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Gestational diabetes mellitus — an analysis of risk factors

Cukrzyca ciążowa — analiza czynników ryzyka

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Abstract

Introduction: Gestational diabetes mellitus (GDM) is associated with an increased frequency of gestational, perinatal and neonatal complications. The aim of the study was to evaluate risk factors for GDM and their predictive value.
Material and methods: The group studied consisted of 510 pregnant women with GDM diagnosed according to World Health Organization (WHO) criteria (GDM). The controls were 1160 pregnant women with normal glucose tolerance (NGT). Multifactorial analysis was performed and odds ratios (OR) were calculated for each risk factor identified.
Results: The GDM patients were significantly older than the NGT subjects (30.1 *vs.* 27.2 years; $p < 0.0001$), had a greater tendency towards obesity before pregnancy (BMI 25.0 *vs.* 21.6 kg/m^2; $p < 0.0001$), more often had relatives with diabetes (40.0 *vs.* 25.7%; $p < 0.01$), had greater parity (third or subsequent pregnancy: 33.6 *vs.* 16.0%; $p < 0.001$) and more often experienced adverse perinatal outcomes (21.4 *vs.* 13.7%; $p < 0.01$). Multivariate analysis revealed the following risk factors for GDM: BMI > 25 kg/m^2 (OR 4.14), a history of macrosomia (OR 2.72), being pregnant for the third time or more (OR 1.8), a family history of diabetes (OR 1.76) and age at gestation > 25 years (OR 1.34). No risk factors were present in 12% of GDM subjects, and at least one risk factor was found in 74.1% of subjects with NGT. No risk factor cluster was found which could be used easily in everyday practice to identify reliably subjects at increased risk of GDM.
Conclusions: Age, overweight and obesity, diabetes in the family, parity, macrosomia and a history of perinatal complications were identified as risk factors for GDM. As no reliable method of identifying subjects at increased GDM risk was found, we suggest that all pregnant women should undergo laboratory screening for GDM. **(Pol J Endocrinol 2008; 59 (5): 393–397)**

Key words: *gestational diabetes mellitus, screening, risk factor*

Streszczenie

Wstęp: Cukrzyca ciążowa (GDM, *Gestational Diabetes Mellitus*) zwiększa ryzyko powikłań ciąży, porodu i powikłań u noworodka. Celem pracy była ocena czynników ryzyka zachorowania na cukrzycę ciążową i ich wartości predykcyjnych.
Materiał i metody: Do grupy badanej włączono 510 ciężarnych kobiet z rozpoznaną według kryteriów Światowej Organizacji Zdrowia (WHO, *World health Organization*) cukrzycą ciążową (grupa GDM, *gestational diabetes mellitus*). Grupę kontrolną stanowiło 1160 kobiet z prawidłową gospodarką węglowodanową w ciąży (grupa NGT, *normal glucose tolerance*). Dla rozpoznanych czynników ryzyka cukrzycy ciążowej wykonano analizę wieloczynnikową oraz wyliczono iloraz szans.
Wyniki: Pacjentki z GDM były starsze (30,1 *vs.* 27,2 lat; $p < 0,0001$), miały wyższy BMI przed ciążą (25,0 *vs.* 21,6 kg/m^2; $p < 0,0001$), częściej miały krewnych z cukrzycą (40.0 *vs.* 25,7%; $p < 0,01$), częściej były wieloródkami (33,6 *vs.* 16,0%; $p < 0,001$) i częściej przebyły niepowodzenia położnicze (21,4 *vs.* 13,7%; $p < 0,01$) niż kobiety z NGT. Na podstawie analizy wieloczynnikowej wyłoniono następujące czynniki ryzyka GDM: BMI > 25 kg/m^2 (OR 4,14); urodzenie dziecka z makrosomią (OR 2,72), 3 lub następne ciąże (OR 1,8), pozytywny wywiad rodzinny w kierunku cukrzycy (OR 1,76) oraz wiek > 25 lat (OR 1,34). U 12% ciężarnych z GDM nie stwierdzono żadnego czynnika ryzyka, a przynajmniej jeden czynniki ryzyka stwierdzono u 74,1% ciężarnych bez zaburzeń tolerancji glukozy w ciąży. Nie udało się znaleźć takiego zestawu czynników ryzyka, który pozwoliłby wyłonić pacjentki z wysokim ryzykiem cukrzycy ciążowej z ogółu ciężarnych.
Wnioski: Wiek, nadwaga i otyłość, rodzinne obciążenie cukrzycą, rodność, makrosomia i niepowodzenia w wywiadzie położniczym są czynnikami ryzyka cukrzycy ciążowej. Ze względu na brak możliwości wyłonienia na podstawie obecności czynników ryzyka kobiet szczególnie zagrożonych cukrzycą ciążową, laboratoryjne badania przesiewowe powinny być wykonywane u wszystkich ciężarnych. **(Endokrynol Pol 2008; 59 (5): 393–397)**

