Family, anthropometric and biochemical factors affecting birth weight of infants born to GDM women

Analiza wybranych czynników rodzinnych, antropometrycznych i biochemicznych wpływających na masę urodzeniową noworodków kobiet z cukrzycą ciążową

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Abstract

Objectives: *Gestational diabetes mellitus (GDM) affects up to 25% of all pregnancies worldwide. If untreated, GDM leads to increased complication rates both, in the mother and the fetus. Early diagnosis and adequate management of GDM are essential to avoid macrosomia. Nonetheless, neonates born to GDM mothers often have high birth weight. The aim of the study was to evaluate selected factors which can affect neonatal birth weight.*

Material and methods: *The study included 152 women with GDM and 58 healthy pregnant controls. Anthropometric data of both parents, maternal biochemical parameters, and neonatal birth weight were collected.*

Results: *The independent factors influencing neonatal birth weight were pregnancy duration, maternal smoking, as well as birth weight and current weight of the father. The risk of delivering a large for gestational age (LGA) infant increases with the diagnosis of GDM, higher maternal pre-pregnancy weight, and higher fasting glycaemia. No correlation between maternal fasting glycaemia, HbA1c, 1,5-AG, lipids and neonatal birth weight was found.*

Conclusions: *Risk factors for LGA include gestational diabetes, high maternal pre-pregnancy weight, and current body weight of the father. Neither HbA1c nor 1,5-AG were reliable predictors of neonatal birth weight and occurrence of LGA in the studied population.*

Key words: **gestational diabetes** / **birth weight** / **LGA** / **macrosomia** /

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Streszczenie

Cel pracy: *Cukrzyca ciążowa (Gestational Diabetes Mellitus – GDM) dotyczy do 25% ciąż na całym świecie. Nieleczona prowadzi do zwiększonej częstości powikłań zarówno u kobiet jak i noworodków. Wczesna diagnostyka i leczenie cukrzycy jest niezbędne do zapobieżenia makrosomii. Mimo tego noworodki kobiet z cukrzycą często mają zwiększoną masę urodzeniową. Celem tego badania była ocena wpływu wybranych czynników które mogą mieć wpływ na masę ciała noworodka.*

Materiał i metody: *Badaniem objęto 152 kobiety z GDM oraz 58 zdrowych kobiet w ciąży. Zebrano dane antropometryczne obojga rodziców, parametry biochemiczne matek, oraz dane dotyczące masy ciała noworodków.*

Wyniki: *Niezależnymi czynnikami które wpływają na masę urodzeniową noworodków są: czas trwania ciąży, palenie tytoniu przez matkę, jak również masa ciała ojca – zarówno aktualna jak I urodzeniowa. Ryzyko urodzenia dziecka z hipertrofią (LGA) wzrasta wraz z diagnozą cukrzycy ciążowej, wyższą masą ciała matki przed ciążą i wyższą glikemią na czczo. Nie stwierdzono korelacji pomiędzy matczyną glikemią na czczo, stężeniem HbA1c, 1,5-AG, i lipidów a masą ciała noworodka.*

Wnioski: *Stwierdziliśmy, że czynnikami LGA są: cukrzyca ciążowa, wysoka masa ciała matki przed ciążą i aktualna masa ciała ojca. Ani HbA1c ani 1,5-AG nie były predykatorami masy ciała noworodka lub wystąpienia LGA w badanej populacji.*

Słowa kluczowe: **cukrzyca ciążowa** / **makrosomia** / **masa urodzeniowa** / **LGA** /

Introduction

Gestational diabetes mellitus (GDM), one of the most common metabolic disorders in pregnancy, is defined as any degree of glucose intolerance with the onset or first recognition during pregnancy and is not considered to be diabetes mellitus type 2 [1]. GDM affects about 5-25% of all pregnant women [2], interfering with fetal development and leading to a number of complications in the newborn. The risk increases with the severity of maternal hyperglycemia. One of most common GDM-induced complications include fetal macrosomia (birth weight >4000 g), or excessive weight in relation to gestational age *(Large for Gestational Age* – LGA), which may result in perinatal injuries, shoulder dystocia, or the need for cesarean section. Macrosomic newborns are more likely to develop obesity or metabolic syndrome later in life [3,4].

