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Cardiovascular Risk Assessment in Women after Pregnancy Complicated by Gestational Diabetes Mellitus: A Cross-Sectional, Single Center Study

ABSTRACT

Objective: The aim of this study was to assess cardiometabolic risk factors and cardiovascular (CV) risk in the early period after pregnancy complicated by gestational diabetes mellitus (GDM).

Materials and methods: Traditional (blood pressure, cholesterol and glucose levels, body mass index, smoking and other) and non-traditional [intima-media thickness (IMT), high-sensitivity C-reactive protein (hsCRP), oxidized low-density lipoproteins (LDL) and homocysteine levels] cardiovascular risk factors were assessed in early (6–12 weeks) postpartum period in 48 women after pregnancy complicated with GDM and in 12 women after uncomplicated pregnancy. The clustering of CV risk factors was assessed, as well as relative cardiovascular risk (according to the guidelines of European Society of Cardiology).

Results: There were no significant differences between both groups with regard to the examined risk factors, with the exception of high-density lipoprotein (HDL) cholesterol level, which was within the norm range in all patients after uncomplicated pregnancy, but only in less than 60% patients after GDM. There were also no difference between the groups in mean number of cardiovascular risk factors or in proportion of patients having 1 or 2, or 3, or ≥ 4 risk factor. Similarly, there was no differences in proportion of patients with different relative cardiovascular risk score. Prevalence of IFG, IGT and DM in the post-GDM group was 13.3%.

Conclusions: In women with GDM in the early postpartum period the prevalence of CV risk factors and CV risk itself is similar to women after non-complicated pregnancy (the only exception was the low HDL cholesterol level and more prevalent carbohydrate metabolism disturbances in the former group). (Clin Diabetol 2023; 12; 3: 164–170)

Keywords: cardiovascular risk, risk factors, diabetes, gestational diabetes

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Background

Gestational diabetes mellitus (GDM, gestational diabetes mellitus), according to the current World Health Organization (WHO) definition following the release of the HAPO study (2013), is defined as a dis-

order of carbohydrate tolerance first diagnosed during pregnancy and not meeting the criteria for diagnosis of diabetes in the general population [1, 2]. The increasingly common diagnosis of GDM has multiple implications. It undoubtedly poses a threat to the normal course of pregnancy, leading to a number of fetal and maternal abnormalities, but it is also important for the further condition of mothers and their children [3]. Both pregnant women with GDM and their offspring are at increased risk for diabetes, usually type 2, obesity, metabolic syndrome and cardiovascular (CV) disease in the future [4]. The number of women diagnosed with gestational diabetes is dynamically increasing. Currently, according to WHO data, 10–25% of pregnancies are complicated by carbohydrate metabolism disorders whereas gestational diabetes constitutes 75–90% of them [5]. Immediately after the introduction of new diagnostic criteria, the GDM prevalence, which previously amounted to 5–7% (in Europe 2–6%), was estimated at 16% of pregnancies [6, 7]. This increase also proves the rapidly increasing prevalence of diabetes, especially type 2 and obesity. Establishing a diagnosis of gestational diabetes identifies a group of young women at particularly high cardiometabolic risk. One recent large meta-analysis revealed a more than 2-fold increased risk of major cardiovascular events during the first decade after GDM [8]. According to current statistics, cardiovascular disease remains the most common cause of death globally and is also the leading cause of death in people with diabetes [9, 10]. Identification of a group of women at particularly high risk for type 2 diabetes, metabolic syndrome and cardiovascular disease at a very early stage of the natural history of cardiometabolic disorders provides a unique opportunity for effective prevention in this increasingly large population. It therefore seems important to determine whether risk factors for diabetes and cardiovascular disease are already present very early after the postpartum period in pregnancies complicated by GDM, and which of these are the strongest predictors of the cardiometabolic disorders development.

The aim of this study was to assess cardiometabolic risk factors in order to evaluate the cardiometabolic risk in the early period after pregnancy complicated by GDM and to determine the predictive factors for the development of cardiovascular disorders and their correlation with carbohydrate disorders during pregnancy.