Słowa kluczowe: *cukrzyca ciążowa, czynniki ryzyka, badania przesiewowe*

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Introduction

The prevalence of gestational diabetes mellitus (GDM) is estimated at 2–4% of all pregnancies in various populations, although there have been reports of prevalence as low as 0.5% in low-risk populations and as high as 10% in subjects with multiple diabetes risk factors. GDM prevalence reported in Poland varies from 1.9 to 3.8% in different regions and these numbers are within the range reported for Caucasians. Some studies suggest that GDM prevalence is related to general diabetes prevalence in a given community [1–6].

Diagnostic criteria and methods have a direct impact on the prevalence of GDM. In many countries screening for glucose intolerance in pregnancy is not routinely conducted, even if recommended [7, 8]. Specifically, in Poland, despite the clear guidelines published by the Polish Diabetes Association in 1994, screening procedures are still not performed in the majority of pregnancies [9]. The identification of GDM risk factors, which is likely to result in increased screening of subjects at greater risk of developing GDM, is therefore of utmost importance.

The first screening criteria for gestational diabetes were proposed in 1973 by O'Sullivan [10]. At present, GDM screening and diagnostic protocols are operating in many countries, although these procedures are not standardised. In 1999 the American Diabetes Association (ADA) and the World Health Organization (WHO) issued independently their guidelines on GDM diagnosis. These two documents are distinctly different. The ADA ceased to recommend screening procedures at a population level and limits their use to women with risk factors for GDM. Female subjects with no family history of diabetes, under 25 years of age and with normal body mass, are at low risk of GDM occurrence and, according to ADA recommendations, need not be subject to screening examination [11, 12]. These recommendations aim at decreasing the costs of diagnostics, as it is estimated that universal screening would involve as many as three million screening tests in the United States annually [13]. The WHO does not preclude screening to a particular group of women. According to WHO guidelines the 75 g oral glucose tolerance test (OGTT) is recommended for GDM diagnosis with the same cut-off values for blood glucose as for the general population. Impaired glucose tolerance (IGT) is considered GDM.

The aim of this study was to assess the prevalence of risk factors for GDM and their significance for diagnosis of the disorder.

Material and methods

Material and glucose assay method

The study was conducted in the Research Institute of the Hospital of the Polish Mother, Łódź, Poland over a 10-year period. A total of 1670 pregnant Caucasian women attending the obstetrics and gynaecology outpatient department were enrolled in the study. The patients, supervised by trained research nurses, filled in a standardised questionnaire comprising questions to elicit a detailed family history of diabetes in close and distant relatives (covering patients' parents, parents' siblings, grandparents, the patients' own siblings, their children and their cousins), age at conception, obstetric history, and pregestational body mass index (BMI). All patients were also examined by a physician. The same procedures were followed for all the patients included in the study, GDM cases and controls alike. The study group consisted of 510 pregnant women with GDM, diagnosed according to WHO and Polish Diabetes Association criteria (GDM). The control group comprised 1160 pregnant women with normal glucose tolerance (NGT). Plasma glucose was measured during a glucose challenge test with the use of hexokinase (the reference method). All biochemical assays were performed with the COBAS-INTEGRA analyser.

Statistical analysis

Differences between the means were assessed with the use of Student's *t*-test after confirming normal distribution of the data with the Shapiro-Wilk test; otherwise the non-parametric Mann-Whitney U test was used. The χ^2 or Fisher's exact test (depending on group count) were used to assess the differences in distribution of qualitative parameters such as the history of macrosomia. Uni- and multivariable logistic regression were used to measure the effect of risk factors on the probability of GDM occurrence. Sensitivity, specificity and positive and negative predictive values were calculated [14, 15].

In all statistical tests the level of significance was accepted at 0.05. Statistical calculations were performed with the use of SPSS v. 6.0 and EGRET software packages.

