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An observational study of the risk of neonatal macrosomia, and early gestational diabetes associated with selected candidate genes for type 2 diabetes mellitus polymorphisms in women with gestational diabetes mellitus

Agnieszka Zawiejska[1], Ewa Wender-Ozegowska[1], Anna Bogacz[2], Rafal Iciek[3], Przemyslaw Mikolajczak[4], Jacek Brazert[3]

[1]Department of Reproduction, Karol Marcinkowski University of Medical Sciences, Poznan, Poland
[2]Department of Stem Cells and Regenerative Medicine, Institute of Natural Fibers and Medicinal Plants, Poznan, Poland
[3]Department of Obstetrics and Women's Diseases, Karol Marcinkowski University of Medical Sciences, Poznan, Poland
[4]Chair of Pharmacology, Karol Marcinkowski University of Medical Sciences, Poznan, Poland

ABSTRACT

Objectives: 1) to analyse the prevalence of selected candidate genes for type 2 diabetes mellitus polymorphisms (IRS1 G972R; ENPP1 K121Q; ADRB3 W64R) among women with gestational diabetes; and 2) to investigate any association between variants of these genes and risk of neonatal macrosomia.

Material and methods: We conducted a prospective observational study of a group of women (N = 140) in singleton pregnancies who delivered at term. Characteristics of the study group at enrolment: age: 32.0 ± 4.9 years; GA: 26.6 ± 7.5 weeks; HbA1c: 5.6 ± 0.6%; fasting blood glucose: 102.3 ± 16.3 mg/dL; insulin treatment (G2DM): 65.7%; chronic hypertension: 11.4%; gestational hypertension: 17.9%; preeclampsia: 1.4%; birth weight: 3590 ± 540 g; birth weight ≥ 4000 g (macrosomia): 18.6%; caesarean section: 44.3%; and female newborns: 57.1%.

Results: The maternal metabolic characteristics at the time of booking did not differ between polymorphisms. Macrosomia was insignificantly more frequent in females (22.5%) than in males (13.3%) (p = 0.193). Only maternal height and body weight at the time of booking significantly predicted birth weight (R = 0.27, p = 0.007; R = 0.25, p = 0.005, respectively). IRS1 G972R GR and ENPP1 K121Q KQ polymorphisms were associated with an insignificantly increased risk for macrosomia. Carriers of the heterozygotic variant of the IRS 1 gene were significantly more likely to be diagnosed with GDM/DiP in the first trimester: OR 5.2, 95% CI: 1.4; 19.2; p = 0.014.

Conclusions: 1) having similar metabolic characteristics, carriers of specific variants of T2DM candidate genes might be at increased risk of delivery of macrosomic newborns; 2) any association between genetic variants and macrosomia in this population might be gender-specific; and 3) allelic variation in the IRS1 gene is associated with early GDM/DiP.

Key words: gestational diabetes; macrosomia; maternal outcome; neonatal outcome; prediabetes

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INTRODUCTION

Hyperglycemia detected in pregnancy known as gestational diabetes mellitus (GDM) or diabetes diagnosed in pregnancy (DiP), is a common complication of pregnancy and is associated with increased fetomaternal risk. Associations between GDM/DiP and short-term adverse perinatal outcomes are well described, and excessive fetal growth and macrosomia are particularly characteristic of this maternal disease [1, 2]. According to recent studies focusing on long-term follow-up of patients, GDM/DiP is a strong predic-

Corresponding author:
Agnieszka Zawiejska
Department of Reproduction, Karol Marcinkowski University of Medical Sciences, 33 Polna St., 60–535 Poznan, Poland
e-mail: azawiejska@ump.edu.pl

tor for type 2 diabetes in women and has been shown to be related to an increased risk of non-communicable disorders in their offspring [3–5].

Type 2 diabetes mellitus (T2DM) is a complex disorder in which multigenic predisposition is strongly shaped by epigenetic (environmental) factors. Although recent studies identify a growing number of genes that can be linked to increased T2DM susceptibility, the risk continues to be significantly influenced by lifestyle interventions. Therefore, the clinical relevance of information obtained from genomic investigations is still a matter of controversies.

