



Impaired fasting glucose as a marker of heterogeneity of gestational diabetes mellitus. A study of 1025 women living in the region of Kuyavia and Pomerania in Poland

Nieprawidłowa glikemia na czczo jako znacznik zróżnicowania cukrzycy ciążowej. Badanie przeprowadzone w populacji 1025 kobiet zamieszkujących Województwo Kujawsko-Pomorskie w Polsce

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Abstract

Introduction: Gestational diabetes mellitus (GDM) is a heterogeneous disease. We hypothesized that fasting hyperglycaemia, defined as impaired fasting glycaemia (IFG), is a marker of metabolic heterogeneity of GDM. The aim of this study was to compare selected metabolic parameters in two groups of women with GDM, one with normal fasting glycaemia (NFG GDM) and another with IFG, to test this hypothesis.

Material and methods: Metabolic parameters of 1025 women with GDM (mean age 29 years): glucose and insulin at 0 OGTT, glucose at 2-h oral glucose tolerance test (OGTT), body mass index before pregnancy, parity, and gestational age at diagnosis of GDM were analyzed. Insulin resistance and β -cell function were evaluated by HOMA indexes (HOMA-IR and HOMA-B) at the diagnosis of GDM.

Results: The IFG GDM group (23%) consisted of isolated IFG (30%), IFG/IGT (60%), and IFG/DM (10%). The NFG GDM group (77%) consisted of isolated IGT (98%) and NFG/DM (2%). Women with IFG GDM were characterized by higher prepregnancy BMI, earlier diagnosis of GDM, higher HOMA-IR ($p < 0.03$), and lower HOMA-B ($p < 0.01$) compared to NFG GDM. In the IFGGDM group, DM was characterized by lower HOMA-B compared with isolated IFG and IFG/IGT. In the NFG GDM group, isolated IGT and DM were characterized by similar HOMA-IR and HOMA-B.

Conclusions: Impaired fasting glucose distinguishes more severe metabolic phenotypes of GDM compared to GDM with normal fasting glucose concentrations. (*Pol J Endocrinol* 2009; 60 (5): 348–352)

Key words: gestational diabetes mellitus, gestational diabetes mellitus — pathophysiology, impaired fasting glycaemia, insulin resistance, β -cell function, HOMA

Streszczenie

Wstęp: Cukrzyca ciążowych (GDM, *gestational diabetes mellitus*) jest chorobą heterogenną. Autorzy przyjęli hipotezę, że hiperglikemia na czczo spełniająca kryterium nieprawidłowej glikemii (IFG, *impaired fasting glycaemia*) może być znacznikiem heterogenności GDM. Celem pracy było porównanie wybranych parametrów metabolicznych w dwóch grupach kobiet z GDM, jednej z prawidłową glikemią na czczo (NFG, *normal fasting glycaemia*) i drugiej z IFG dla sprawdzenia powyższej hipotezy.

Materiał i metody: Porównano parametry metaboliczne 1025 kobiet z GDM (śr.wiek 29 lat): stężenie glukozy i insuliny na czczo, stężenie glukozy w 2-godzinym doustnym teście tolerancji glukozy (OGTT, *oral glucose tolerance test*), wskaźnik masy ciała (BMI, *body mass index*) przed ciążą, ilość przebytych ciąż oraz tydzień rozpoznania GDM. Insulinooporność oraz czynność komórek β trzustki oceniono metodą HOMA (HOMA-IR i HOMA-B) przy rozpoznaniu GDM.

Wyniki: Grupa IFG GDM (23%) składała się z podgrup z izolowaną IFG (30%), IFG/IGT (60%) oraz IFG/DM (10%). Grupa NFG GDM (77%) składała się z podgrup z izolowaną IGT (98%) oraz z NFG/DM (2%). Grupa IFG GDM charakteryzowała się wyższym BMI przed ciążą, wcześniejszym rozpoznaniem GDM, większym wskaźnikiem HOMA-IR ($p < 0,03$) oraz mniejszym wskaźnikiem HOMA-B ($p < 0,01$) w porównaniu z grupą NFG GDM. W grupie IFG GDM podgrupa z DM charakteryzowała się mniejszym wskaźnikiem HOMA-B w porównaniu z izolowaną IFG oraz IFG/IGT. W grupie NFG GDM w podgrupach z izolowaną IGT oraz IGT/DM wskaźniki HOMA-IR oraz HOMA-B nie różniły się istotnie.