Materials and methods

Study design

This was a cross-sectional, single center study. The project was approved by the Bioethics Committee of the District Medical Council in Zielona Góra (KB Resolution No.17/79/2017 dated 17 July 2017). All patients have provided an informed consent to the study. For the purpose of this publication the data obtained during the first visit, which took place between the 6 and 12 postpartum week, were used.

Study population

Recruitment was conducted among patients treated in the Diabetes Outpatient Clinic of the University Hospital in Zielona Góra and in cooperating obstetrics-gynecology offices. The invitations to participate in the study was sent to women in the first postpartum week. A total of 150 invitations were sent out to the patients with GDM diagnosed previously according to the IADPSG criteria, and from those patients 48 women with GDM responded positively. Additional 12 women with uncomplicated pregnancy were recruited as a control group out of 200 women to whom the invitation was sent. One of the participants with GDM recruited for the study was excluded from the full evaluation because of failure to complete all of the tests scheduled at the 1st visit.

Inclusion criteria: GDM diagnosed previously according to the IADPSG criteria, informed consent for the participation in the study.

Exclusion criteria: Severe psychiatric disorder, any medical condition which was in the opinion of the investigator unsuitable for inclusion in the study.

Definitions of obtained variables and measurements

During the first visit medical history was collected, with dietary history with the use of KomPAN questionnaire (minimal set of questions), which was interpreted according to Wadolowska [11] and evaluation of physical activity with the International Physical Activity Questionnaire (IPAQ) (Polish version, short version), which was interpreted according to Biernat et al [12]. Anthropometric data were measured and body composition analysis was performed using the Tanita BC-418 bioelectrical impedance method. Fasting blood samples were taken from each participant and oral glucose tolerance test with 75 g of glucose was performed. Ultrasonographic evaluation of carotid arteries was performed in the diagnostic laboratory of the Clinical Neurology Department of the University Hospital in Zielona Góra. The thickness of the intima-media complex was determined by high-resolution ultrasonography. The examination was performed with a Toshiba device equipped with a 7.5 MHz linear transducer. A series of measurements and interpretation of results were performed according to the Mannheim Intima-Media Thickness Consensus [13].

Table 1. Characteristics of the Study Groups

Parameter	GDM group N = 48	Non-GDM group N = 12	P
Age [years, median with 25–75%]	33 (29–36)	32.5 (29–36.5)	NS[a]
BMI [kg/m^2]	25.4 ± 5.7	25.1 ± 5.3	NS[a]
Waist–hip ratio (WHR)	0.84 ± 0.08	0.81 ± 0.05	NS[a]
Systolic blood pressure [mmHg]	105.1 ± 14.5	103.3 ± 9.1	NS[a]
Diastolic blood pressure [mmHg]	69.9 ± 9.6	68.6 ± 8.7	NS[a]
Total cholesterol [mg/dL]	205.2 ± 42.5	207.9 ± 42.0	NS[a]
LDL cholesterol (mg/dL)	129 ± 41.7	117.1 ± 32.1	NS[a]
Triglycerides (mg/dL)	101 ± 38.7	80.5 ± 31.0	NS[a]
HDL cholesterol (mg/dL)	55.4 ± 13.4	67.0 ± 7.9	NS[a]
Fasting glucose (mg/dL)	89.7 ± 8.4	77.1 ± 8.2	NS[a]
2-hour blood glucose in OGTT 2h (mg/dL)	93.2 ± 31.7	NA	NA[a]
HOMA-IR	3.0 ± 2.5	2.2 ± 2.2	NS[a]
Diabetes mellitus*	1 (2.1%)	0	NA
Impaired fasting glucose*	3 (6.3%)	0	NA
Impaired glucose tolerance*	2 (4.2%)	0	NA
Primiparous	24 (50%)	6 (50%)	NS[b]
Multiparous	24 (50%)	6 (50%)	
Complications of pregnancy other than GDM**	17 (35.4%)	2 (16.7%)	NS[b]
Diabetes mellitus in 1st grade relatives	13 (27.1%)	1 (8.3%)	NS[b]
Diabetes mellitus in 2nd and 3rd grade relatives	16 (33.3%)	4 (36.4%)	NS[b]
Cardiovascular disease	1 (2.1%)	1 (2.1%)	NS[b]
Cardiovascular diseases in 1st grade relatives	11 (22.9%)	2 (18.2%)	NS[b]
Cardiovascular diseases in 2nd and 3rd grade relatives	14 (29.2%)	2 (18.2%)	NS[b]
Hypertension before pregnancy	1 (2.1%)	0 (0%)	NS[c]
Hypothyroidism before pregnancy	5 (10.0%)	0 (0%)	NS[c]
Other chronic diseases before pregnancy	4 (8.4%) (epilepsy in 2 patients. thrombophilia, hyperthyroidism)	2 (16.7%) (hyperthyroidism, adrenal adenoma)	NS[c]