The assessment of metabolic control based on self-monitoring of blood glucose levels, fasting and after meals, remains the standard practice in diabetes care of pregnant women with GDM. HbA1C levels are commonly used to evaluate the metabolic control of diabetes, and 1,5-anhydro-D-glucitol (1,5-AG) might also be useful. HbA1C indicates the average value of blood glucose over the 3 months before the testing [5], while 1,5-AG is a deoxyglucose and one of the relatively recent markers of short-term hyperglycemia. Low serum concentration of 1,5-AG shows a single episode of hyperglycemia within two days before the test or multiple episodes that took place during the last 3-4 weeks [6]. 1,5-AG is the most sensitive of the currently available markers of short episodes of hyperglycemia (especially postprandial hyperglycemia) in patients with diabetes type 1 and 2, people with impaired glucose tolerance, and women with GDM [7,8]. Numerous researchers believe that 1,5-AG may be useful in monitoring blood glucose levels in diabetic patients as a complement to A1C testing, even if A1C values are correct [9,10].

The rate of macrosomia is several times higher in the offspring of mothers with GDM than women with normal glucose metabolism. Excessive fetal weight gain is caused by fetal hyperinsulinemia induced by fetal hyperglycemia, which depends largely on the concentration of glucose in maternal blood in the third trimester of pregnancy [11]. There are also other known maternal factors promoting the incidence of macrosomia, including overweight and obesity before pregnancy, multiparity, advanced age, and high weight gain during pregnancy. In turn, smoking - being a strong risk factor of fetal hypotrophy - lowers the incidence of macrosomia [12-15].

The aim of the study was to evaluate the influence of selected factors that may significantly affect neonatal birth weight in the population of women with gestational GDM including paternal factors.

Material and methods

The study was performed between 2012-2013 and included 136 Caucasian women: 106 diagnosed with gestational diabetes mellitus (GDM group) and 31 pregnant women (NGT group) in whom gestational diabetes was excluded. GDM was diagnosed if fasting blood glucose was ≥100 mg/dL and/or 120 min. ≥140 mg/dL during 75 OGTT.

Data on maternal age, education, smoking, birth weight, prepregnancy weight and familial history of diabetes were obtained from patient survey. Data on paternal age, birth weight and current weight of the father were obtained directly from the subjects. Data on time and mode of the delivery as well as neonatal birth weight were obtained from the medical records.

Venous blood samples was collected twice from all participants (between 27 and 32 weeks and again between 34 and 39 weeks of gestation) to assess the metabolic parameters. Serum levels of fasting glucose, HbA1c, lipid profile and 1,5-AG were evaluated. Macrosomia was diagnosed in newborns with the birth weight of ≥4000 g, and LGA if the birth weight exceeded the 90th percentile.

Anthropometric characteristics of the mother and the father, parameters regarding control of carbohydrate metabolism during pregnancy (fasting blood glucose, HbA1c concentration and the concentration of 1,5-AG), parameters of lipid metabolism during pregnancy (total cholesterol, HDL and LDL cholesterol, triglycerides) and maternal smoking during pregnancy were analyzed.

The study was approved by the Local Ethics Committee. The patients were familiarized with the study protocol and their written informed consent was obtained.

The results were statistically analyzed using PQStat software - license number 01500256 (PQStat Software, Poland). Normal distribution of the analyzed data was checked using the Kolmogorov-Smirnov test with the Lillefor's amendment and the Shapiro-Wilk test.

Quantitative variables with normal distribution were compared using the Student's t-test and multivariate analysis of variance (ANOVA). Mann-Whitney rank test was used for variables without normal distribution. The significance of differences in the variances of the tested parameters was verified with the Fisher-Snedecor test. The relationship between metabolic parameters and birth weight was expressed by the Pearson or Spearman correlation coefficient, depending on data normality. Multivariate linear regression – for numerical factors and multivariate logistic regression - for binary factors regression were performed in order to assess the influence of the factors affecting neonatal birth weight. The p-value of <0.05 was considered as statistically significant.

Results

Table I shows the anthropometric characteristics of mothers and fathers in the studied groups.

Pregnant women with GDM had lower height, higher weight and higher pregestational BMI. Fathers of the children born to GDM mothers had higher body weight and BMI than the fathers of the children of healthy mothers. There were no differences between the groups in terms of parental birth weight.

In the GDM group, both fasting blood glucose and HbA1C were significantly higher than in the NGT group, while the concentration of 1,5-AG in the serum of women with gestational diabetes was significantly lower (8.73±0.33; 16.34±1.1; p<0.000001). No statistically significant correlation of lipid metabolism parameters with neonatal birth weight in the GDM and NGT group was found (data not shown).

The analysis of the obstetric results revealed no significant differences between the groups, except for a significantly higher number of newborns with LGA (32.07% vs. 6.45%, p=0.005). There were no cases of macrosomia in the NGT group.

We did not find any statistically significant correlations, either between HbA1c or 1,5-AG and neonatal body weight in both groups – the results are shown in Table II.

