ONLINE FIRST

ISSN: 0423-104X

e-ISSN: 2299-8306

High prevalence of early (1st trimester) gestational diabetes mellitus in Polish women is accompanied by insulin resistance similar to women with polycystic ovary syndrome (PCOS)

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DOI: 10.5603/EP.a2021.0095

Article type: Original paper

Submitted: 2021-08-04

Accepted: 2021-09-20

Published online: 2021-11-04

High prevalence of early (1st trimester) gestational diabetes mellitus in Polish women accompanied by marked insulin resistance — comparison to PCOS model

Running headline: Marked 1st trimester insulin resistance and high prevalence of early GDM

10.5603/EP.a2021.0095

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Abstract

Introduction: Both pregnancy and polycystic ovary syndrome (PCOS) constitute insulin-resistant states that are associated with an increased prevalence of glucose intolerance. Some women demonstrate significant insulin resistance (IR) and develop gestational diabetes (GDM) even in the 1st trimester. We compared surrogate IR indices in 1st-trimester pregnant women and in women with PCOS (Rotterdam consensus criteria).

Material and methods: We performed a 75-g oral glucose tolerance test (OGTT) with insulin measurements in 106 healthy 1st-trimester pregnant women at 9.9 ± 2.6 weeks of gestation and in 418 women with PCOS. We assessed IR (HOMA-IR, QUICKI, Matsuda, Belfiore, and Stumvoll indices) as well as the prevalence of GDM according to the IADPSG and World Health Organization (WHO) (1999) criteria.

Results: Despite having a slightly lower BMI ($p = 0.027$), pregnant women had either similar (QUICKI, Belfiore index, $Stumvoll_{0\text{-}120\ min}$) or greater IR than women with PCOS (e.g. HOMA-IR 3.85 ± 6.11 vs. 2.64 ± 2.04, $p = 0.002$), while only the Matsuda index demonstrated less IR in pregnant women ($p = 0.003$). The correlation between IR indices in pregnant women showed marked variability, ranging from $r = 0.334$ (HOMA-IR vs. Belfiore index) to $r = –1.0$ (HOMA-IR vs. QUICKI, $p < 0.001$). This was accompanied by a high prevalence of GDM (14.2% and 9.4%, IADPSG and WHO criteria, respectively). Women with GDM diagnosed according to IADPSG criteria demonstrated greater IR than pregnant women without GDM. In women with GDM diagnosed according to WHO (1999) criteria these differences were visible only for OGTT-derived IR indices (Belfiore, Matsuda, and $Stumvoll_{0\text{-}120}$ index).

Conclusions: Depending on the choice of IR indices, healthy 1st-trimester pregnant women demonstrate either similar or greater IR than women with PCOS, and this is accompanied by a high prevalence of early GDM. It remains to be established whether GDM screening should be performed in the 1st trimester.

Key words: gestational diabetes mellitus; GDM; insulin resistance; pregnancy; PCOS; polycystic ovary syndrome; HOMA-IR; QUICKI; Belfiore index; Matsuda index; Stumvoll index

Introduction

Gestational diabetes (GDM) is one the most common disorders in pregnancy, associated with adverse pregnancy outcomes, but diagnostic criteria vary from different countries and regions [1]. Although standard screening by means of an oral glucose tolerance test (OGTT) is usually performed between 24 and 28 weeks [2], the choice of such timing is rather arbitrary, given that a significant number of women may develop GDM at earlier stages of pregnancy [3]. There is, however, no doubt that both GDM [4] and polycystic ovary syndrome (PCOS) [5] represent insulin-resistant states, where PCOS is associated with a high prevalence of glucose intolerance [6]. There are endocrine recommendations that women with PCOS should undergo OGTT in order to quantify the risk of glucose intolerance and type 2 diabetes [7]. Although pregnancy *per se* constitutes an insulin-resistant state [8], it is not clear at what stage of pregnancy IR approaches the magnitude observed in PCOS, where universal screening for glucose intolerance is often recommended. Although it is universally recognised that the euglycaemic hyperinsulinaemic clamp method [9] constitutes the "gold standard" for IR assessment, this technique is too laborious and complicated for use outside research settings. Hence, we have endeavoured to assess several surrogate IR parameters in healthy 1st-trimester pregnant women and compare these data to women diagnosed with PCOS. In addition, we have assessed the prevalence of GDM in the 1st trimester of pregnancy according to the more recent International Association of Diabetes and Pregnancy Study Groups (IADSPG) [10] and older WHO (1999) criteria [11, 12].

