Components of metabolic syndrome in women after gestational diabetes

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Abstract: Objectives. The aim of the study was to evaluate the risk of occurrence of metabolic syndrome (MS) in females who suffered from gestational diabetes mellitus (GDM). **Patients and methods.** 495 letters were sent to patients with a history of GDM treated in the Department between 1993–2002. One hundred and fifty-three (30.9%) patients who responded positively formed the study group. Out of them 74 had already been treated for diabetes mellitus, and glucose intolerance was found in 5 subjects. Seventy-four patients had been subjected to a 75 g Oral Glucose Tolerance Test, as well as the control group that consisted of 155 subjects, in whom GDM during pregnancy was excluded. In all patients lipid parameters, blood pressure, height, weight and waist circumference were measured and body mass index (BMI) was calculated. Metabolic syndrome was diagnosed according to the modified NCEP-ATP III criteria from 2005 (3 of 5 had to be fulfilled). **Results.** Patients from the study group were older than from the control group ($p < 0.05$), higher was their BMI at the time of the index pregnancy, as well as after the observation time ($p < 0.0001$). Metabolic syndrome was developed in 47 (30.7%) patients of the study group and 8 (5.2%) patients from the control group ($p < 0.001$). The study group presented all components of MS significantly more often than the control group – in both groups, we found respectively: abnormal waist circumference – 57% vs. 37.6% ($p < 0.005$), hypertension – 18.9% vs. 1.9% ($p < 0.001$), elevated fasting glycemia – 79.1% vs. 1.9%, hypertriglyceridemia – 21.6% vs. 2.6% ($p < 0.0001$), and decreased concentrations of high-density lipoprotein cholesterol – 11.1% vs. 2.6% ($p < 0.005$). **Conclusions.** Patients who suffered from GDM are at high risk for carbohydrate disturbances and metabolic syndrome in the following year. Therefore, they should be under continuous medical surveillance that would enable early detection and treatment of the metabolic disturbances.

Key words: gestational diabetes mellitus, metabolic syndrome, risk factors

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as glucose intolerance of a different grade, detected or first diagnosed during pregnancy. The disease develops mainly in the second half of gestation, as a result of insulin resistance induced by increased levels of estrogens, progesterone, prolactin and placental hormones [1,2]. Insulin resistance of target tissues results from a decreased sensitivity of insulin receptors and impaired post-receptor mechanisms [1-3]. The process is additionally aggravated by placental insulinases that inactivate the circulating insulin. Usually, a normal glucose metabolism is restored after the delivery, however, women with a history of GDM are at risk of future diabetes (mostly type 2 diabetes) and metabolic syndrome [3-5].

Metabolic syndrome is increasingly acknowledged as a major clinical and epidemiological factor for type 2 diabetes and cardiovascular complications, mainly because of its raising prevalence and association with atherosclerosis. According to the revised NCEP-ATP III criteria (2005), the metabolic syndrome may be diagnosed, if 3 out of the following criteria are met: waist circumference >88 cm in women, serum triglycerides (TG) levels >150 mg/dl, serum high-density lipoprotein (HDL) cholesterol level <50 mg/dl, blood pressure ≥130/80 mmHg and fasting glycemia ≥100 mg/dl [6].

Early identification of particular components of metabolic syndrome (MS) and integrated prophylactic actions, supported – if necessary – with a pharmacological approach, is aimed at reducing cardiovascular morbidity and mortality and the improvement of quality of life in a large population.

The aim of our study was to investigate a prevalence of MS in women with a history of GDM.

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Received: August 21, 2007. **Accepted in final form:** October 12, 2007.
Conflict of interest: none declared.
Pol Arch Med. Wewn. 2007; 117 (10): 457-461

Table 1. Characteristics of the study and control groups

	Study group n = 153	Control group n = 155	p
Follow-up time (years)	6.0 ±2.7	5.1 ±2.7	<0.05*
Age in the first pregnancy (years)	28.3 ±6.0	26.5 ±3.7	<0.05
BMI before studied pregnancy (kg/m^2)	26.0 ±5.7	21.2 ±2.3	<0.0001
BMI after the observation time (kg/m^2)	26.6 ±6.0	21.7 ±2.3	<0.0001
Diabetes in I relatives (%)	54 (35.3)	14 (9.0)	<0.0001**

* Mann-Whitney's U test
** χ^2 test
The data are shown as mean ±standard deviation or number (percent). BMI – body mass index

PATIENTS AND METHODS

Four hundred and ninety-five women treated in the Department of Obstetrics and Women Diseases between 1993-2002 because of pregnancy complicated with GDM were invited to participate in the study. We received feedback information from 153 patients (30.8%). Seventy-three women were treated for diabetes mellitus or impaired glucose tolerance. In remaining 74 participants glucose metabolism was assessed.