Wnioski: Występowanie nieprawidłowej glikemii na czczo u kobiet z GDM wyróżnia niekorzystny metabolicznie fenotyp w porównaniu z kobietami z prawidłową glikemią na czczo. (*Endokrynol Pol* 2009; 60 (5): 348–352)

Słowa kluczowe: cukrzyca ciążowych, cukrzyca ciążowych — patofizjologia, nieprawidłowa glikemia na czczo, insulinooporność, czynność komórek β , HOMA



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Introduction

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. Several studies [1–5] suggest pathophysiological heterogeneity of different categories of carbohydrate metabolism disturbances, which are classified as GDM. Recently Di Cianni et al. [6] reported that a worsening of glucose tolerance in pregnant women was accompanied by the progression of insulin secretory dysfunction and insulin resistance. Metabolic characteristics of impaired fasting glucose (IFG), either as an isolated category, combined with IGT(IFG/IGT), or with DM(IFG/DM) in women with GDM, has not been studied. In non-pregnant women, isolated IFG is a consequence of insulin resistance and beta-cell dysfunction [7, 8]. The isolated IGT is due to inadequate compensatory insulin secretion [8], the combined category IFG/IGT is due to both types of metabolic disorders [7, 8].

We hypothesized that IFG may reflect a distinct, more severe metabolic phenotype characterized by beta-cell dysfunction and/or insulin resistance assessed by HOMA indexes, compared with normal fasting glucose GDM.

To test this hypothesis we sought to compare selected clinical, anthropometrical, and pathophysiological parameters in two groups of women with GDM: one group consisted of isolated IFG combined with IGT(IFG/IGT) or DM(IFG/DM), and the another group consisted of isolated IGT combined with DM(NFG/DM).

Material and methods

A total of 1080 GDM subjects treated at the Regional Centre for Intensive Diabetologic and Obstetric Care at the Dr J Biziel University Hospital in Bydgoszcz between 2002 and 2006 were examined for the study. The diagnosis of GDM was established in accordance with the model used in Poland [9]. Modified World Health Organisation diagnostic criteria for GDM were used [9]. We enrolled only those GDM subjects who had either normal (60 to < 100 mg/dL) or elevated (100 to < 126 mg/dL) fasting plasma glucose, *e.g.* impaired fasting glucose according to modified WHO criteria. The data of subjects who had fasting plasma glucose concentrations ≥ 126 mg/dL were eliminated for the purpose of the present study. The following data were collected for all women: age, prepregnancy BMI, parity, gestational age at GDM diagnosis, insulin at 0 OGTT, and glucose at 0 and 2-h OGTT at the GDM diagnosis.

BMI was estimated by dividing the body weight (in kilograms) by the square of the height (in metres). Insulin resistance and beta-cell function were assessed

using the Homeostasis Model Assessment (HOMA) method. A HOMA value for each subject was calculated from the fasting concentrations of insulin and glucose according to the equations described by Mathews and Hosker [10]: $\text{HOMA-IR} = \text{insulin (uU/mL)} \times \text{glucose (mmol/L)} / 22.5$.

$$\text{HOMA-B\%} = (20 \times \text{insulin (uU/mL)}) / (\text{glucose (mmol/L)} - 3.5)$$

Blood samples for insulin and glucose measurements were drawn from subjects in a fasting state. Serum glucose was determined in the venous blood by the glucose oxidase method on an Olympus AU 400 analyzer (reference values 3.31–5.51 mmol/L) and the serum insulin concentration in the venous blood using the immunoenzymatic method (MEIA) on an AxSYM analyzer (reference values 2–25 uU/mL).

Statistical analysis

Data were analyzed using Statistica software for Windows by StatSoft. The Shapiro-Wilk test was used to determine whether each variable had a normal distribution. These variables were expressed as means \pm SD. The Kruskal-Wallis test and the U Mann-Whitney test were used to compare selected groups. A value < 0.05 was defined as significant.