As GDM/DiP and type 2 diabetes share clinical phenotypes, namely several pathomechanisms and risk factors, both diseases are now considered to be a clinical manifestation of an ongoing process that accumulates over time in a woman's lifetime. Therefore, several studies have investigated for a possible common genetic background in these disorders. Observational data from different cohorts worldwide, confirm there is a significantly increased prevalence of the T2DM risk variants of particular candidate genes in women with gestational diabetes [6]. However, this association was only confirmed in the case of some candidate genes. Moreover, studies of small cohorts often produce conflicting results, and all conclusions are relevant for specific populations. Also, data from GDM cohorts refer to only a few T2DM candidate genes out of a large number of identified risk variants. Additionaly, for some associations, maternal BMI was found to be a possible or actual determining factor explaining the relationships found by researchers [7–10].

Importantly, the majority of available data only focuses on links between the genetic profile and the prevalence of GDM in particular cohorts. There have only beeen a small number of studies that have looked into a possible relationship between the variants and the degree of maternal hyperglycemia. None of the research currently available has addressed fetomaternal outcomes, abnormal growth trajectories, or maternal metabolic profiles in GDM pregnancies. Therefore, although it may be useful from the point of view of the populations, the available research evidence is not helpful for perinatal risk assessment and profiling.

The aim of our study was to analyse the prevalence of particular polymorphisms of selected candidate genes for type 2 diabetes mellitus (IRS1 G972R; ENPP1 K121Q; ADRB3 W64R) in a cohort of Polish women with gestational diabetes and to investigate any associations between variants of these genes and birth weights in the cohort.

We hypothesised that being a carrier of a specific variant of the candidate gene for type 2 diabetes is associated with an altered risk for excessive fetal growth and neonatal macrosomia. We also hypothesised that this association might show a sexually dimorphic pattern, that is, differ between female and male neonates.

MATERIAL AND METHODS

We designed a prospective observational trial to answer our research question. All those patients in singleton pregnancy who were referred to our tertiary-level unit of antenatal care for further treatment of GDM/DiP were considered eligible for our study. Finally, 199 women agreed to participate in the study and each gave their informed consent. Our protocol was reviewed and approved by the Bioethical Committee at the University of Medical Sciences in Poznan. The research project received funding from the Polish Ministry of Science (grant No: NN407 536538).

We selected the data of N = 140 women who delivered at term (gestational age of 37 or more gestational weeks) for the analysis so as to investigate any association between the genes we studied and birth weights. From our cohort, we collected data on maternal anthropometrics, and lipid and glycemic profiles at booking. We also performed an ultrasound examination of the fetal growth and body composition. Then, patients had their blood taken, which was processed and stored for further assaying. After delivery, we collected data on birth weight, delivery mode, and adverse maternal and neonatal outcomes. Macrosomia was defined as a birth weight of 4000g or more. We sub-divided our study population according to all the polymorphisms studied: IRS1, ADRB3 and ENPP1.

All biochemical tests were performed in the accredited laboratory of the academic hospital, which holds ISO 9000 quality management certification.

Genomic DNA was extracted from venous blood samples using the QIAamp Blood Kit (Qiagen GmbH, Hilden, Germany) according to the manufacturer's protocol. Analysis of the IRS1 G972R, ENPP1 K121Q and ADRB3 W64R polymorphisms was performed using the PCR-RFLP method. The primers for ADRB3 and ENPP1 used in the PCR, the length of amplified products and the conditions of the PCR were applied as previously described [11, 12]. Primer sequences for the G972R polymorphism of the ISR1 gene were as follows: forward 5'-GTG ATC AGT CTG GCT ACT TGT -3', reverse 5'- TGC CTG TTC GCA TGT CAG CAT AGC -3' (348bp). The PCR were performed in a thermocycler (PTC-200, MJ Research, USA). PCR products were digested with the appropriate restriction enzymes, such as SmaI (Fermentas, Lithuania) for ISR1, AvaII (Fermentas, Lithuania) for ENPP1 and MvaI (Fermentas, Lithuania) for ADRB3. The lengths of fragments of the polymorphisms we studied were as follows: IRS1 G972R GG (203 bp, 117 bp, 28 bp), GR (231 bp, 203 bp, 117 bp, 28 pz), RR (231 bp, 117 bp), ENPP1 K121Q KK (238 bp), KQ (238 bp, 148 bp, 90 bp), QQ (148 bp, 90 bp) and ADRB3 W64R WW (99 bp, 62 bp), WR (161 bp, 99 bp, 62 bp), RR (161 bp). PCR-RFLP products were separated using electrophoresis in 3% agarose gel with ethidium bromide and they were visualised under UV light.