Material and methods

The study included 106 healthy pregnant women at 9.9 ± 2.6 weeks of gestation (mean ± SD), age 30.21 ± 5.7 years, and body mass index (BMI) 24.93 ± 5.43 kg/m^2 and 418 women of age 24.61 ± 6.58 years (mean ± SD) and BMI 26.53 ± 6.83 kg/m^2 who underwent investigations for irregular periods, hirsutism, or biochemical hyperandrogenism in the Polish Mother's Memorial Hospital Research Institute in Lodz, Poland. In the latter group a diagnosis of PCOS was established according to the Rotterdam consensus criteria [13]. All patients (i.e. pregnant women and women with PCOS) underwent glucose and insulin measurements during 75 g OGTT, where measurements were performed at 0, 60, and 120 minutes. In all patients we also assessed

concentrations of thyroid-stimulating hormone (TSH), free thyroxine (FT4), and free triiodothyronine (T3).

All PCOS patients were subjected to an identical investigation protocol that included hormonal assessment (prolactin, total testosterone, androstenedione, DHEAS, 17-hydroxy-progesterone, cortisol after 1 mg overnight dexamethasone suppression test, fasting blood lipids, and intravaginal pelvic ultrasound). If clinically indicated, additional tests (e.g. IGF-I, growth hormone during OGTT, 17-hydroxy-progesterone measurements after 250 µg of intravenous Synacthen, 24-hour prolactin secretion profiles) were performed. All investigations were performed in the early follicular phase of either a spontaneous cycle or after induction of menstrual bleeding with a progestogen (usually dydrogesterone [Duphaston®] 10 mg twice a day for ten days).

Insulin resistance (Belfiore) index (IRI) was calculated from changes of glycaemia and insulinaemia during a 75 g oral glucose tolerance test (OGTT) according to the method described by Belfiore et al. [14], where IRI (Belfiore) was calculated through the following formula:

$$ISI_{(Gly)} = 2/[1/(INSp \times GLYp)] + 1,$$

where INSp and GLYp are the measured insulin and glycaemic areas. In normal subjects ISI(gly) are always around 1, with maximal variations between 0 and 2. This method is based on changes of glycaemia and insulinaemia during OGTT.

The HOMA-IR index [15] was calculated according to the formula:

$$HOMA\text{-}IR = [fasting\ glucose]\ (mmol/L) \times [fasting\ insulin]\ (\mu U/mL)/22.5).$$

QUICKI index [16] was calculated according to the formula:

$$QUICKI = 1/[\log(I_0) + \log(G_0)],$$

where I_0 denotes fasting insulin, and glucose [G_0 denotes fasting glucose].

The Matsuda index [17] was calculated according to formula:

$$ISI_{Matsuda} = 10^4/(G_0 \times I_0 \times G_{mean} \times I_{mean})^{1/2},$$

where: I_0, fasting plasma insulin concentration (IU/l); G_0, fasting plasma glucose concentration (mg/dL); G_{mean}, mean plasma glucose concentration during OGTT (mg/dl); and I_{mean}, mean plasma insulin concentration during OGTT (U/L).

Because there are several formulae used to calculate the Stumvoll index [18], we chose the two most commonly used formulae:

$$\textbf{Stumvoll}_{0,\ 120}\ \textbf{index} = 0.156 - 0.0000459 \times I_{120}\ (pmol/L) - 0.000321 \times I_0\ (pmol/L) - 0.00541 \times G_{120}\ (mmol/L),$$

where: I_0, fasting insulin (pmol/L); I_{120}, insulin concentration at 120 min of OGTT (pmol/L); and G_{120}, glucose concentrations at 120 min of OGTT (mmol/L).