Multivariate regression analysis was performed and adequate analytical models were created to assess the relationship of individual parameters with infant birth weight. In Model 1, adjusted to maternal factors of pre-pregnancy body weight and fasting plasma glucose, the following proved to be significant: pre-pregnancy BMI β= -31.86 p=0.04, and smoking β= -456.63 p=<0.000001. The model is statistically significant (p=<0.000001)

Model 2 was extended to include paternal factors, which turned out to be significantly associated with neonatal birth weight. In that model, smoking remained significant, while maternal pre-pregnancy BMI lost its predictive power with regard to infant birth weight. The model is statistically significant (p=<0.000001) (Table III).

Table I. Characteristics of the study group.

Anthropometric characteristics of mother	GDM n=106 x±SD Median	NGT n=31 x±SD Median	P
Age [years]	30.2±0.36 30	28.87±0.6 29	>0.05
Height [m]	1.64±0.004 1.64	1.66±0.11 1.65	**0.01**
Pregestational weight [kg]	67.24±1.25 65	64±1.58 62.5	**0.041**
BMI [kg/m^2]	25.29±0.4 24.15	23.05±0.52 22.49	**0.007**
Birth weight [g]	3202±42 3250	3309±54 3300	>0.05
Anthropometric characteristics of father	**GDM mother**	**NGT mother**	**P**
Age [years]	32.1±5.51 31.5	31.79±5.99 30	>0.05
Height [m]	1.79±0.07 1.8	1.78±0.07 1.79	>0.05
Weight [kg]	86.96±12.55 85	81.88±11.71 79	**0.008**
BMI [kg/m^2]	27.05±3.3 26.73	25.68±3.62 24.88	**0.0098**
Birth weight [g]	3579±441 3500	3606±376 3525	>0.05

Table II. Correlation between HbA1c and 1,5-AG with neonatal birth weight in studied groups.

Parameter		GDM	NGT
HbA_{1c}	*R*	0,1	-0,16
	95CI	<-0,12;0,32>	<-0,42;0.12>
	P	**0,34**	**0,25**
1,5-AG	*R*	-0,15	0,03
	95CI	<0,33;0,02>	<-0,25;0,32>
	P	**0,08**	**0,81**

Within the study population, a subgroup of mothers whose newborns were included in the >90 percentile (LGA) group was distinguished: 47 in the GDM group and 6 in the NGT group. In that subgroup, the individual characteristics of mothers and fathers were compared. In the GDM group, mothers of LGA newborns had higher birth weight, body weight and BMI before pregnancy as compared to mothers with NGT, but these differences were not statistically significant. Only one difference was statistically significant - women with GDM were shorter than women with NGT (p=0.022). Paternal factors such as paternal birth weight, height, and current weight of fathers of LGA newborns did not differ significantly between GDM and NGT groups, although fathers in the GDM group were shorter and their body weight was higher, which translated into statistically significantly higher BMI (27.08±3.72 vs. 23.53±1.75, p=0.02).

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Birth analysis using logistic regression methods was performed in order to evaluate the influence of maternal and paternal factors on the incidence of LGA. Two analytical models were created: model 1 – taking into account only maternal factors, and model 2 – which incorporated also paternal features. Model 2 was statistically stronger (AUC=0.83, sensitivity 67%, specificity 87%) than Model 1, which used only the maternal factors (AUC=0.74, sensitivity 5%, specificity 99%), and the difference was statistically significant. The results are presented in Table IV. Along with the diagnosis of GDM in the mother, the risk of having a LGA newborn increased almost 6-fold, 1,1-fold for every kg of weight before pregnancy, and once with an increase in fasting blood glucose by 1 mg/dl. Maternal smoking decreased the risk of having a child with LGA.

Discussion

Gestational diabetes is the most common metabolic disorder developing during pregnancy. Although adequate treatment allows to reach and sustain normoglycemia, women with GDM are at increased risk of delivering a child with high birth weight.

Indicators of compensation such as blood glucose, HbA1C, and the 1,5-AG are assessed in order to monitor the severity of impaired carbohydrate metabolism. Of these parameters, only HbA1c concentration is a well-proven predictor of chronic complications among patients with diabetes mellitus type 1 and 2 [16, 17]. There is also evidence that HbA1c as a marker of hyperglycemia may be useful for the diagnosis of gestational diabetes [18]. However, due to the many limitations of the studies performed so far (poor strength of evidence), A1C is still an insufficient basis for the diagnosis of GDM [19].

The second parameter considered in our study was 1,5-anhydro-D-glucitol. It is a short-term indicator of metabolic control which evaluates glycaemia during the first and second week preceding the measurement [20]. As expected, 1,5-AG concentration was significantly lower in the group of women with gestational diabetes than in controls, no correlation with birth weight was detected. In an earlier study, Nowak et al., observed a correlation between 1,5-AG concentration and the risk of LGA or macrosomia in the group of patients with type 1 diabetes [10].