Statistical analysis was performed using SPSS 14.0.2PL for Windows (IBM®, Armonk, USA). We tested the normality

of our data using the Kolmogorov-Smirnov test, and then we used appropriate parametric or nonparametric tests to ascertain the differences between the parameters in each of the subgroups. Odds ratios and 95% confidence intervals were calculated for proportions of fetal end-points. Multiple logistic regression and ROC analyses were performed to identify predictors for neonatal macrosomia in the group. Variables were presented as means ± standard deviation or medians (interquartile range). $P < 0.05$ was considered as statistically significant, with a Bonferroni correction used for multiple group testing.

RESULTS

The characteristics of our study group are summarised in Table 1. Our participants were recruited from patients who had been referred to our clinic by local units for further antenatal care — this explains the high proportions of women with early GDM, on insulin therapy, or who had been diagnosed with chronic or gestational hypertension.

The initial metabolic profiles of our patients and the final fetomaternal outcomes did not differ with any statistical significance between carriers of the studied gene variants, except for the statistically significant difference in the gestational age at enrolment between the IRS1 G972R GG and GR subgroups (27.5 ± 7.0 vs 21.1 ± 9.6; p = 0.014). Heterozygotes were significantly more likely to be diagnosed with GDM/DiP in the first trimester: OR 5.2, 95% CI: 1.4; 19.2; p = 0.014.

The gestational weight gain and prevalence of maternal obesity were similar when the carriers of the genetic variants we investigated were compared. For many patients, pre-pregnancy body weight data was either not available or was self-reported, and therefore of limited accuracy. However, the pre-pregnancy data we did have, and the patients' body weight at enrolment, that was measured in our department, clearly indicated a population with excessive body weight prior to pregnancy.

Maternal anthropometric and metabolic parameters did not differ significantly between the groups of women who delivered normal-weight newborns compared with macrosomic newborns (Tab. 2).

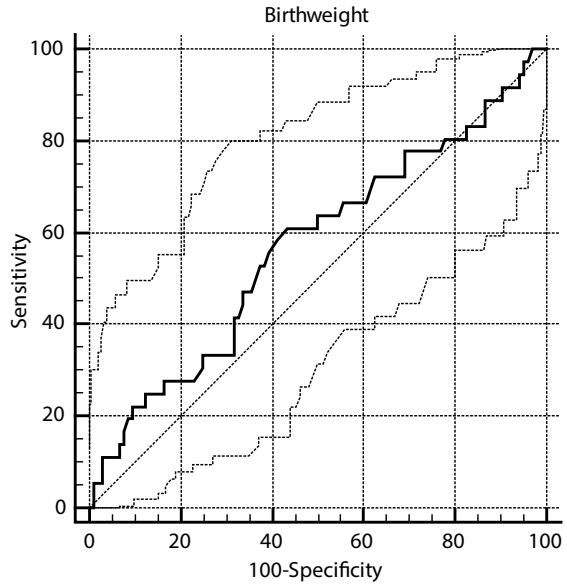
Macrosomia was insignificantly more frequent in females (22.5%) compared with males (13.3%) OR 1.9, 95% CI: 0.8, 4.7; p = 0.193. In our study group, only the maternal heights and body weights at the time of booking were significant in predicting birth weights (R = 0.27, p = 0.007; R = 0.25, p = 0.005, respectively). We found, in the whole cohort, and

