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Similarities and differences in the pathophysiology of gestational diabetes between primigravidas and multiparas in the evaluation of the HOMA index at the time of diagnosis Part I: Evaluation of insulin resistance

Abstract

Background. Insulin resistance and defect in pancreatic beta cell function are the two main pathogenic mechanisms of gestational diabetes mellitus (GDM). Multiparity is a risk factors of GDM. The relationship between multiparity and key pathogenic mechanisms of GDM is still unknown. The aim of the study was to evaluate and compare some of the clinical and biochemical parameters as well as the severity of insulin resistance in a group of primiparas and a group of multiparas with GDM.

Material and methods. The study initially included 337 women recently diagnosed with GDM. Two groups were distinguished: one consisting of 164 women with GDM diagnosed in their first pregnancy (primigravidas) and 112 women with GDM diagnosed in their third or subsequent pregnancy (multiparas). We measured serum fasting glucose and insulin levels in the venous blood, and insulin resistance was assessed using the HOMA-IR index.

Results. The multiparas were generally older than the primigravidas (25.05 ± 5.20 years old *vs*. 22.46 ± 4.43 years old, $P < 0.0001$) and their had a higher pregestational BMI (33.54 ± ± 5.15 kg/m^2 *vs.* 26.99 ± 4.17 kg/m^2, $P < 0.0001$). There were no significant differences between both groups in the time of diagnosis, weight gain, fasting serum glucose and insulin levels and the HOMA-IR index (2.88 ± 3.62 *vs*. 4.24 ± 10.87). There was a positive correlation between HOMA-IR and BMI in both groups ($P < 0.001$). In the multiparas with HOMA-IR > 10, the value of this parameter was independent of BMI.

Conclusions. At the time of diagnosis, insulin resistance assessed using the HOMA-IR index in the primigravidas and in the multiparas was similar. In both study groups, the severity of insulin resistance depended on pregestational BMI. In the multiparas with HOMA-IR > 10, its value was independent of BMI.

key words: gestational diabetes mellitus, parity, insulin resistance, HOMA-IR index

Introduction

Gestational diabetes mellitus (GDM) is one of the strongest risk factors of type 2 diabetes, metabolic syndrome and early development of atherosclerosis. The aetiology, pathogenesis and pathophysiology of GDM have not been fully elucidated. It seems that the principal pathophysiological mechanisms of GDM are chronic insulin resistance [1, 2] and abnormal function of pancreatic beta cells [3, 4]. Multiparity is one of the risk factors of GDM. Interrelationships between the number of pregnancies and complications have not been elucidated. While according to some researchers [5], multiparity does not affect the incidence of type 2 diabetes in women without any previous abnormalities of carbohydrate metabolism, other scientists confirm the presence of such association [6, 7]. Isolated studies also suggest the link between multiparity, GDM and type 2 diabetes

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mellitus [8]. The aim of our study was to investigate and compare some of the clinical parameters and the main pathophysiological mechanisms of GDM, insulin resistance and pancreatic beta cell function in primigravidas and multiparas.

The first part of this article reports on the results of insulin resistance investigations.

Material and methods

The study initially included 577 women recently diagnosed with GDM, 18–48 years old, managed at the Regional Centre for Intensive Diabetologic and Obstetric Care, Independent Public Healthcare Establishment, The Dr J. Biziel Provincial Hospital in Bydgoszcz, between 2002 and 2004. Two groups were formed, one consisting of 337 women with GDM diagnosed in their first pregnancy (primigravidas) and the other one consisting of 240 women with GDM diagnosed in their third or subsequent pregnancy (multiparas). The diagnosis of GDM was established in accordance with the model used in Poland [9].

A history was taken and a general physical examination including the measurement of weight was performed in each patient. The following laboratory parameters were tested: HbA_{1c}, fasting serum insulin and glucose levels in the venous blood (after 12 hours of fasting). The laboratory tests were performed at the hospital's Department of Analytics. Serum glucose was determined in the venous blood by the glucose oxidase method on the Olympus AU 400 analyser (reference values 3.31–5.51 mmol/l), glycated haemoglobin in the venous blood by the turbidimetric method (reference values < 6%) and the serum insulin concentration in the venous blood by the immunoenzymatic method (MEIA) using the AxSYM analyser (reference values 2–25 μU/ml).