Results

A total of 1025 women with GDM were divided into two main groups based on the fasting plasma glucose concentration according to the WHO modified criteria used in Poland: one group ($n = 789$ –77%) of subjects with normal fasting glucose ($60 \leq 100$ mg/dL) — the normal fasting glucose GDM (NFG GDM) group, and a second group ($n = 236$ –23%) with impaired fasting glucose ($100 \leq 126$ mg/dL) — the impaired fasting glucose GDM (IFG GDM) group.

Compared with NFG GDM, the IFG GDM group was characterized by a higher prepregnancy BMI, higher HOMA-IR, and a lower HOMA-B ($p < 0.01$) (Table I). The GDM was diagnosed earlier in the IFG GDM group compared to the NFG GDM group (Table I).

The IFGGDM group was further divided into three subgroups based on 2-hour plasma glucose concentration during the standard 75-g OGTT according to modified WHO criteria: isolated IFG (2-h glucose < 140 mg/dL), IFG/IGT (2-h glucose between 140 and 200 mg/dL), and IFG/DM (2-h glucose ≥ 200 mg/dL). Data were compared to each other, isolated IFG, IFG/IGT, and IFG/DM. Both indexes, HOMA-IR and the HOMA-B, were slightly (non-significantly) higher in IFG IGT compared with isolated IFG.

The IFG/DM subgroup characterized significantly lower HOMA-B compared with the other subgroups

Table I. Metabolic parameters in the two groups of women with GDM with normal (NFGGDM) and impaired (IFG GDM) fasting glycaemia

Tabela I. Parametry metaboliczne w dwóch grupach GDM z prawidłową (NFG GDM) i nieprawidłową (IFG GDM) glikemią na czczo

Parameter	NFG GDM N = 789			IFG GDM N = 236			p
	M	Me	SD	M	Me	SD	
Age (years)	29.62	29.00	5.03	29.87	30.00	5.07	0.5005
Parity	1.96	2.00	1.18	2.08	2.00	1.18	0.1626
Pregnancy index at diagnose	28.73	29.00	4.28	26.73	28.00	6.45	< 0.0001
BMI [kg/m ²]	22.99	21.21	4.06	25.81	24.09	6.01	< 0.0001
Insulin [μ U/L]	13.30	10.70	12.16	14.80	12.70	9.43	0.1565
HOMA-IR	2.65	1.98	3.10	3.25	2.71	2.28	0.0363
HOMA-B	539.29	295.36	907.34	322.45	184.42	712.91	0.0122
Glucose at 0 OGTT [mg/dL]	84.06	85.00	8.60	108.77	106.00	9.79	< 0.0001
Glucose at 2-h OGTT [mg/dL]	155.99	152.00	18.82	155.55	152.00	34.50	0.7985

BMI — body mass index; OGTT — oral glucose tolerance test

Table II. Metabolic parameters in three subgroups of IFG GDM women according to glycaemia at 2-h OGTT

Tabela II. Parametry metaboliczne w trzech podgrupach kobiet IFG GDM w zależności od glikemii w 2-godzinnym OGTT

Parameter	IFG/NGT N = 70			IFG/IGT N = 141			IFG/DM N = 25			p
	M	Me	SD	M	Me	SD	M	Me	SD	
Age (years)	28.73	28.00	4.46	30.06	30.00	4.93	32.04	31.00	6.67	0.0802
Parity	1.94	2.00	0.96	2.10	2.00	1.20	2.40	2.00	1.55	0.7061
Diagnosis of GDM (week)	25.81	27.50	7.20	27.09	28.00	6.21	27.20	28.00	5.41	0.7980
BMI [kg/m ²]	25.67	23.34	6.86	25.57	24.09	5.49	27.58	28.03	6.34	0.3094
Insulin [μ U/mL]	13.74	12.55	6.64	15.38	12.75	10.74	13.98	13.00	6.68	0.9767
HOMA-IR	2.93	2.64	1.65	3.35	2.69	2.56	3.48	3.49	1.43	0.5235
HOMA-B	257.70	228.99	156.22	366.12	182.48	859.56	135.22	97.56	127.19	0.0060 ¹⁻³ 0.0067 ²⁻³
Glucose at 0 OGTT [mg/dL]	106.41	104.5	9.08	108.63	106.00	8.81	116.50	112.50	13.34	0.0187 ¹⁻² 0.0002 ¹⁻³ 0.0039 ²⁻³
Glucose at 2-h OGTT [mg/dL]	117.64	120.00	15.41	162.95	160.00	18.78	218.72	214.00	19.34	< 0.0001 ¹⁻² < 0.0001 ¹⁻³ < 0.0001 ²⁻³