Because inclusion of parameters such as age and BMI, in our opinion, could enrich the analysed models, based almost exclusively on glucose and insulin, we decided to include in our analysis also a formula for the Stumvoll index that incorporates demographic data, such as age and BMI:

$$\textbf{Stumvoll}_{demographics} = 0.222 - 0.00333 \times BMI - 0.0000779 \times I_{120} - 0.000422 \times AGE,$$

where: I_{120} denotes insulin concentration at 120 min of OGTT (pmol/L).

Patients, with PCOS, who were diagnosed with type 2 diabetes according to high fasting blood glucose criterion (glucose concentrations > 7.0 mmol/L) were not included into the study, as OGTT is not indicated in such circumstances.

Description of statistical methods: Shapiro-Wilk and D'Agostino-Pearson tests were used to test the normality of distributions. The t-Student and Mann-Whitney methods were used to compare parameters (after applying the Fisher-Snedecor test). A variance analysis method (ANOVA) was used to compare multiple groups. $P < 0.05$ was taken as statistically significant.

Ethics

The study was approved by the Ethics Committee of the Polish Mother's Memorial Hospital — Research Institute, decision no. 78/2017.

Results

A comparison of demographic characteristics and IR indices between healthy 1st-trimester pregnant women (n = 106) and our PCOS cohort (n = 418) is presented in Table 1, while details of their IR indices percentile spread are presented in Table 2. The pregnant women were older than women with PCOS (30.21 ± 5.71 years vs. 24.61 ± 6.58 years, $p < 0.001$) but had lower BMI (24.93 ± 5.43 kg/m^2 vs. 26.53 ± 6.83 kg/m^2, $p = 0.027$).

The results of the correlation analysis between IR indices in pregnant women are presented in Table 3. There was a highly significant correlation between all IR indices

($p < 0.001$), but there were marked differences in coefficients of correlations, denoting that several women classified as insulin resistant according to one IR index (i.e. either above 75^{th} or 90^{th} percentile) might be classified as not insulin resistant according a different IR index.

Application of the IADPSG GDM criteria revealed that 15 women (15/106, i.e. 14.2%) fulfilled criteria for GDM, while 10 women (9.4%) fulfilled WHO (1999) GDM criteria. Analysis of IR indices in women with GDM and without GDM is presented in Table 4. In women diagnosed with PCOS impaired fasting glucose (IFG) was present in 4.06% (17/418), while impaired glucose tolerance (IGT) was present in 8.85% (37/418) of the investigated subjects. Women with GDM_{IADPSG} were more insulin resistant according to all IR indices with the exception of $Stumvoll_{demographics}$, while women diagnosed with GDM according to WHO (1999) criteria were more insulin resistant only when OGTT-derived IR indices were taken into account, i.e. the IRI (Belfiore), Matsuda, and $Stumvoll_{0\text{-}120}$ indices.

Discussion

In our study we have demonstrated a high prevalence of early GDM, i.e. in the 1^{st} trimester of pregnancy, accompanied by marked insulin resistance, which was similar or even higher than in our PCOS cohort, depending on the IR indices employed. Such a situation occurred despite the absence of major obesity, where the average BMI of 24.93 ± 5.43 kg/m^2 was significantly lower than in women with PCOS (26.53 ± 6.83 kg/m^2, $p = 0.027$). The prevalence of early GDM was higher in our cohort, when IADPSG criteria were employed, despite well described reduction in fasting plasma glucose in the 1^{st} trimester in pregnancy [19]. The above-mentioned prevalence of early GDM, based on the OGTT-derived criteria, was even higher than in a 1^{st}-trimester Indian cohort (24 out of 298 women, i.e. 8.05%) [20], although a prevalence similar to our data (16.3%) was also reported [21].