*hypothyroidism (de novo), gestational cholestasis, thrombocytopenia, anemia; [a]Mann Whitney; [b]Chi square test with Yates correction; [c]Fisher exact test
BMI — body mass index; GDM — gestational diabetes mellitus; HDL — high-density lipoproteins; HOMA-IR — Homeostatic Model Assessment for Insulin Resistance; LDL — low-density lipoproteins; NS — not significant; OGTT — oral glucose tolerance test;

Laboratory tests. Blood samples obtained from all patients during visit 1 were analyzed. Insulin and HbA1c was determined by enzyme-linked immunosorbent assay (ELISA), glucose was measured by enzyme-linked immunosorbent assay with hexokinase, total cholesterol was measured, and blood count was performed in the Central Laboratory of the University Hospital in Zielona Góra. The results of 75 g oral glucose tolerance test (OGTT) performed according to the recommendations given before delivery in the above-mentioned laboratory were analyzed. The results of OGTT performed during pregnancy available in the medical records of the patients (medical histories or pregnancy charts) were also analyzed.

In all patients a cardiovascular risk was assessed according to the guidelines of European Society of Cardiology [14].

Statistical analysis

Variables are shown as mean ± standard deviation or median ± lower and upper quartile or as number with a percentage value. Statistical analyses were performer using statistic package Dell Inc., Dell Statistica, version 13. Distribution of values was tested with the Shapiro-Wilk test. According to the distribution, the t-Student or non-parametric Mann-Whitney tests were used for comparisons between the groups. For comparison of nominal variables, the Chi square test with Yates correction was used.

Results

The basal characteristics of the study groups are shown in Table 1 and selected traditional and non-traditional cardiovascular risk factors are shown in Table 2.

Table 2. Prevalence of Cardiovascular Risk Factors in the Examined Groups

Risk factor	GDM group N = 48	Non-GDM group N = 12	P
Systolic blood pressure > 140 mmHg	2 (4.3%)	0 (0%)	NS[a]
Diastolic blood pressure > 90 mmHg	2 (4.2%)	0 (0%)	NS[a]
Total cholesterol >200 mg/dL	24 (50%)	7 (58.3%)	NS[b]
LDL cholesterol >100 mg/dL	36 (75%)	11 (91.7%)	NS[b]
HDL cholesterol < 50 mg/dL	20 (41.7%)	0 (0%)	0.005[a]
Triglycerides > 150 mg/dL	7 (14.6%)	1 (8.3%)	NS[b]
BMI ≥ 25 kg/m^2	20 (41.7%)	3 (25%)	NS[b]
BMI ≥ 30 kg/m^2	11 (22.9%)	2 (16.7%)	NS[b]
Waist–hip ratio (WHR) ≥ 0,8	34 (70.8%)	7 (58.3%)	NS[b]
Visceral fat index > 12	0 (0%)	0 (0%)	—
Insufficient physical activity*	10 (21.7%)	3 (25%)	NS[c]
Non-healthy diet**	28 (60.9%)	8 (66.7%)	NS[b]
Healthy diet ***	0 (0%)	0 (0%)	—
Actual smoking	2 (4.2%)	0 (0%)	NS[a]
Smoking before pregnancy	2 (4.2%)	1 (8.3%)	NS[b]
Intima-media thickness (IMT) CCAS	0.47 (0.44–0.5)	0.49 (0.385–0.525)	NS[d]
Intima-media thickness (IMT) CCAD	0.463 ± 0.065	0.456 ± 0.057	NS[e]
Oxidized LDL	718 (161–3987.7)	717.15 (359.5–2283.7)	NS[d]
High-sensitivity C-reactive protein (CRP)	2.95 (0–12.92)	1.27 (0–9)	NS[a]
Homocysteine	1 (2.1%)	1 (8.3%)	NS[b]