Insulin resistance was assessed using the HOMA-IR index (Homoeostasis Model Assessment) according to Mathews and Hosker [10].

$$\text{HOMA-IR} = (\text{insulinaemia } [\mu\text{U/ml}] \times \text{glycaemia } [\text{mmol/l}])/22.5$$

Statistical analysis

The statistical analysis was performed using *Statistica for Windows* (StatSoft). The testing for normal distribution by the Shapiro-Wilk test demonstrated that the distribution of the variables did not overlap with the normal distribution. The analysis was therefore performed using the non-parametric Kruskall-Wallis test, assuming the P values of ≤ 0.05 to be statistically significant. The variability was reflected by the mean (X) and the standard deviation (SD).

Spearman's correlation coefficients were also assumed to be significant at the P values of ≤ 0.05, in which case they were marked with an asterisk. The analysis of dependency for the qualitative variables was performed using the χ^2 test, providing both the contingency coefficients and the Cramer's V. The P values of ≤ 0.05 were considered statistically significant.

Results

Table 1 shows a comparison of the analysed parameters in the population of primigravidas and the population of multiparas. Multiparas were older than primigravidas and had a higher pregestational BMI. Both groups differed with respect to the gestational week of GDM diagnosis, weight gain, fasting serum glucose and insulin levels, HbA_{1c} and the HOMA-IR index at the time of diagnosis. Figure 1 (the histogram) shows the number of women from both groups in each range of the HOMA-IR index (0–20 with increments of 2, 20–120 with increments of 20). Table 2 presents the results of correlation testing. A negative correlation between HOMA-IR and BMI was observed in both groups. No correlation was found in both groups between the HOMA-IR index and the number of past pregnancies in the entire population or the age. Tables 3 and 4 show the results of the numbers of women in each of the HOMA-IR ranges (0–2, > 2–10 and > 10–120) relative to the number of past pregnancies. The statistical analysis did not reveal these relationships. Table 5 presents a comparison of BMI for each of the HOMA-IR ranges (0–2, > 2–10 and > 10–120) in both groups.

In the group of primigravidas, women with a HOMA-IR of 0–2 had a lower BMI than women with HOMA-IR values of 2–10 or > 10. There were no differences in BMI between women with HOMA-IR values of 2–10 and > 10. In the group of multiparas, however, women with HOMA-IR values of 2–10 had a higher BMI than women with a HOMA-IR of 0–2. BMI did not differ in the remaining ranges of HOMA-IR. The severity of insulin resistance in multiparas with a HOMA-IR of > 10 was independent of BMI. The results of investigations of these relationships are presented in Table 5 and in Figures 2 and 3.

Discussion

Our study did not reveal any differences between primigravidas and multiparas (women with GDM diagnosed during their third or subsequent pregnancy) with

Table 1. Characteristics of the women and the parameters under evaluation in the study groups

Parameter	1st pregnancy				3rd or subsequent pregnancy				P value
	N	X	SD	MIN MAX	N	X	SD	MIN MAX	
Age (years)	337	26.99	4.17	18.00 48.00	240	33.54	5.15	22.00 45.00	**< 0.0001**
BMI [kg/m^2]	331	22.46	4.43	16.02 42.11	227	25.05	5.20	14.38 50.78	**< 0.0001**
Gestational age in weeks at the time of GDM diagnosis	339	29.04	4.27	9.00 38.00	239	29.30	4.96	7.00 40.00	0.1212
Weight gain [kg]	327	9.42	4.97	–3.00 30.00	224	8.96	4.95	–6.00 31.00	0.4066
Glucose level [mmol/l]	194	5.67	10.26	2.66 81.00	137	5.47	9.87	2.25 100.00	0.1408
Insulin level [μU/l]	220	15.29	21.67	3.40 249.26	150	12.26	9.40	2.90 66.40	0.1264
HbA_{1c} (%)	118	5.55	0.52	4.70 8.30	76	5.64	0.61	4.30 8.20	0.3057
HOMA-IR	**164**	**4.24**	**10.87**	**0.51 108.23**	**112**	**2.88**	**3.62**	**0.40 26.99**	**0.4228**