In our study we have assessed several surrogate markers of IR indices in pregnant women in the first trimester of pregnancy. It is not clear whether insulin resistance indices derived in the first trimester from fasting values (such as HOMA-IR or QUICKI) have a predictive role for GDM, with some studies showing some benefit [e.g. 22, 23] and others not [e.g. 24]. It must be appreciated, however, that fasting

insulin resistance indices provide only a partial estimate of body insulin sensitivity, because they mainly reflect changes in hepatic insulin sensitivity [25, 26], while it is known that approximately 80% of insulin-mediated glucose disposal occurs in the periphery in both healthy and diabetic conditions [27]. Hence, OGTT-derived IR indices, such as the Belfiore, Matsuda, or Stumvoll index, provide additional information on peripheral insulin resistance that may differ from hepatic insulin sensitivity. Indeed, some authors [20] suggest that values of the Matsuda index below 5.5 during the 1st trimester of pregnancy were predictive for future development of GDM with 71% sensitivity and 62.5% specificity. It should be noted that the mean value of the Matsuda index (5.0328) was similar in our pregnant GDM cohort diagnosed according to the IADPSG criteria.

In our previous study [28], we reported a significant but rather moderate correlation between fasting and OGTT-derived IR indices in women with PCOS, and now we have also demonstrated the same phenomenon for 1st-trimester pregnant women (Table 3). Hence, in our opinion, with the multitude of mathematical models, there is no universal “gold standard” for the assessment of insulin sensitivity derived from surrogate markers of insulin resistance. In such circumstances caution is required for a predictive value of any surrogate IR index for future development of GDM.

In our study, however, we did not attempt to determine any predictive values for surrogate IR indices, but we did attempt to quantify insulin sensitivity in the first trimester healthy pregnant women. Our study clearly demonstrates that in the first trimester, even in women with a normal mean BMI, there is already considerable insulin resistance, similar or even higher than in women with polycystic ovary syndrome. Furthermore, our PCOS cohort represented hospitalised patients, i.e. those likely to have more pronounced symptoms (and also likely to have more IR) than women with milder, community-based PCOS, who do not undergo any detailed hormonal assessment. The Matsuda index represented the only exception, although it should be noted that in the original paper by Matsuda and DeFronzo [17] glucose and insulin were measured during OGTT at 30-minute intervals, while in our case a simplified formula (i.e. timing at 0, 60, and 120 minutes) was employed.

Polycystic ovary syndrome is widely recognised for an increased prevalence of pre-diabetic states (i.e. impaired fasting glucose [IFG] and impaired glucose tolerance

[IGT]), which was present in 4.06% (17/418) and 8.85% (37/418), respectively, in our PCOS cohort. A similar prevalence of IGT (9.4%) was noted in Czech women with PCOS [29], i.e. in a population that is in ethnic terms very similar to Polish, although notably there was a much higher prevalence of IFG (12.3%). In pregnancy, each case of IFG would be classified as GDM according to IADPSG criteria, while all cases of IGT would be classified as GDM according to WHO (1999) criteria. Hence, it is not surprising that marked insulin resistance in our 1st-trimester cohort was reflected in a high prevalence of early GDM. In our opinion, these observations should prompt reassessment of whether formal OGTT should be performed earlier in pregnancy.

Pregnancy constitutes a diabetogenic state characterised by a progressive decline in insulin sensitivity, reaching its nadir in the 3rd trimester [30, 31]. Despite this, the rationale for early screening for GDM remains debatable. This is because data from Italy [32] and China [33] demonstrated that at least 50% of women with raised 1st-trimester fasting glucose (i.e. above 5.1 mmol/L and up to 6.9 mmol/L) have no GDM after 24 weeks of gestation. It should be noted, however, that the IADPSG recommendation lowered the fasting glucose threshold to diagnose GDM in comparison to previous (1999) WHO criteria, but later the IADPSG did not recommend the application of these criteria in the 1st trimester, thus replacing the formal recommendation with sort of statement of intent, i.e. *Normative data regarding early pregnancy glycaemia and consequences of its detection and treatment are urgently required and should be a priority for future research* [34].