A hundred and fifty-five healthy women in uncomplicated pregnancy served as a control group. The controls were recruited from patients covered with antenatal care in our Department. Only patients with a negative screening for GDM and those who gave their consent were enrolled into the study.

In all participants the following parameters were investigated: age, time that elapsed since the delivery in the study group, blood pressure, body mass index (BMI) prior to the index pregnancy and after the follow-up time, obstetrical history and family history.

Methods of the study

A 75 g Oral Glucose Tolerance Test (OGTT) was performed in all individuals without a history or symptoms of diabetes and in the controls according to World Health Organisation recommendations. Blood samples were taken from each participant to assess TG and HDL-cholesterol levels. The samples were centrifuged and serum was assayed in the Hospital Laboratory using commercially available kits (Roche Diagnostics) and equipment (Hitachi 912 analizer).

The results of 75 g OGTT were analysed following reference values published by the Polish Diabetologic Society in 2006 [7]. Metabolic syndrome was diagnosed following the revised NCEP-ATP III criteria from 2005 [6]. The protocol of the study was approved by the Bioethical Committee at the Poznan University of Medical Sciences and all participants gave an informed consent.

Statistical analysis

Statistical analysis was performed using the Statistica 6.0 for Windows software. Results are expressed as mean ±SD, unless otherwise stated. The significance of the differences between study groups was tested using the t-Student test, the Mann-Whitney's U test, or the ANOVA, according to the data distribution and number of groups tested. Differences in categorical variables were tested using the χ^2 test. The results with $p < 0.05$ were considered statistically significant.

RESULTS

Characteristics of the study group are given in Table 1. The average period between the index pregnancy and participation in the study was 6.0 ±2.7 years for the study group and 5.1 ±2.7 years for the controls ($p < 0.05$).

Women with a history of GDM were significantly older. They also showed significantly higher BMI when conceiving. The difference remained also after the pregnancy was completed. Thirty-five percent of the women from the study group reported having first-degree relatives with diabetes, comparing to 9% of the controls ($p < 0.0001$).

As many as 30.7% of subjects from the study group showed features of the metabolic syndrome, compared to 5.2% of the controls ($p < 0.001$). Particular components of MS and their prevalence in the study group are given in Table 2. All features occurred more frequently in individuals with a history of GDM. Fasting hyperglycemia was a common finding showed by 79% of diabetic subjects. The second most frequent feature was increased waist circumference found in 50% of individuals.

Pre- and post-gestational BMI in patients and controls are shown in Table 3. A significant difference in the prevalence of overweight and obesity was demonstrated in the study group compared to the controls (28.1% and 22.2% vs. 5.2% and 1.2%, respectively; $p < 0.00001$). A normal body weight was found in 45.8% of the diabetic subjects and 86.5% of controls. The difference in overweight and obesity remained significant also when the post-gestational BMI was analysed (24.8% and 32.0% vs. 8.4% and 0%, respectively). Moreover, in 2% of participants with a GDM history morbid obesity was diagnosed (BMI >40 kg/m^2).

In Table 4 data on glucose tolerance are summarized. Seventy-nine individuals with a positive history of GDM had type 2 diabetes or glucose intolerance (74 and 5 patients, respectively) diagnosed before they entered the study. Out of the remaining 74 patients, in 12 (7.8%) diabetes was diagnosed following a 75 g OGTT performed in our study, whereas im-

paired glucose tolerance and impaired fasting glycemia was found in 7 (4.5%) and 12 (17%) subjects, respectively. Only 29 participants from the study group (19%) showed no abnormalities in 75 g OGTT. The proportion of controls with no symptoms of any form of glucose intolerance was 98.1%, whereas in 2 of them (1.3%) diabetes was diagnosed after glucose loading.