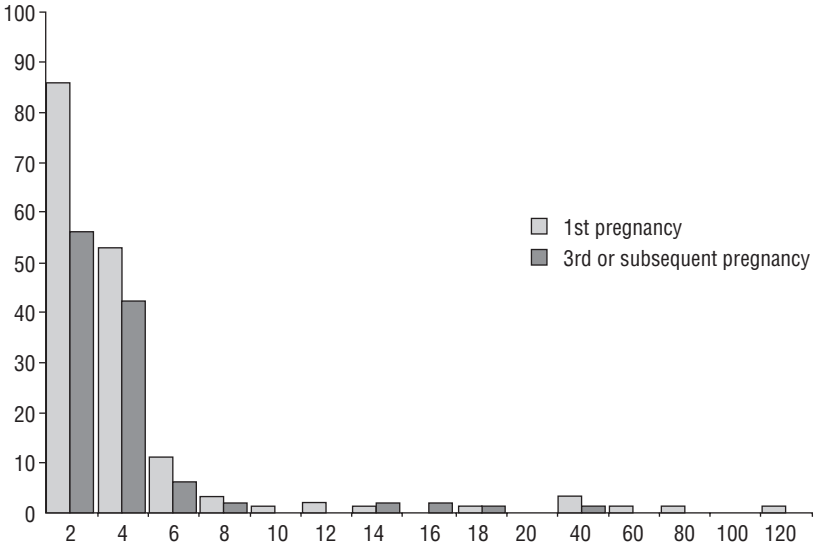

Figure 1. A histogram of the number of patients in HOMA-IR ranges from 0–120 in the study groups

Table 2. Coefficients of correlation between the HOMA-IR index and the number of pregnancies in the entire population, age and BMI in the study groups

	Study group	R_s	P value
Age	1st pregnancy	0.0164	0.8354
	3rd or subsequent pregnancy	–0.0882	0.3548
BMI	1st pregnancy	0.3619	**< 0.0001**
	3rd or subsequent pregnancy	0.4663	**< 0.0001**
Number of pregnancies	Entire population	–0.0443	0.3828

Table 3. Bivariate table with the statistical evaluation of the relationship between HOMA-IR in ranges: 0–2, 2–10, > 10, and the number of pregnancies in the study groups

HOMA-IR range	1st pregnancy		3rd or subsequent pregnancy		Total
	N	%	N	%	N
< 2	86	52.44	56	50.00	142
2–10	68	41.46	50	44.64	118
> 10	10	6.10	6	5.36	16
Total	164	100.00	112	100.00	276

$\chi^2 = 0.297$ (P = 0.8619); contingency coefficient = 0.0328; Cramer's V = 0.0328

Table 4. Differences in the percentage indexes for HOMA-IR ranges: 0–2, 2–10, > 10 in the study groups

HOMA-IR range	1st pregnancy			3rd or subsequent pregnancy		
	N	%	P value	N	%	P value
< 2 (I)	86	52.44	**0.0472**$^{I–II}$	56	50.00	0.4226$^{I–II}$
2–10 (II)	68	41.46	**< 0.0001**$^{II–III}$	50	44.64	**< 0.0001**$^{II–III}$
> 10 (III)	10	6.10	**< 0.0001**$^{I–III}$	6	5.36	**< 0.0001**$^{I–III}$
Total	164	100.00		112	100.00	

Table 5. Mean values of BMI in HOMA-IR ranges: 0–2, 2–10, > 10 in the study groups

Group	BMI [kg/m^2]									P value
	HOMA-IR ≤ 2 (I)			HOMA-IR 2–10 (II)			HOMA-IR > 10 (III)			
	N	M	SD	N	M	SD	N	M	SD	
1st pregnancy	83	21.41	3.00	66	23.83	4.86	10	24.53	4.05	**0.0004**$^{I–II}$ **0.0319**$^{I–III}$ 0.4702$^{II–III}$
3rd or subsequent pregnancy	50	22.64	3.93	47	26.92	5.09	6	24.42	2.24	**< 0.0001**$^{I–II}$ 0.1311$^{I–III}$ 0.3190$^{II–III}$

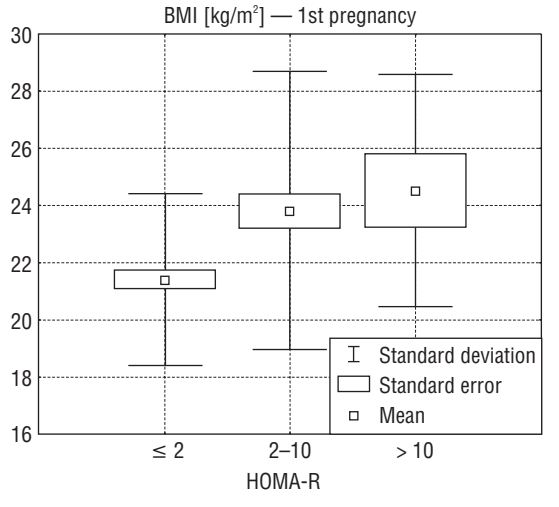

Figure 2. Mean values of BMI in HOMA-IR ranges: 0–2, 2–10, > 10 in the group of primigravidas