*based on IPAQ short form analysis, **KomPAN questionnaire [Dietary Habits and Nutrition Beliefs Questionnaire] — Health Diet Index; *** KomPAN questionnaire — Unhealthy Diet Index; [a]Fisher exact test; [b]chi square test with Yates correction; [c]Fisher Freeman Halton; [d]Mann-Whitney test; [e]t-Student test
BMI — body mass index; HDL — high-density lipoproteins; LDL — low-density lipoproteins; NS — not significant

As can be seen, both groups did not differ significantly with regard to age, number of previous childbirths, history of various diseases. There was also no difference in regard to blood pressure, carbohydrates' metabolism, body mass index (BMI), waist–hip ratio (WHR) and different behavioral parameters (Tab. 2). The only parameter that occurred more frequently in women with a GDM history was low HDL cholesterol level. It was within the normal range in all patients from the control (non-GDM) group, but only in less than 60% patients with a complicated pregnancy.

The examined non-traditional cardiovascular risk factors (IMT, oxidized LDL, hsCRP and homocysteine level) also did not differ significantly between groups (Tab. 3). There were also no differences between the groups in mean number of cardiovascular-risk-factors or in proportion of patients having 1 or 2, or 3, or ≥ 4 risk factors. Similarly, there was no difference in proportion of patients with different relative cardiovascular risk scores (Tab. 4).

In the early postpartum period, in only 6 women disturbances of carbohydrate metabolism were found; in three of them (6,7%) impaired fasting glucose, in two impaired glucose tolerance (4,4%), and in one woman diabetes mellitus (2,2%).

Discussion

Since the first definition and diagnostic criteria have been presented in the 1960s by O'Sullivan, gestational diabetes was recognized as a predictor of the development of diabetes [4, 15]. The introduction of new diagnostic criteria for GDM after the announcement of the HAPO study results [2], which correlate more with complications of pregnancy than with long-term maternal metabolic complications, did not change this fact. Systematic reviews conducted after 2013 confirms at least sevenfold higher risk of developing diabetes in women after pregnancy in which abnormalities of carbohydrate metabolism qualified as gestational diabetes appeared [16]. Moreover, the results of prospective and retrospective analyses performed in the recent years have provided new data indicating a significant increase in cardiovascular risk in this expanding group of young women. The augmented cardiovascular risk is linked to the development of type 2 diabetes in these women, which is diagnosed in approximately 50% within the

Table 3. Prevalence of Selected Non-Traditional Cardiovascular Risk Factors in the Examined Groups

Parameter	GDM group N = 48	Non-GDM group N = 12	p
Intima-media thickness:			
CCAS	0.47 (0.44 – 0.5) n = 46	0.49 (0.385–0.525) n = 12	NS[a]
CCAD	0.463 ± 0.065 n = 46	0.456 ± 0.057 n = 12	NS[c]
Oxidized LDL	718 (161–3987.7)	717.15 (359.5–2283.7)	NS[a]
hsCRP	2.95 (0–12.92)	1.27 (0–9)	NS[a]
Homocysteine	1 (2.1%)	1 (8.3%)	NS[b]

[a]Mann-Whitney test; [b]Chi square test with Yates correction; [c]t-Student test
hsCRP — high-sensitivity C-reactive protein; NS — not significant