In our study group, we also investigated the prevalence of metabolic abnormalities characteristic of metabolic syndrome in relation to alterations in glucose metabolism. The prevalence of particular features of metabolic syndrome among women with a positive GDM history is summarized in Table 5. Twenty-four out of 74 individuals with the postpartum diagnosed diabetes developed full metabolic syndrome. In addition, we noted the highest BMI in this subgroup. Interestingly, metabolic syndrome was diagnosed in 17.2% of subjects with a normal glucose metabolism, in 15.4% of patients with isolated fasting hyperglycemia, in 58.3% of women with impared glucose tolerance (IGT) and in 58.3% of women with diabetes diagnosed during our study. The lowest BMI, systolic pressure, and serum TG levels were characteristic of individuals with normal results of 75 g OGTT, whereas women with altered glucose tolerance showed markedly increased serum TG levels.

DISCUSSION

An increasing world-wide epidemic of obesity has been noted in the first decade of our century. Comparing to the 1990s, a 74% increase has been reported [8]. According to available data, obesity and obesity-associated type 2 diabetes is the main underlying reason for an increased risk of cardiovascular diseases, particularly in women [8,9].

According to the definition, three out of the five following criteria have to be met to diagnose metabolic syndrome: visceral obesity, increased TG levels, decreased HDL-cholesterol levels, increased blood pressure and elevated fasting glycemia. Considering these criteria, metabolic syndrome may be diag-

Table 2. Components of metabolic syndrome in analyzed groups of women

Analyzed parameter	Study group n = 153	Control group n = 155	p**
Waist circumference >88cm	88 (40)* (57.5)	57 (36.7)	<0.005
Hypertension ≥130/85 mmHg	29 (14)* (18.9)	3 (1.9)	<0.001
Fasting glycemia ≥100 mg/dl	121 (42)# (79.1)	3 (1.9)	<0.0001
Triglycerides >1.7 mmol/l (150 mg/dl)	33 (13)* (21.6)	4 (2.6)	<0.0001
HDL-cholesterol <1.03 mmol/l (<50 mg/dl)	17 (7)* (11.1)	4 (2.6)	<0.005

* group without detected carbohydrate disturbances before blood collection
** χ^2 test
# 3 women with IGT had normal fasting glycemia
The data are shown as number (percent). HDL – high-density lipoproteins, IGT – impaired glucose tolerance

Table 3. Body mass index (BMI) among patients with GDM and in the control group (before index pregnancy and after the observation time)

BMI (kg/m²)	Before pregnancy		After the observation time	
	GDM n = 153	Control group n = 155	GDM n = 153	Control group n = 155
<18.5	6 (3.9)	11 (7.1)	3 (1.9)	6 (3.9)
18.5–24.9	70 (45.8)	134 (86.5)*	63 (41.2)	136 (87.7)*
25.0–29.9	43 (28.1)	8 (5.2)*	38 (24.8)	13 (8.4)*
>30	34 (22.2)	2 (1.2)*	49 (32)	
>35	–	–	9 (5.9)	0*
>40	–	–	3 (2.0)	

* χ^2 test – p <0.0001
The data are shown as number (percent). GDM – gestational diabetes mellitus

nosed even in 47 million of USA citizens, mainly due to a 61% increase in the prevalence of obesity between 1991–2000 [8]. Association between metabolic syndrome and insulin resistance is commonly acknowledged, therefore women with a history of gestational diabetes appear to be a group at a particular risk for metabolic syndrome induced by insulin resistance and overweight/obesity. Unfortunately, only around 30% of invited women decided to participate in our study, which may reflect a lack of awareness of the disease risk.

We diagnosed metabolic syndrome in 47 (30.2%) women from the study group compared to 5.2% of the controls. Increased waist circumference and fasting glycemia were the most common features of metabolic syndrome noted in our group. However, it should be noted that waist circumference exceeding 88 cm was found in one out of three individuals.

Increased body weight is commonly recognized as a main risk factor associated with further development of glucose intolerance and metabolic syndrome [8-10].

Our study showed that overweight and obesity were significantly more common findings in women with a GDM history compared to the controls. Furthermore, these abnormalities usually persisted, or even aggravated after the delivery. In around 38% of women from this group BMI was >29 kg/m^2 and morbid obesity was diagnosed in 2% of them.

Results of the Nurses' Heart Study indicate a close association between an increased mortality rate and obesity in women [11,12]. Moreover, according to data collected within the Framingham Heart Study, obesity is an independent risk factor for coronary heart disease, which corresponds with the Nurses' Heart Study results [11]. These studies noted a more than threefold increase in cardiovascular disease related morbidity in women with BMI >29 kg/m^2. Additionally, the Framingham Study also demonstrated that waist-to-hip ratio is a more sensitive predictor for the future coronary heart disease than BMI alone [11].