Yet, there are data showing that early GDM is clearly associated with worse pregnancy outcomes [35.36], with possible benefits of early intervention [37]. Indeed, Immanuel and Simmons [38], based on the data from 13 cohort studies, concluded that early-onset GDM is associated with increased perinatal mortality (relative risk [RR]: 3.58 [1.91, 6.71]) and neonatal hypoglycaemia (RR: 1.61 [1.02, 255]). Hence, in our opinion, the bulk of evidence supports earlier screening for GDM, although there is some debate as to whether screening should be selective or universal [39]. Liu et al. [40] demonstrated that neonates of mothers with early GDM (diagnosed between 18 and 20 weeks of gestation, with a prevalence of 21.5%, i.e. in 124 out of 576 women) were at a higher risk of being large for gestational age (odds ratio [OR]: 3.665; 95% CI: 1.006–11.91) and were more prone to neonatal hyperinsulinemia (OR: 3.652; 95% CI: 1.152–

10.533). On the other hand, Hong et al. [41] reported no benefit of early screening in terms of the rate of Caesarean delivery, pre-eclampsia, or macrosomia. In a recent study by Nakashini et al. [42] the authors reported that 47.3% (69/146) of women with GDM (IADPSG criteria before 20 weeks of gestation) had subsequently normal 2nd OGTT at 24–28 weeks, predominantly due to a decline in fasting glucose levels. On the strength of that, the authors generally advised against early GDM screening.

In view of our data demonstrating significant IR already in the first trimester of pregnancy, such an approach is highly debatable. However, we agree that OGTT in the earlier stages in pregnancy is fraught with the possibility of “false positive” GDM diagnosis, but 50% of these women had an abnormal 2nd OGTT (i.e. they also had “standard” GDM) and were found to have higher frequency of pre-term birth and a clear trend towards greater prevalence of macrosomia (20% vs. 8.75%) [42]. In general terms, no harm can be done if women, even if subsequently found to have a “false positive” OGTT, are advised to follow a more healthy diet and pay more attention to the amount and glycaemic index of their food. One cannot also fully rule out the possibility that women with an abnormal early OGTT may change their eating habits, which in turn might influence their 2nd OGTT, i.e. increasing the likelihood of a normal OGTT result. From a doctor’s perspective, we cannot envisage the situation in which we see an abnormal OGTT result and fail to recommend at least some healthy dietary changes. Indeed, not doing so might even be considered unethical. Our personal experience also taught us that women in pregnancy are generally more determined to implement (at least temporarily) changes to their diet, in comparison to non-pregnant subjects with unhealthy eating habits. Indeed, our impression is supported by research data [43].

The main limitation of study is related to the fact that women from our pregnant cohort were not followed throughout the entire pregnancy because they were later managed by several different practitioners. Also, there was no perfect matching between our pregnant and PCOS cohorts, but in our opinion this drawback is compensated by the fact that women with PCOS had higher BMI, which, if anything, should render them more insulin resistant.

In summary, in our study we have demonstrated that healthy women in the 1st trimester of pregnancy already have significant insulin resistance, similar to or even greater than women with polycystic ovary syndrome. This is accompanied by high

prevalence of early GDM, according to both the more recent (IADPSG) and older WHO (1999) criteria. In our opinion, our data point to the conclusion that there is a need for a reappraisal of the value of earlier screening for gestational diabetes mellitus.

Acknowledgements

The study was supported by statutory funds from The Medical University of Lodz and Polish Mother's Memorial Hospital Research Institute

Authors' information

The study has been accepted for presentation as an audio-poster during 23rd European Congress of Endocrinology, Prague, 22-26 May 2021.

Conflict of interests

The authors declare that they have no competing interests.

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Table 1. Comparison of demographic characteristics and IR indices between healthy 1st-trimester pregnant women and a cohort with polycystic ovary syndrome (PCOS)

	Pregnant 1st trimester (n = 106)*			**PCOS (n = 418)**			**p**
	mean	**SD**	**SEM**	**mean**	**SD**	**SEM**	
AGE	*30.21*	*5.71*	*0.53*	*24.61*	*6.58*	*0.32*	*< 0.001*
BMI	*24.93*	*5.43*	*0.53*	*26.53*	*6.83*	*0.34*	*0.027*
HOMA	*3.85*	*6.11*	*0.62*	*2.64*	*2.04*	*0.11*	*0.002*
$IRI_{Belfiore}$	1.14	1.09	0.12	1.19	0.42	0.023	0.522