Results

The GDM subjects were found to be significantly older than the NGT subjects: 30.1 ± 5.9 *vs.* 27.2 ± 4.9 yrs ($p < 0.0001$). Mean BMI was significantly higher in the GDM group than in subjects with NGT: 25.0 ± 5.1 *vs.*

Table I. *The prevalence of risk factors of gestational diabetes in GDM and NGT groups*
Tabela I. *Występowanie czynników ryzyka cukrzycy ciążowej w grupach GDM i NGT*

Risk factor	GDM (n = 510)		NGT (n = 1160)		p
	n	%	n	%	
Age at conception > 25 years	378	74.1	676	58.3	< 0.001
Pregestational BMI > 25 kg/m^2	200	39.4	128	11.2	< 0.001
Obstetrical failure	109	21.4	304	13.7	< 0.001
History of macrosomia	56	11.0	25	2.2	< 0.001
≥ 3 pregnancies	171	33.6	186	16.0	< 0.001
Family history of diabetes	204	40.0	298	25.7	< 0.001

Table II. *Odds ratio (OR) for GDM for each risk factor analysed — the results of univariate analysis*
Tabela II. *Iloraz szans poszczególnych czynników ryzyka cukrzycy ciążowej — wyniki analizy jednoczynnikowej*

Risk factor	OR	95% CI	p
History of macrosomia	5.60	3.45–9.08	< 0.05
Pregestational BMI > 25 kg/m^2	5.16	3.99–6.65	< 0.05
≥ 3 pregnancies	2.65	2.08–3.37	< 0.05
Age at conception > 25 yrs	2.05	1.63–2.58	< 0.05
Family history of diabetes	1.93	1.55–2.40	< 0.05
Obstetrical failure	1.72	1.31–2.25	< 0.05

95% CI — 95% confidence interval

Table III. *Relative risk (expressed as odds ratio [OR]) of GDM in multivariate analysis*
Tabela III. *Ryzyko względne (wyrażone jako iloraz szans) cukrzycy ciążowej — analiza wieloczynnikowa*

Risk factor	OR	95% CI	p
Pregestational BMI > 25 kg/m^2	4.14	3.17–5.42	< 0.001
History of macrosomia	2.72	1.60–4.65	< 0.001
≥ 3 pregnancies	1.80	1.30–2.49	< 0.001
Family history of diabetes	1.76	1.38–2.24	< 0.001
Age at conception > 25 years	1.34	1.04–1.73	0.023
Obstetrical failure	1.00	0.71–1.42	> 0.05

95% CI — 95% confidence interval

21.6 ± 3.3 kg/m^2 ($p < 0.0001$). In obese patients (BMI ≥ 30 kg/m^2) GDM occurrence was four times higher than in women with normal body weight, and almost twice as high as in overweight subjects (BMI 25–30 kg/m^2). The prevalence of the analysed risk factors in both groups is given in Table I.

Each analysed risk factor was found significantly more often in the subjects with GDM than in those with NGT. Odds ratios for GDM occurrence were calculated for each risk factor. In the absence of a given risk factor the OR equalled 1. In the univariate analysis the most significant risk factor for prediction of GDM occurrence was foetal macrosomia in previous pregnancies, as this increased the risk more than fivefold (OR 5.6) when compared to women who had had children with normal birth weights in previous pregnancies. Excessive body weight before pregnancy was also a strong risk factor (OR 5.16). The results of univariate analysis are presented in Table II.

Multivariate logistic regression analysis demonstrated that the risk of GDM was significantly increased in women with: BMI > 25 kg/m^2, three or more previous pregnancies, a family history of diabetes, > 25 years and a history of macrosomia (Table III).

The sensitivity, specificity and positive and negative predictive values for all the risk factors analysed are presented in Table IV. No one factor of those analysed was sufficiently strong in the recognition of GDM.

Co-existence of the risk factors was analysed in the subjects studied. The distribution of multiple risk factors was differed significantly between the two groups ($p < 0.0005$) (Table V). Of the women with GDM, 12% had no risk factors, while only a quarter of the NGT subjects presented no risk factors.

In order to determine whether a single or combination of risk factors would improve the identification of those with GDM, both multiple logistic regression analysis and linear/square discriminative analysis were undertaken. However, neither model had sufficient predictive power. The use of multiple logistic regression analysis enabled only 31.8% of future GDM cases to be identified (*i.e.* only 31.8% of those subjects for whom the model predicted GDM development actually had GDM according to OGTT results), and for square discriminative analysis the figure was 46.9%, so that by risk factors alone at best only 240 out of 510 women with GDM would have been identified. Concordance of both models with the OGTT results for NGT ranged

Table IV. *Sensitivity, specificity and positive and negative predictive values for each risk factor analysed*
Tabela IV. *Czułość, swoistość, pozytywna i negatywna wartość predykcyjna poszczególnych czynników ryzyka cukrzycy ciążowej*

Risk factor	Sensitivity	Specificity	Positive predictive value	Negative predictive value
History of macrosomia	11.0	97.8	69.1	71.4
Pregestational BMI > 25 kg/m^2	39.2	89.0	61.0	76.9
≥ 3 pregnancies	33.5	84.0	47.9	74.2
Age at conception > 25 years	74.1	41.7	35.9	78.6
Family history of diabetes	40.0	74.3	46.0	73.8
Obstetrical failure	21.4	73.8	26.4	68.1