It should be also noted that obesity itself is not only one of clustered risk factors constituting the metabolic syndrome but also a risk factor for some cancers, like endometrium, breast or gall bladder cancer [13-15]. Clinical studies demonstrated that approximately 50% of women with a GDM history develop overt diabetes during less than 10 years after delivery [3,16]. In our study group, prevalence of different forms of carbohydrate metabolism abnormalities was as high as 81% within a relatively short follow-up period of 6 years, on average, where-

Table 4. Changes in carbohydrate metabolism in the study and the control groups

	Normal value (n, %)	IFG (n, %)	IGT (n, %)	DM (n, %)	Changes in carbohydrate metabolism diagnosed before the study (after pregnancy) (n, %)
Study group n = 153	29 (19)	26 (17)	7 (4.5)	12 (7.8)	79 (74 DM + 5 IGT; 48.4 + 3.3) DM = 86 (56.2)
Control group n = 155	152 (98.1)	0	1 (0.6)	2 (1.3)	0

* patients with IGT already diagnosed before the study

DM – diabetes mellitus, IFG – impaired fasting glycemia, others – see Table 2

Table 5. Selected components of metabolic syndrome among women after pregnancy with GDM in relation to currently detected disturbances (n = 153)

Analyzed parameter	Patients without disturbances n = 29	Diabetes mellitus treated after pregnancy n = 74	Diabetes mellitus detected during study n = 12	IGT n = 12	IFG n = 26
Metabolic syndrome (n, %)	5 (17.2)	24 (32.4)	7 (58.3)	7 (58.3)	4 (15.4)
BMI (kg/m^2)	23.4 ±3.9	32.0 ±17.0	29.5 ±7.1	28.3 ±5.6	27.0 ±5.9
Mean systolic pressure (mmHg)	118 ±14	132 ±21	137 ±21	130 ±19	127 ±12
Mean diastolic pressure (mmHg)	77 ±10	85 ±9	85 ±9	84 ±14	82 ±12
Triglycerides (mg/dl)	94 ±52.2	153.2 ±74.1	168.5 ±112.9 (52–437)	143.6 ±108.1 (58–359)	93.8 ±71.3 (29–382)
HDL-cholesterol (mg/dl)	66 ±13.5	58.9 ±18	60.8 ±14.1	62.6 ±19.8	65.5 ±16.2

The data are shown as mean ±standard deviation or number (percent). Abbreviations – see Tables 1, 2 and 4

as a total proportion of glucose intolerance and diabetes in the controls was less than 2%. As expected, there is a positive association between the time elapsed after the delivery and the prevalence of glucose intolerance/diabetes. Other studies regarding the Polish population with a similar follow-up period reported a fifty-percent prevalence of diabetes in women with a history of GDM [16,17].

In a separate analysis of women with diabetes/IGT diagnosed before the study, we found other features of metabolic syndrome in 24 individuals with diabetes (32.3%) and 80% (4 out of 5) of participants with IGT.

A particularly high average serum TG levels in IGT subgroup should be also noted as it may be a reason for further monitoring and treatment of metabolic syndrome in these women.

Twenty years ago, Reaven pointed out that even moderately elevated serum TG level may play a pivotal role in the development of further metabolic abnormalities and this is also an independent risk factor for cardiovascular diseases [18]. A modern treatment of diabetes includes also a reduction in this risk, therefore, a regular assessment of lipid-associated risks should be an important part of therapy monitoring.

In conclusion, our findings demonstrate that women with a history of GDM constitute a group at a high risk for future glucose intolerance and metabolic syndrome. We are much concerned about the small proportion of women who decided to participate in our study (30%). Moreover, only 50% of those who finally took part in this study had their glucose tolerance tested after the delivery. Such striking numbers imply that unfortunately, there is still a lack of awareness of further risks associated with gestational diabetes, not only among patients but also among the health care staff.

Impaired glucose tolerance during gestation which manifests itself as gestational diabetes should be considered as a prediabetic state with all possible further consequences, including atherosclerosis, obesity, dyslipidemia, altered fibrinolysis, diabetes and coronary heart disease. Early detection of these abnormalities might enable to initiate appropriate treatment procedures in order to prevent clinical manifestations of diabetes mellitus and metabolic syndrome.

We conclude:

1) Women with a history of GDM are a population at a high risk for future glucose intolerance, diabetes and metabolic syndrome
2) Women with a history of GDM require a special medical care focusing on early detection of metabolic abnormalities and initiating an appropriate treatment.

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