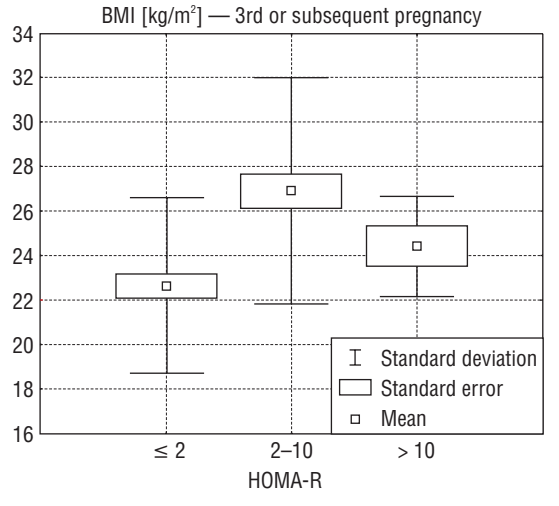

Figure 3. Mean values of BMI in HOMA-IR ranges: 0–2, 2–10, > 10 in the group of multiparas

respect to the severity of insulin resistance as assessed by the HOMA-IR index at the time of GDM diagnosis.

In both groups, in half of the women, the insulin resistance index HOMA-IR fell within the normal limits. This is rather interesting given the fact that these women presented with chronic insulin resistance and in most cases the diagnosis of GDM was established in the second half of the pregnancy, when insulin resistance sharply increases as a result of the action of placental hormones. Of note is also the presence of high HOMA-IR values, especially among the primigravidas, reaching in several cases up to 120. The considerable scatter of HOMA-IR values points to a significant variability of the severity of insulin resistance in primigravidas and multiparas at the time of GDM diagnosis. The statistical analysis did not, however, demonstrate any relationship between the number of women in each of the HOMA-IR ranges and the number of past pregnancies. In the compared populations, we failed to demonstrate any relationship between the number of past pregnancies or age and the values of the HOMA-IR index. A relationship between the HOMA-IR values and the number of pregnancies could, however, be present because women with GDM are characterised by chronic insulin resistance, and recurrent insulin resistance in multiparas could increase it.

In both primigravidas and multiparas, the value of HOMA-IR index depended on pregestational BMI. Polish observations emphasise the paramount pathophysiological importance of pregestational excessive weight or obesity for the development of GDM [11]. While in the groups we compared, multiparas had a higher BMI than primigravidas, the insulin resistance marker HOMA-IR at the time of GDM diagnosis was similar in both populations. This finding may point to the weak relationship between insulin resistance and BMI in the population of multiparas and therefore a relatively stronger dependence on other factors. We therefore investigated the relationship between HOMA-IR and BMI in both groups for the normal range (HOMA-IR < 2) and for HOMA-IR values of ≤ 10 or higher. Results of this analysis suggested that in multiparas with GDM with HOMA-IR > 10 non BMI-dependent causes of insulin resistance should be taken into account. As regards the potential causes, one cannot exclude the relatively higher amount of abdominal fat in multiparas due to the higher BMI values and older age [12, 13]. One should also take into consideration the family history of type 2 diabetes (not analysed in the present publication) as well as obesity, the potential effect of lower physical activity before pregnancy and the differences in the interaction between insulin resistance and the pregnancy-induced mechanisms [4, 14].

Reports on recurrent GDM in subsequent pregnancies mention the following risk factors: multiparity, older age, weight gain between subsequent pregnancies [15, 16], pregestational obesity and macrosomia. It therefore seems that in women with GDM, subsequent pregnancies contribute to GDM recurrences and that the exacerbation of pathophysiological mechanisms, including insulin resistance (association between obesity and macrosomia), plays a potential role in this process. According to our observations, women with no previous impairment of carbohydrate metabolism, subsequent pregnancies do not affect the severity of insulin resistance.

In summary, we would suggest that the prevention of GDM should first of all involve the maintenance of normal body weight in the case of primigravidas, and various management options, including drug therapy, in the case of multiparas, with the aim being to achieve or maintain the highest possible sensitivity of tissues to insulin.

Conlcusions

1. Insulin resistance as assessed by the HOMA-IR index at the time of GDM diagnosis in primigravidas and in multiparas is similar.
2. In both populations, there exists a considerable variability in the severity of insulin resistance and the relationship between insulin resistance and BMI before pregnancy.
3. In multiparas with HOMA-IR values of > 10, other than BMI-dependent causes of insulin resistance should be taken into account.

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