¹IFG/NGT; ²IFG/IGT; ³IFG/DM; GDM — gestational diabetes mellitus; BMI — body mass index; OGTT — oral glucose tolerance test

($p < 0.001$). In the above selected subgroups of carbohydrate metabolism disturbances, fasting glucose concentrations increased progressively in successive groups. Table II presents the results of the comparison of parameters in the above-named subgroups.

The NFG GDM group was further divided into two subgroups depending on 2-h glucose in 75-g OGTT test according to WHO modified criteria [9]. Women with isolated IGT and with DM(NFG/DM) were placed into

one category. In the NFGGDM subpopulation, 775 women (98%) had isolated IGT, and 141 women (2%) had DM (NFG DM). The isolated IGT characterized higher BMI compared to NFG/DM. The categories did not differ from one another in HOMA-IR and HOMA-B. There was a trend towards a higher (non-significantly) value of HOMA-B in the NFG DM compared to isolated IGT. Table III presents the division into groups, along with their metabolic parameters.

Table III. Metabolic parameters of NFG GDM women in two subgroups according to 2-h OGTT glycaemia

Tabela III. Parametry metaboliczne w dwóch podgrupach kobiet z NFG GDM w zależności od glikemii w 2-godzinnyim OGTT

Parameter	NFG/IGT N=775			NFG/DM N=14			p
	M	Me	SD	M	Me	SD	
Age (years)	29.62	29.00	5.02	29.79	30.50	5.47	0.7782
Parity	1.95	2.00	1.16	2.38	2.00	2.26	0.9234
Diagnosis of GDM (week)	28.73	29.00	4.29	28.64	29.00	3.97	0.8913
BMI [kg/m ²]	23.04	22.23	4.06	20.39	19.48	3.14	0.0065
Insulin [μU/L]	13.32	10.70	12.19	11.67	7.50	8.73	0.5716
HOMA-IR	2.65	1.98	3.11	2.36	2.00	1.54	0.9841
HOMA-B	538.89	295.36	910.32	580.59	381.03	585.41	0.7139
Glucose at 0 OGTT [mg/dL]	84.07	85.00	8.61	83.21	83.50	8.40	0.7417
Glucose at 2-h OGTT [mg/dL]	154.92	151.00	17.05	215.29	206.50	18.25	< 0.0001

GDM — gestational diabetes mellitus; BMI — body mass index; OGTT — oral glucose tolerance test

Discussion

In the whole population of GDM women in the region of Kuyavia and Pomerania in Poland, women with normal fasting glucose (NFG GDM) were the decisive majority (77%). In the remaining percentage (23%) of women, impaired fasting glucose (IFG) occurred as an isolated category and as a combined category with IGT(IFG/IGT) or with DM(IFG/DM) according to 2-h post-challenge glucose concentrations (IFG GDM group). These two groups of women with GDM presented different metabolic phenotypes.

In comparison with NFG GDM, IFG GDM women were characterized by a higher prepregnancy body mass index (BMI), higher insulin resistance (HOMA-R), and lower beta-cell function (HOMA-B) at the diagnosis of GDM.

In the latter group, GDM was diagnosed earlier than in the NFG GDM group.

It seems that the earlier occurrence of abnormalities of carbohydrate metabolism in the IFG GDM group could be the result of higher insulin resistance and lower beta-cell function compared with NFG GDM, rather than the progression of NFG GDM. In the IFG GDM group, the most frequent abnormality of glucose regulation was IFG/IGT (60%); less frequent was isolated IFG (30%); and the least frequent was IFG/DM (10%).