Short stature, overweight and obesity before pregnancy are widely regarded as factors predicting the occurrence of GDM [21,22]. Moses and Mackay, as well as Ogonowski and Miazgowski found that women with gestational diabetes are shorter and have lower leg length to height percentage ratio and that short stature is an independent predictive factor for the development of GDM [23, 24].

In our study, special attention has been paid to identification of factors that promote the birth of newborns with birth weight >90 percentile (LGA). In the literature, high pre-pregnancy BMI, excessive maternal weight gain during pregnancy, gestational diabetes, history of delivery of a child with the weight of >90 percentile, and maternal hyperlipidemia are mentioned as factors predisposing to delivering a baby with macrosomia or LGA [25, 26].

The diagnosis of gestational diabetes turned out to be a predisposing factor for having an LGA baby. In our study, women with GDM gave birth to infants with LGA significantly more often than healthy controls (32.07 % vs. 6.45%, p=0.005). Also, the diagnosis of gestational diabetes increased the risk of LGA 3.75-fold, and after taking into account paternal factors up to more than 5-fold (OR 5.83, 95% CI <1.52-22.35>). Many researchers reported similar observations, although other reports do not confirm this hypothesis [27, 28].

In our analysis, we tried to put some emphasis on certain paternal factors, such as current weight and birth weight that might influence fetal weight and incidence of LGA. Shah et al., in their systematic review of nearly 36 studies, concluded that data on the influence of paternal factors such as body mass, height and birth body mass remain limited, and in cases of some factors the results were often contradictory. The most reliable and extensive data included paternal birth weight – lower paternal birth weight was associated with lower infant birth weight, and the risk of low birth weight [29]. As most authors cited in our review, we are of the opinion that the influence of paternal factors on infant body weight is of genetic origin, but the behavioral factors, which remain very difficult to assess, might also play a significant role.

In light of ambiguous reports in the literature, the correlation between HbA1c, which is widely recognized for being an

Table III. Results of multivariate regression for birth weight.

Birth weight [g]	Model 2			
	B	95%CI	p	
Mother's weight before pregnancy	10.26	<-1.71-22.25>	0.09	R^2=0.39 F=6.72 **p<0.000001**
Mother's BMI before pregnancy	-31.85	<-65.35-1.64>	0.06	
Mother's smoking	-427.45	<-576.57--278.33>	**<0.000001**	
Fasting glycaemia	4.11	<-0.78-9.0>	0.1	
Father's actual weight	-8.73	<-16.93--0.53>	**0.03**	
Father's birth weight	0.16	<0.02-0.3>	**0.02**	

R2 – determination coefficient, F – significance factor of model parameters

Table IV. Logistic regression results for birth mass of LGA newborn.

LGA	Model 2				
	B	OR	95%CI	p	
GDM/NGT	1.76	5.83	<1.52-22.35>	**0.01**	**AUC=0.83 p<0.000001**
Mother's pregestational weight	0.10	1.10	<1.0-1.20>	**0.02**	
BMI before pregnancy	-0.29	0.74	<0.58-0.94>	**0.016**	
Smoking	-1.75	0.17	<0.04-0.65>	**0.009**	
Fasting glycaemia	0.04	1.04	<1.0-1.08>	**0.01**	
Actual father's weight	-0.06	0.93	<0.87-0.99>	**0.03**	

indicator of metabolic control, and the risk of having a child with high birth weight requires further evaluation [30]. Some researchers observed that women with GDM who failed to achieve A1C of <5.6% before the delivery more often gave birth to LGA newborns [31]. On the other hand, in a study population of 502 women with GDM a positive linear correlation between the analyzed parameters was not confirmed [32]. The analysis of the results obtained in the HAPO study also did not confirm the relationship between HbA1c and the incidence rate of complications [33]. Similar results were obtained in our study and we found no correlation between birth weight in the LGA group and the values of HbA1c and 1,5-AG. Based on the limited data available in the literature, it is difficult to confirm the usefulness of 1,5-AG determination in the evaluation of metabolic control in GDM, and prediction of complication risk. Further studies involving larger populations of patients appear to be necessary to justify the use of these assays for routine therapeutic proceedings.

Conclusions

Based on our findings, it seems safe to formulate the following conclusions:

1. Risk factors for giving birth to a neonate with LGA include gestational diabetes, high maternal weight before pregnancy, high fasting glucose, and paternal current body weight.
2. Both, HbA1c and 1,5-AG were not predictors of newborn weight and occurrence of LGA in our studied population.

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