest child born before	0.081	< 0.01
HDL-C	0.06	< 0.05

Univariate analysis demonstrated that birth weight of the largest child born before was the strongest independent predictor of a birth weight in our study group, accounting for around 8% of the variation. Pre-pregnancy BMI and HDL-C alone predicted 6% of the variation in the dependent variable.

We also involved investigation of the combined influence of metabolic alterations and birth weight of the largest child born before on birth weight and the prevalence of macrosomia. Distributions of these parameters are given in Table 3. At the end we analysed birth weight and the proportion of LGA newborns in the subgroup of individuals with different numbers of altered parameters. We used values for particular characteristics given in Table 3 above the 75th percentile and below the 25th percentile for HDL-C. Results are given in Table 4 and Fig.1.

Table 3 – Табела 3

Distribution of metabolic characteristics and birth weight of largest child born previously
Дистрибуција на метаболните карактеристики и родилната тежина на најголемото дете родено претходно

Variables	25 th percentile	75 th percentile
Pre-pregnancy BMI (kg/m ²)	23	30
Birth weight-largest child born before (g)	3200	4000
HDL-C (mmol/l)	1.3	1.8

We found a significant difference in birth weight and the prevalence of LGA when comparing pregnant women with the different numbers of altered characteristics (values within the highest or the lowest quartile). the proportion of macrosomic newborns varied from 27% in individuals with no abnormalities to 80% in patients with 3 characteristics changed.

Table 4 – Табела 4

Birth weight and % of LGA newborns in relation to altered characteristics
Родилна тежина и % од ГТВ новородени во релација со променети карактеристики

Number of altered characteristics	N	Birth weight (g)	% of LGA
0	43	3529 ± 489	27.9%
1	34	3579 ± 941	41.2%
2	14	3809 ± 960	64.3%
3	5	4640 ± 250	80%
p		< 0.01*	< 0.001**

* Kruskal-Wallis test ** Chi2 test

Maternal metabolic characteristics defined as altered: pre-pregnancy BMI above 75th percentile, birth weight of largest child born previously above 75th percentile, HDL-C concentration below 25th percentile.

Променетите метаболни карактеристики на мајката се дефинирани како: БМИ пред бременост над 75-от перцентил, родилна тежина на најголемо дете родено претходно над 75-от перцентил, концентрации на ХДЛ холестерол под 25-от перцентил.

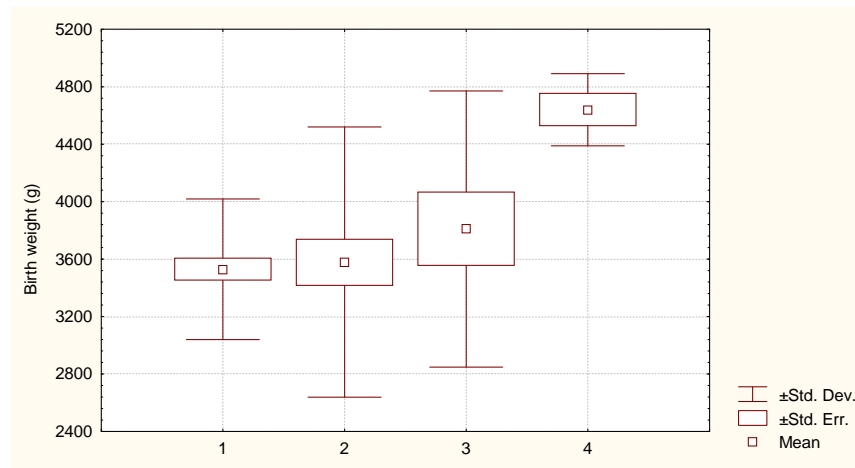


Figure 1 – Birth weight in relation to altered maternal characteristics (p < 0.01)
Слика 1 – Родилна тежина во релација со променети карактеристики кај мајката (p < 0.01)

Discussion

In our study we found a significant association between birth weight and the following variables: pre-pregnancy BMI, HDL-C and birth weight of a

large child born previously. Kitijama *et al.* [19] analysed the maternal hypertriglyceridaemia, maternal fasting plasma glucose, pre-pregnancy BMI and gestational change in maternal body weight, but only hypertriglyceridaemia was a significant risk factor for LGA. The same methodology concerning TG concentrations was also applied by Di Cianni *et al.* [20] who reported a significant association between elevated maternal TG levels, pre-pregnancy BMI, weight gain during pregnancy and 2-hours OGTT glycaemia. Similar, Lin *et al.* [21] found that fasting glucose on the 100-g OGTT correlates closely with birth weight and is an independent risk factor for macrosomia. The latter findings are not supported by our results, we did not find that glycaemia values during 100-g OGTT or TG are associated or predict neonatal birth weight. Some differences in results may be attributed to different ethnic background (Kitijama *et al.* investigated Japanese gravitas). We must note that we analysed only glycaemic values during 100-g OGTT, not fasting or postprandial glycaemic values during pregnancy. Clausen *et al.* [22] did not find that TG levels before 20 weeks of gestation are associated with birth weight. But later in pregnancy TG levels were independent predictors for birth weight. Thus, maternal TG levels may be a significant determinant of foetal overgrowth in our study, too, but in late and not in early pregnancy when we measured TG. We found that low serum HDL-C was associated with an increased risk of LGA, independent of BMI as in the Clausen *et al.* results.