Table 1. Characteristics of the study group

Age [years]	32.0 ± 4.9
Gestational age at diagnosis [weeks]	24.3 ± 9.8
Gestational age at booking [weeks]	26.6 ± 7.5
HbA1c at booking [%]	5.6 ± 0.6
Fasting blood glucose at booking [mg/dL]	102.3 ± 16.3
Maternal height [cm]	167.0 ± 6.5
Maternal prepregnancy body weight [kg]	91.2 ± 15.0
Maternal weight at booking [kg]	92.5 ± 20.4
Maternal prepregnancy BMI [kg/m^2]	32.8 ± 5.6
Gestational weight gain [kg] data available for N = 42 patients	6.8 ± 7.1
Maternal prepregnancy obesity [%] data available for N = 53 patients	65.4
Chronic hypertension [%]	13.6
Gestational hypertension [%]	17.9
Preeclampsia [%]	1.4
Insulin therapy [%]	65.7
HbA1c > 6.5% at booking [%]	6.3
GDM diagnosed in the first trimester [%]	33.3
GA at delivery [weeks]	39 ± 1
Birth weight [g]	3592 ± 540
Females/males [%]	57/43
Birth weight > 4000 g [%]	18.6
Birth weight > 4000 g in female neonates/male neonates [%]	22.5/13.3

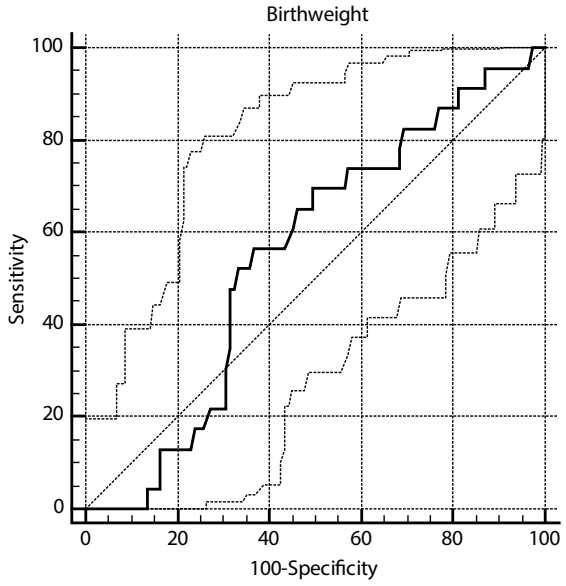
Table 2. Metabolic and anthropometric characteristics of participants who delivered normal-weight vs macrosomic newborns

Maternal parameter	Normal-weight newborns N = 114	Macrosomic newborns (birth weight > 4000 g) N = 26	p
Maternal age [years]	31.9 ± 5.0	32.2 ± 4.4	0.865
Gestational age at diagnosis [weeks]	19.7 ± 8.9	24.7 ± 7.7	0.218
Gestational age at booking [weeks]	26.4 ± 7.5	27.9 ± 7.6	0.480
HbA1c at booking [%]	5.6 ± 0.6	5.5 ± 0.4	0.902
Fasting blood glucose at booking [mg/dL]	102.2 ± 16.5	102.5 ± 16.1	0.913
Maternal height [cm]	166 ± 7	169 ± 6	0.058
Maternal prepregnancy body weight [kg]	90.6 ± 14.6	93.1 ± 17.0	0.656
Maternal weight at booking [kg]	91.9 ± 20.0	101.0 ± 21.9	0.058
Maternal prepregnancy BMI [kg/m^2]	33.1 ± 5.4	32.0 ± 6.4	0.380
Gestational weight gain [kg]	5.9 ± 6.8	10.8 ± 7.1	0.055
Gestational hypertension/ preeclampsia [%]	15.9	28.0	0.161
Chronic hypertension [%]	13.6	16.0	0.754
Insulin therapy [%]	67.5	53.8	0.385
HbA1c > 6.5% at booking [%]	7.7	0	0.347



AUC (area under curve)	Cutoff value	Sensitivity	Specificity	p
Whole cohort				
0.57 95% CI: 0.55; 0.69	> 3620 g	61.1%	56.7%	0.234
LR for the cutoff value : 1.4 (1.0; 2.0)				
Female neonates				
0.6 95% CI: 0.49; 0.71	> 3640 g	66.7%	61.0%	0.184
LR for the cutoff value: 1.7 (1.1; 2.7)				