The results of many studies have shown a similarity of pathophysiological mechanisms in GDM and type 2 diabetes [11–15]. In the non-pregnant population, isolated IFG is due to reduced [7] or progressive decline hepatic insulin sensitivity [8] combined with impairments in basal insulin secretion and first-phase insulin release [7, 8]. The IFG/IGT is additionally characterized

by a progressive decline of insulin secretion secondary to the low insulin sensitivity [8].

The results of the current study suggest beta-cell dysfunction rather than insulin resistance as the main cause of worsening glucose tolerance status in both groups of women with GDM, irrespective of fasting glucose concentrations. The more pronounced defect of insulin secretion assessed by HOMA-B in the IFG GDM group compared to the NFG GDM group is in agreement with the above-cited observations in non-pregnant women [7, 8].

Our results show that the IFG/IGT subgroup of women with GDM is also characterized by a slightly (non-significantly) higher insulin secretion compared to isolated IFG, and that the lowest insulin secretion is characterized by the DM(IFG/DM) subgroup compared to isolated IFG and IFG/IGT.

The isolated IGT and NFG/DM is characterized by a similar HOMA index value of insulin resistance and insulin secretion. A similar finding was shown by Festa et al. [16] in non-pregnant women. These authors observed slightly increased insulin secretion assessed by HOMA-B in isolated IGT and DM(NFG/DM), and decreased HOMA-B when DM was diagnosed according to fasting glucose or both fasting and post-challenge glucose criteria.

An interesting finding in our study is the higher insulin secretion in the IFG/IGT subgroup of women with GDM compared to isolated IFG. A recently published study shows similar findings referring to the first phase of insulin secretion in the non-pregnant population [8]. Therefore, it can be suggested that IFG/IGT is a specific category of glucose dysregulation, both in the non-pregnant population and in women with GDM. Currently, IFG/IGT is classified together with isolated IGT in one group.

The results of the present study and studies of other authors [7, 8, 16] suggest similar trends in the pathophysiology of isolated IFG, IFG/IG, isolated IGT, and IGT/DM assessed by HOMA-IR and HOMA-B.

There are several studies on the issues of the metabolic phenotype of carbohydrate metabolism disturbances in pregnant women [1, 3–5]. The observations of Ryan et al. [5] concerning the metabolic characteristics of GDM women with fasting hyperglycaemia show a higher insulin resistance in comparison with pregnant women without carbohydrate metabolism disturbances examined in late pregnancy. Kjos et al. [1] reported higher prepregnancy BMI in the population of women with GDM and with fasting hyperglycaemia in comparison with GDM women with normal fasting glucose.

The mechanisms of fasting hyperglycaemia in GDM and their relation to obesity are similar to those in type 2 diabetes [12]. They involve a combination of insulin resistance, a decrease in suppression of liver glucose production [12], and a decrease in insulin secretion for the level to insulin resistance [17, 18].

Previous studies [3, 4, 13] report the progressive increase of insulin resistance as the main cause of worsening glucose tolerance from NGT through IGT to DM.

The inconformity of the results of our current studies with the above-cited studies could be partly explained by the specificity of the HOMA method, which is based on fasting insulin and glucose, and in fact evaluates basal insulin resistance and basal insulin secretion [19, 20].

Overall, our results demonstrate the dominant occurrence of GDM with normal fasting glucose and the much less frequent occurrence of GDM with impaired fasting glucose. The latter form of GDM represents a more severe metabolic phenotype of women with GDM. This study suggests that the two groups of women with GDM may have different aetiological and pathophysiological origins, which in turn may have implications for the treatment of GDM.

It seems that women with GDM and impaired fasting glucose require more frequent control of carbohydrate metabolism post partum, especially those with IFG/DM.

Conclusions

1. Isolated IFG, IFG/IGT, and IFG/DM, as a group of women with GDM, is characterized by earlier diagnosis of GDM, higher prepregnancy BMI, higher insulin resistance, and lower beta-cell function compared to GDM with normal fasting glucose.

2. The GDM with impaired fasting glucose consists of three subgroups: isolated IFG, IFG/IGT, and IFG/DM, with slightly higher beta-cell function in IFG/IGT compared to isolated IFG, and lower beta-cell function in DM compared to other subgroups.
3. The GDM with normal fasting glucose consists of two subgroups: NFG/IGT and NFG/DM, with similar beta-cell function and similar insulin resistance.

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