Table 4. Relative Cardiovascular Risk According to the European Society of Cardiology Guidelines

Relative risk score	1	2	3	4	5	6	7	8	10	12
GDM group (N,%)	41 (85,4%)	6 (12,5%)	1 (2,1%)	0	0	0	0	0	0	0
Non-GDM group (N,%)	11 (91,7%)	1 (8,3%)	0	0	0	0	0	0	0	0
P	NS	NS	NS							

GDM — gestational diabetes mellitus; NS — not significant

first 10 years after a pregnancy complicated by GDM [17, 18]. Swedish National Diabetes Registry reports that diagnosis of type 2 diabetes before the age of 40 years increases total and cardiovascular mortality twofold, the risk of heart failure almost fivefold, ischemic heart disease fourfold, and the risk is even higher when diabetes is diagnosed in young women [19].

Developing diabetes mellitus is however not the only responsible factor. A recent analysis of 9 studies conducted between 1950 and 2018, covering populations of 5,390,591 women and 101,424 cardiovascular events, revealed a twofold higher risk of CV incidents in women after GDM but also a 56% higher risk of cardiovascular incidents in women who did not develop type 2 diabetes after a pregnancy complicated by GDM [8]. This study showed also that the increased CV risk was greatest during the first 10 years after parturition and decreasing thereafter. This early increase of CV risk after pregnancy complicated by GDM may be not associated with the development of postpartum type 2 diabetes, but rather be explained by GDM itself, but also by the increase in CV risk factors during and after pregnancy. Indeed, a proportion of CV risk explained by postpartum diabetes may not exceed 25% (20). As the determinants of the increased risk of cardiovascular diseases in women after GDM are still unclear, it is important to determine to what extent it is increased in the early postpartum period together with the assessment of predictive factors in order to determine the appropriate, most effective preventive strategies in this group. In this study, an attempt was made to assess the cardiovascular risk in the 6–12 weeks after parturition complicated by GDM.

During recruitment to the study, it was noted that many women with GDM do not report to postpartum OGTT assessment. Even with a telephone reminder it was only about 50%, the figure consistent with the observations of other researchers [21–24]. Most of the women who refused to participate in the study have justified this with lack of time and a necessity to care for a small child.

In order to estimate the cardiovascular risk in the study group, due to the young age of patients, it was not possible to apply the commonly used Risk Score Card, which is recommended to stratify the risk of death from cardiovascular causes within 10 years in the population over 40 years of age (currently SCORE 2 also defines the risk of myocardial infarction and/or stroke) [14, 25]. According to European Society of Cardiology recommendations, the cardiovascular risk assessment was performed by determining the presence of CVD risk factors and estimating relative risk [14]. The relative risk in 12.5% of women after GDM was twofold higher and in 2.5% threefold higher compared with the same age women of the general population, in spite of the fact,

that at least in the comparison with the control group, the frequency and magnitude of assessed cardiovascular risk factors was similar. The analysis did not reveal any statistically significant difference in the prevalence of CV risk factors or CV risk level between women with GDM and the control group, saving lower HDL cholesterol level in the former one (Tab. 2). However, many of cardiovascular risk factors were numerically greater in the GDM group, and if the sample were increased, statistical significances may appear, as some researchers were able to show increased CV risk factors in the GDM population. For example, Freire et al. found an increase in intima-media thickness in young women at different periods of time after GDM that was significant and comparable to changes in patients with metabolic syndrome [26].

This was a biggest limitation of this study: the results need to be interpreted with caution because of relatively small sample. Especially the control group was small, due to a complete lack of interest in participation in the study of women with non-GDM pregnancies.

Conclusions

In conclusion, in women with GDM in the early postpartum period the prevalence of cardiovascular risk factors is similar to women after non-complicated pregnancy (the only exception was the low HDL cholesterol level in the former group). However, prevalence of carbohydrate metabolism disorders in the early period after pregnancy complicated by GDM exceeds the prevalence of type 2 diabetes registered in the general population.

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Conflict of interests

None declared.

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