Figure 1A. Birth weight as an indicator of maternal ENPP1K121Q KQ polymorphism



AUC (area under curve)	Cutoff value	Sensitivity	Specificity	p
Whole cohort				
0.55 95% CI: 0.47; 0.6	> 3560 g	69.6%	50.4%	0.376
LR for the cutoff value: 1.4 (1.0; 1.9)				
Female neonates				
0.52 95% CI: 0.41; 0.64	> 3470 g	85.7%	42.4%	0.748
LR for the cutoff value: 1.5 (1.1; 2.0)				

Figure 1B. Birth weight as an indicator of maternal IRS1 G972 GR polymorphism

Table 3. Prevalence of variants in the study population

ADRB		
RR 3.6%	WR 11.4%	WW 85.0%
ENPP1		
KQ 25.7%	KK 74.3%	
IRS-1		
GR 16.4%	GG 83.6%	

in the females analysed separately, that IRS1 G972R GR and ENPP1 K121Q KQ polymorphisms were associated with an insignificantly increased risk for macrosomia (respectively: 17.5% vs 11.5% for the GR polymorphism, p = 0.568; and 25.0% vs 16.3% for the KQ polymorphism, p = 0.319). No significant relationship was found in our cohort between birth weight and allelic variability in the ADRB3 gene.

There was no significant association between birth weights and the distribution of the genetic variants we studied; however, women who delivered newborns weighing more than 3620g were more likely to be carriers of the ENPP1 K121Q KQ variant (Fig. 1A), and this trend was even stronger in the sub-group who gave birth to girls (Fig 1A). Patients who gave birth to newborns weighing more than 3560 g were more likely to be carriers of the IRS1 G972R GR variant (Fig 1B). This association, although weaker, was also confirmed in a separate analysis of the mothers of girls (Fig 1B). For both genes, we found no threshold linking birthweight to a likelihood of being a carrier of the specific gene variant in those women who gave birth to boys.

The prevalence of specific polymorphisms for the whole cohort are presented in Table 3. We did not note any association between the variants of the genes we studied, and neonatal sex.

DISCUSSION

There is a growing prevalence of gestational diabetes mellitus in the general population of pregnant women. This

disease is now identified as one of the main health burdens behind increased maternal and neonatal morbidity, from the perspectives of both the short-term and long-term implications. Therefore, both international and local organisations are calling for more studies on the risk factors, effective prevention modes and mechanisms of maternofetal intergenerational transmission of non-communicable disorders [13, 14].

In our cohort, we linked some maternal and neonatal traits to genetic variations of well-described candidate genes for T2DM. Our results add to a new area of research because most available data concerns allelic variations of the candidate genes and their associations with the risk of gestational diabetes itself. Only one report has described an assocation between genetic variations and how severe the hyperglycemia was, and whether the women were responding to the therapy, or [15].

In our study group, we found that a slightly increased risk of excessive birth weight was associated with the variant of the insulin receptor substrate-1 gene. A protein encoded by this gene is involved in insulin signalling in target tissues, and some studies, including one Turkish study, have found an association between its genetic variation and a more severe GDM phenotype; that is, they found higher insulin levels and higher fasting glucose [16]. In our cohort, we did not confirm these differences. In comparison, the Turkish data were collected from a smaller group of patients diagnosed with a 100 g OGTT. Moreover, our participants were recruited from a population that had been referred to an academic unit for further care due to the ineffective initial treatment they had received or because of other co-morbidities. Therefore, our cohort might have been biased towards more severe phenotypes. Nevertheless, even if our study subgroups did not differ in terms of maternal characteristics, our observation of an association between increased birth weight and genetic variants of the IRS-1 gene remains in line with other available evidence on the regulating role of IRS-1 in determining insulin response [17]. Contemporary data on perinatal outcomes in GDM populations consider birth weight as a result of complex maternal metabolic disarrangements that are strongly mediated by maternal insulin resistance. In our study population, which was sub-divided by IRS-1 polymorphisms, we also noticed similar proportions of other surrogate markers of severe insulin resistance in pregnancy, such as pre-pregnancy obesity, excessive body weight gain, or gestational hypertension. Therefore, our findings might suggest that specific genetic variations in the IRS-1 gene could be associated with accelerated fetal growth, even if metabolic changes that are specific to late pregnancy mask any differences in the background insulin resistance caused by allelic mutations of this gene. Alternatively, certain specific polymorphisms of the IRS-1 gene might be associated with elevated insulin resistance in early pregnancy that triggers accelerated fetal growth – undetected before the third trimester of gestation – prior to the affected individual presenting with gestational dysglycemia. The placenta is now recognised as a key-player by autonomously regulating fetal access to maternal nutrients. Hence, we could hypothesise that the maternal metabolic phenotype produced by genetic variations in the IRS-1 could be dysregulating the placental function from early in the pregnancy.

