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Intergenerational transmission of macrosomia in women with gestational diabetes and normal glucose tolerance

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ABSTRACT

Objectives: It has been suggested that neonatal macrosomia may contribute to increased risk of obesity and type 2 diabetes in later life. Much less is known about the association between maternal birth weight (MBW) and offspring birth weight (OBW). This retrospective study evaluated the prevalence of macrosomia in women with treated gestational diabetes mellitus (GDM) and normal glucose tolerance during pregnancy. The study also investigated associations between MBW and OBW.

Study design: Medical records of 519 pregnant women with treated GDM and 766 women with normal glucose tolerance, referred to the Gestational Diabetes Outpatient Clinic in Szczecin, Poland, were analyzed. The following data were assessed: maternal age, pregravid body weight, height, gestational weight gain, prior GDM, prior macrosomia, MBW and OBW. Birth weight was classified as small for gestational age (SGA), appropriate for gestational age (AGA), large for gestational age (LGA) and macrosomia (≥4000 g). OBW was obtained from birth certificates, and MBW was obtained from birth certificates or self-report.

Results: The overall prevalence of macrosomia was 8.1%, and was comparable in subgroups of women with and without GDM (7.7% and 8.4%, respectively; $p = 0.905$). The frequencies of SGA, AGA and LGA did not differ between study groups. A positive correlation was found between MBW and OBW in women with treated GDM ($r = 0.211$, $p < 0.001$) and in women with normal glucose tolerance ($r = 0.220$, $p < 0.001$). Regardless of glucose tolerance status during pregnancy, the greatest proportion of macrosomic babies were born to mothers who were themselves born macrosomic (26.5% in mothers with GDM and 20.0% in mothers with normal glucose tolerance; $p = 0.631$). On logistic regression, MBW was found to be a robust predictor of macrosomia in offspring [odds ratio (OR) 1.64, 95% confidence interval (CI) 1.15–2.36 in women with treated GDM; OR 1.35, 95% CI 1.07–1.76 in women with normal glucose tolerance). Other independent predictors of fetal macrosomia were gestational weight gain, prior macrosomia and pregravid body mass index (BMI).

Conclusions: MBW, prior macrosomia, pregravid BMI and gestational weight gain were predictors of macrosomia in offspring, but GDM was not. High MBW seems to contribute to intergenerational transmission of macrosomia.

Introduction

Macrosomia is a clinically significant risk factor for obstetric complications and metabolic disorders in adult life, such as metabolic syndrome [1], type 2 diabetes [2] and obesity [3]. While increased rates of macrosomia were reported primarily in infants of mothers with pregravid or gestational diabetes mellitus (GDM), later studies also linked the risk of macrosomia with factors other than maternal hyperglycaemia during pregnancy, such as pregravid overweight/obesity, excess net gestational weight gain, advanced age at gestation, multiparity, postdate pregnancy, and genetic or ethnic predispositions [4–10]. Several studies have shown the possible influence of maternal birth weight (MBW) on offspring birth weight (OBW). Tavares et al. demonstrated that MBW was an independent predictor of OBW, and that this maternal factor had a stronger effect on OBW than gestational age [11]. Similarly, Ahlsson et al. [12] found that women born with a

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high birth weight experienced a nearly two-fold increase in the risk of macrosomic birth. All these observations suggest that, independent of concomitant GDM, women who were themselves born macrosomic tend to give birth to macrosomic infants. In addition, over the last few decades, despite the improvement in general health status, increases have been reported in mean birth weight [13] and the rate of macrosomia [6,14].

Between 2002 and 2011, the incidence of obesity among women aged 18–34 years increased by nearly 70% in Poland, and there was a dynamic increase in the overall incidence of type 2 diabetes [15]. On the other hand, the incidence of GDM is relatively low in Poland, estimated at 5%. This study investigated associations between MBW and OBW in ethnically homogeneous groups of pregnant Polish women with treated GDM and normal glucose tolerance in relation to other well-defined factors that may contribute to risk of macrosomia.

Patients and methods

This retrospective study recruited pregnant women who were referred consecutively to the Gestational Diabetes Outpatient Clinic in Szczecin, Poland between January 2009 and December 2011 due to abnormal findings on a 50-g glucose challenge test (OCT) or a 75-g glucose oral tolerance test (OGTT). In women with abnormal OCT results, the diagnosis of GDM was confirmed by OGTT using the World Health Organization's cut-off values [16] if fasting glucose was ≥110 mg/dl (6.1 mmol/l) or 2-h glucose was ≥140 mg/dl (7.8 mmol/l), as described in detail elsewhere [17]. The control group was selected from consecutive women who delivered in the same period at a single university-affiliated centre located in the same area, had normal OCT or OGTT results, and were not diagnosed with GDM until delivery. Women with and without GDM were enrolled from those aged >18 years with a singleton pregnancy. Women who had been diagnosed with diabetes prior to pregnancy, received steroids or beta-mimetics during pregnancy, or had any concomitant disease requiring medical treatment were excluded. Overall, the medical records of 1285 women (519 women with treated GDM and 766 women without glucose intolerance during pregnancy) were analyzed.