Table V. *Distribution of risk factors in the groups studied*
Tabela V. *Rozkład czynników ryzyka w badanych grupach*

Study groups	No. of risk factors					
	0	1	2	3	4	5 or 6
GDM* (%)	12.0	22.7	26.7	19.4	12.2	7.1
NGT (%)	25.9	39.1	21.5	9.7	3.0	0.8

*Prevalence distributions in GDM and NGT are significantly different ($p < 0.0001$)

from 84–94%. Thus, while both methods were able to identify those without GDM, neither model could accurately identify even half of the women with GDM according to the OGTT.

Discussion

It has been well established that several genetic and constitutional factors are associated with susceptibility to the development of GDM. Most authors consider older age, being overweight, a family history of diabetes, multiparity, macrosomia in earlier pregnancies and previous GDM or IGT as the best predictors of GDM [1, 2, 5, 16–18].

In our study the subjects with GDM were significantly older and had a greater tendency to obesity than women with NGT. An age over 25 years and excessive body mass before pregnancy has been shown to increase the risk of gestational diabetes by 50–220%. Three quarters of the women with GDM were older than 25 years in comparison with slightly more than half in the non-diabetes group. Diabetic women were more often overweight than non-diabetes subjects: 39.4 *vs.* 11.2% ($p < 0.0005$). An age > 25 years increased the risk of GDM almost twofold (RR 2.05), and BMI > 25 kg/m^2 over fivefold (RR 5.16). These findings are in agreement with the results of many other authors [5, 16–19].

A family history of diabetes is another similarity between GDM and type 2 diabetes. In our study 40% of GDM patients and 20.4% of women with NGT claimed to have a first degree relative with diabetes ($p < 0.05$). Family history of diabetes was a strong risk factor for GDM, as it increased the risk by 90%. Salomon et al. found this factor to increase the risk by 68% [18]. In the light of a number of studies, a family history of diabetes seems to be a reliable predictor of GDM, although it should always be regarded with caution, as some patients may not be aware, for a variety of reasons, of medical conditions which afflict their relatives [20, 21].

Multiparity was found to be a significant risk factor for GDM. In contrast to our findings, the studies by Vamberque, Berkus, Griffin et al. did not find any correlation between parity and diabetes, but the cohorts studied were women with a mild degree of hyperglycaemia (one abnormal value in 100 g OGTT) [16, 22, 23]. Bearing a child of birth weight > 4000 g was also a significant risk factor for GDM. This was also found in the study performed by Ogonowski et al. in a Polish population [5]. Adams et al. reported macrosomia as high as 44% in undiagnosed GDM. Similar findings were published by Nasrat [24, 25]. Other authors have observed an increased frequency of macrosomia in women in whom GDM was not confirmed but who had one abnormal value in diagnostic tests [26, 27].

Although many authors have reported that the factors mentioned in the current study significantly increase the risk of GDM, there is some dispute as to be benefits of universal screening as opposed to screening by specific risk factors [16, 21, 27].

Clearly, while risk factors appear to be more likely to be present in women with GDM than in women without the disease, they are neither sufficiently sensitive nor specific. In our study one risk factor for GDM was found in 88% of the diabetes subjects and in 74.1% of the healthy women. Of all the GDM subjects 12% had no risk factors whatsoever. In the studies in a Polish population risk factors were present in 44.4% to 68.4% of the groups [4, 28]. Other studies show that one or more GDM risk factors may be found in from 20 to 90% of pregnant women [27, 29, 30].

Had the testing for GDM been performed only in the subjects with at least one risk factor, 61 women with GDM would have gone undetected and therefore untreated. Most studies agree that subsequently at least 20 of these women would have experienced an adverse perinatal outcome. Moreover, multivariate regression and square discrimination models failed to create a configuration of risk factors which would significantly increase the probability of GDM occurrence and reduce the number of subjects requiring further testing. Weeks et al. report that they would have missed 43% of GDM cases had they tested only at-risk subjects. In this group over 50% of the subjects needed insulin to control their diabetes [30]. These findings are in agreement with our results and support the argument for testing glucose tolerance in all pregnant women, and not in only those at increased risk of GDM.

Conclusions

Age, obesity, diabetes in the family, parity, macrosomia and perinatal complications have been identified as risk factors for GDM. Nevertheless, a substantial number of women with GDM present with none of these risk factors, and their specificity and sensitivity in the recognition of GDM are very low. We believe that, as no reliable method has been found using risk factor clustering to identify subjects at increased risk of GDM, all pregnant women should be screened for gestational diabetes mellitus.

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