Recent studies have consistently shown that maternal BMI is a strong independent predictor of the birth weight in GDM pregnancies [19, 22, 23]. In their study, Charlotte *et al.* [24] concluded that maternal obesity is a major risk factor for LGA in pregnancies complicated by gestational diabetes. According to them, the incidence of LGA infants was significantly higher in obese women than in those with lower BMI, which is comparable with our findings. Because our results show that maternal obesity is a predictor for LGA in GDM, an active approach should be taken to obesity among women of childbearing age.

The percentage of LGA newborns in our study group was 31.5%, which is higher in comparison with findings in past studies [19]. Also, in our study we report a significant increase (almost eight-fold) in the prevalence of LGA following the presence of altered maternal characteristics. Upon closer analysis, we observed that all the patients with 2 altered characteristics had elevated BMI, accompanied by a significant increase in birth weight. Our results suggest that foetal overgrowth seems to be driven by other factors, possibly a cluster of metabolic alterations associated with maternal obesity, as we observed elevated maternal BMI in 36.5% of LGA in our study group. These results are almost identical with the results of Zawiejska *et al.* [7]. They also found that the birth weight of the largest child born previously was the strongest independent predictor of a birth weight, even stronger (19%) than in our study. Skjaren *et al.*

documented that women who have given birth to an LGA infant once before are much more likely to do so again [25].

Maybe different factors are responsible for foetal overgrowth at different gestational ages. However, a number of maternal characteristics are responsible for LGA in GDM. Further studies are necessary to confirm our findings.

Conclusion

Pre-pregnancy BMI, HDL-C (during pregnancy) and birth weight of a large child born previously are the independent predictors for LGA, but results of glucose levels during OGTT are not useful in the prediction of LGA in GDM pregnancies. Probably several factors and other maternal metabolic parameters than glucose levels during OGTT are responsible for the risk of LGA.

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Резиме

АСОЦИЈАЦИЈА ПОМЕГУ ФЕТАЛНИОТ РАСТ И РАЗЛИЧНИТЕ МЕТАБОЛНИ КАРАКТЕРИСТИКИ НА МАЈКИ СО ГЕСТАЦИСКИ ДИЈАБЕТЕС

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Цел: Да откриеме дали постои асоцијација помеѓу феталниот раст и метаболните карактеристики на мајки со гестациски дијабетес (ГДМ).

Материјали и методи: Во студијата беа вклучени 200 последователни бремени жени кои се јавија на Клиниката за ендокринологија, дијабетес и метаболни нарушувања во Скопје, во периодот од 02.2006 до 02.2009 со единечна бременост и дијагностициран ГДМ според ADA критериуми. На учесниците им беа испитувани следните параметри: индекс на телесна маса пред бременост, 100 гр орален глукозен толеранс тест (ОГТТ), гликолизирани хемоглобин, вкупни липиди, вкупен холестерол, триглицериди, HDL-, LDL-холестерол. Родилната телесна тежина и преваленцата на голема телесна тежина за гестациската возраст (ГТВ) беа крајна цел на испитувањето.

Резултати: Постоеше статистички значајна асоцијација помеѓу родилната тежина и индексот на телесна маса пред бременоста на мајката, HDL-C и родилната тежина на најтешкото дете родено претходно. Родилната тежина на најтешкото дете родено претходно се покажа како најсилен независен фактор за ГТВ. Преваленцата на ГТВ се зголемуваше (од 27% до 80%) со зголемување на бројот на променетите карактеристики на мајката.

Заклучок: За разлика од индексот на телесна маса пред бременоста на мајката, HDL-C (за време на бременоста) и родилната тежина на најтешкото дете родено претходно, резултатите од ОГТТ не се корисни во предвидувањето на

ГГВ. Веројатно повеќе фактори и метаболни параметри на мајката различни од нивото на гликоза за време на ОГТТ се одговорни за ГГВ кај оваа група на пациентки.

Клучни зборови: гестациски дијабетес, голема телесна тежина за гестациската возраст, макросомија, метаболни параметри, ОГТТ.

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