The following data were analyzed: maternal age, height, pregravid weight and body mass index (BMI), gestational weight gain, MBW and OBW. Pregravid overweight and obesity were classified as 25.0–29.9 kg/m^2 and ≥30.0 kg/m^2, respectively. Using the standard classification, OBW was categorized as small for gestational age (SGA; weight <10th percentile), appropriate for gestational age (AGA; weight between 10th and 90th percentiles), large for gestational age (LGA; weight >90th percentile) [18] and macrosomia (birth weight ≥4000 g). Additionally, the following risk factors for GDM were recorded: prior GDM, multiparity, prior macrosomia and history of type 2 diabetes in maternal parents. Pregravid weight was established based on the woman's medical history and a comparison of this value with entries in the pregnancy records from the first weeks of pregnancy. MBW for 846 women (65.8%) was obtained from hospital discharge birth certificates. In the remaining cases, data were self-reported. In all cases, OBW was obtained from hospital discharge birth certificates.

This study was approved by the Ethics Committee of the Pomeranian Medical University in Szczecin. Reporting of the study conforms with the STROBE statement for cohort studies [19].

Statistical analysis

Results have been presented as mean ± standard deviation. The Shapiro–Wilk's test was used to test for normality, whereas the *F*-test (by Snedecor) and Brown–Forsythe's test were used to assess the homogeneity of variances. In the case of normal distribution and equal variances, means were compared using Student's *t*-test; otherwise, non-parametric methods were used. Chi-squared test for independence, with Yates' correction, was used to determine if qualitative variables were related. MBW was analyzed in the following five subgroups: <2500 g, 2500–2999 g, 3000–3499 g, 3500–3999 g and ≥4000 g. In each weight category, frequencies of SGA, AGA, LGA and macrosomia were calculated separately in women with treated GDM, normal glucose tolerance and the entire study population. Chi-squared test for trend was used to determine whether the prevalence of fetal outcomes differed between the MBW categories. The relationship between pairs of quantitative variables with normal distributions was presented using Pearson's linear correlation coefficient, whereas Spearman's rank correlation coefficient was calculated for pairs of variables with non-normal distributions. The odds ratio (OR) of macrosomia depending on risk factors was assessed by univariate and multivariate logistic regression. In the multivariate analyses, the effect of the following risk factors was examined: age, pregravid body weight and BMI, multiparity, weight gain during pregnancy, family history of type 2 diabetes, history of GDM and history of giving birth to a child with birth weight ≥4000 g. The level of statistical significance of the tests was established at $p < 0.05$. Calculations were performed using Statistica 8.0 PL (StatSoft, Poland).

Results

Table 1 shows the baseline characteristics of women with and without GDM and fetal outcomes. Compared with women with normal glucose tolerance during pregnancy, women with treated GDM were older, shorter, and had higher pregravid weight and BMI. The frequencies of overweight and obesity, prior GDM and family history of type 2 diabetes were higher in women with treated GDM. Apart from dietary treatment of diabetes, more than half (50.3%) of the women with GDM required insulin therapy, which was initiated at 29.6 ± 4.5 weeks of gestation with a mean daily insulin dose of 17.4 ± 10.4 IU. MBW and OBW were comparable in women with and without GDM. The overall prevalence of neonatal

Table 1
Baseline characteristics of women with and without gestational diabetes mellitus (GDM) and fetal outcomes.

	GDM (n = 519)	Without GDM (n = 766)	p-Value
Maternal birth weight (g)	3192 ± 533.8	3236.7 ± 562.9	0.169
Age (years)	30.71 ± 4.5	29.32 ± 4.8	0.0001
Height (cm)	164.9 ± 5.6	166.3 ± 5.9	0.0001
Pregravid weight (kg)	66.6 ± 13.9	63.7 ± 12.3	0.0001
Pregravid body mass index (kg/m^2)	24.51 ± 4.9	22.90 ± 4.0	0.0001
Pregravid overweight (n)	23.70% (123)	17.23% (132)	0.0001
Pregravid obesity (n)	12.5% (61)	6.65% (51)	0.0001
Weight gain during pregnancy (kg)	14.36 ± 5.9	14.89 ± 6.1	0.122
Fasting plasma glucose (mg/dl)	86.1 ± 10.5	81.7 ± 9.1	0.0001
Preterm delivery (<37 weeks) (n)	6.55% (34)	6.65% (51)	0.939
Neonate birth weight (g)	3310.5 ± 496.2	3305.7 ± 508.9	0.865
Prior GDM (n)	7.32% (38)	1.82% (14)	0.0001
Prior macrosomia (n)	7.32% (38)	5.48% (42)	0.181
Multiparity (n)	45.85% (238)	40.99% (314)	0.083
Parental type 2 diabetes (n)	27.55% (143)	10.83% (83)	0.0001
Small for gestational age (n)	5.39% (28)	6.40% (49)	0.801
Appropriate for gestational age (n)	74.57% (387)	73.62% (564)	0.755
Large for gestational age (n)	12.33% (64)	11.61% (89)	0.764
Macrosomia (≥4000 g) (n)	7.70% (40)	8.35% (64)	0.905

Data are presented as mean ± standard deviation or percentage (n). Conversion factor to SI units for glucose: mmol/l = mg/dl/18.