One important aspect of our findings was that we confirmed an association between gestational dysglycemia diagnosed in early pregnancy and specific allelic variations of the IRS-1 gene. Our observation also supports hypotheses on the early pregnancy origins of fetal overgrowth, as women with these polymorphisms entered their pregnancies with a more severe insulin resistance and were more likely to give birth to large newborns. We also observed an association between at least one gene, among numerous candidate genes, for T2DM and maternal perinatal complications, in that we found a strong relation between variations in the IRS-1 gene and hyperglycemia diagnosed in early pregnancy. The group of women diagnosed with hyperglycemia early in their pregnancy presents a particular challenge to antenatal care providers due to a lack of uniform recommendations for GDM/DiP screening in early pregnancy. Accumulating data from clinical observations suggests an increased risk for fetomaternal complications when compared with results for GDM/DiP diagnosed at a standard gestational age. Also, this early-diagnosed population of pregnant women seems more likely to develop cardiometabolic complications in later life. Notably, our data confirmed that genetic factors can contribute to the increased risk of gestational and post-partum complications, and this would make lifestyle and behavioural interventions less effective.

As with the findings for the IRS-1, the ENPP-1 gene is critical for insulin function. A class II transmembrane glycoprotein product encoded by ENPP-1 is overexpressed in many target tissues for insulin in individuals at risk of metabolic syndrome, insulin resistance and future obesity. ENPP-1 polymorphisms are also associated with diabetic vascular complications [18, 19]. Also, our study confirmed a link between this gene and larger birth weights and specific genetic variations. Moreover, this ENPP-1 association was more pronounced in the sub-group of female newborns.

For both the genes that are crucial for insulin action, we noted a trend towards a stronger association between specific polymorphisms and birth weights for female newborns. The aggregated body of evidence points towards sex-associated differences in the risk and prognosis of type 2 diabetes mellitus [20]. Moreover, common metabolic risk factors for type 2 diabetes in the female sex are associated

with a less favourable prognosis, and women need specifically tailored interventions to address the specific risks [21]. Our data remain in line with these published findings, as we traced these gender-related differences back to maternofetal interactions. One might conclude from our findings that maternal insulin resistance has a more remarkable impact on fetal development if the pregnant woman has a daughter. Our study also confirmed the early onset of metabolic impairment that is likely to result in increased whole-life morbidity in affected women, thus increasing their reproductive health risks and reducing their life expectancy. Moreover, our observations also add to an existing body of evidence on the matrilineal intergenerational transmission of noncommunicable disorders. Our data also confirm how important it is to develop effective interventions to prevent increased perinatal risks associated with the maternal metabolic profile. Notably, such interventions should optimally predate pregnancy — recent data points to the postpartum, or interpregnancy period, as a promising educational window to improve fetomaternal safety in future gestations. Unfortunately, our results also indicate that environmental interventions in populations that are genetically predisposed to *diabesity* need to be carefully designed, and that such interventions probably should take account of the genetic profile of the targeted population, even if genetic susceptibility accounts only for a small proportion of the risk [22].

CONCLUSIONS

Conclusions: 1/ having similar metabolic characteristics, carriers of specific variants of T2DM candidate genes might be at increased risk for a delivery of macrosomic newborns; 2/ associations between genetic variants and macrosomia in carriers of specific variants of T2DM candidate genes may be gender-specific; 3/ allelic variation in the IRS1 gene is associated with early GDM/DiP.

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