QUICKI	0.348	0.048	0.005	0.344	0.034	0.002	0.336
Matsuda	*9.19*	*9.61*	*1.05*	*6.88*	*5.12*	*0.28*	*0.003*
$Stumvoll_{0,\ 120}$	0.069	0.079	0.008	0.075	0.046	0.003	0.358
$Stumvoll_{Demographics}$	*0.105*	*0.045*	*0.005*	*0.085*	*0.058*	*0.003*	*0.003*

Mann-Whitney U-test. Variables with significant statistical differences are marked in italics

Table 2. Characteristics of insulin resistance indices in healthy 1st-trimester pregnant women (n = 106)

Percentiles	HOMA-IR	95% CI	$IRI_{Belfiore}$	95% CI	QUICKI	95% CI	Matsuda	95% CI	$Stumvoll_{0,120}$	95% CI	$Stumvoll_{Demographics}$	95% CI
2.5	0.49		0.39		0.434		38.08		-0.206		-0.0012	
5	0.58	0.34–0.80	0.44	0.25–0.51	0.421	0.477–0.398	28.26	18.99–56.03	-0.099	-0.245–-0.028	0.006	-0.016–0.049
10	0.81	0.58–0.93	0.51	0.41–0.60	0.397	0.422–0.388	19.00	13.58–28.71	-0.027	-0.128–0.035	0.049	0.004–0.058
25	1.10	0.94–1.23	0.74	0.59–0.88	0.377	0.387–0.371	10.78	8.89–13.92	0.058	0.033–0.077	0.089	0.055–0.098
75	3.43	2.65–4.22	1.31	1.19–1.41	0.318	0.3299–0.309	3.54	2.47–4.83	0.112	0.104–0.119	0.132	0.126–0.139
90	6.23	4.22–19.92	1.63	1.38–1.72	0.294	0.309–0.2560	1.79	1.36–2.58	0.129	0.119–0.141	0.146	0.139–0.191
95	18.78	6.29–29.28	1.71	1.61–9.62	0.258	0.293–0.245	1.40	0.685–1.79	0.138	0.129–0.146	0.185	0.147–0.211
97.5	28.97		1.74		0.246		0.96		0.143		0.203	

Table 3. Correlation between insulin resistance indices in the group of healthy 1st-trimester pregnant women (n = 106)

	$IRI_{Belfiore}$	**QUICKI**	**Matsuda**	**$Stumvoll_{0, 120}$**	**$Stumvoll_{Demographics}$**
HOMA	0.334	-1	-0.820	-0.701	-0.394
$IRI_{Belfiore}$	-	-0.334	-0.763	-0.745	-0.557
QUICKI	-	-	0.820	0.701	0.394
Matsuda	-	-	-	0.938	0.605
$Stumvoll_{0, 120}$	-	-	-	-	0.598

Table 4. Comparison of insulin resistance indices between healthy 1st-trimester pregnant women without GDM and women who fulfilled IADPSG GDM criteria (n = 15) and those who fulfilled WHO GDM criteria

	Pregnant 1st trimester GDM-free (n = 91)				**GDM (IADPSG) (n = 15)**				**GDM (WHO) (n = 10)**				**Pregnant 1st trimester GDM-free vs. GDM_IADPSG**	**Pregnant 1st trimester GDM-free vs. GDM_WHO**
	Mean	**Median**	**SD**	**SEM**	**Mean**	**Median**	**SD**	**SEM**	**Mean**	**Median**	**SD**	**SEM**	**p**	**p**
Age	30.21	30	5.71	0.53	31.86	31.00	6.19	1.60	28.10	27	3.51	1.11	0.4818	0.1425
BMI	24.93	23.67	5.43	0.53	26.56	25.94	5.36	1.43	26.97	28.78	5.96	1.88	0.2129	0.2621
HOMA	3.86	1.94	6.115	0.62	6.38	2.46	9.20	2.55	5.511	2.29	9.02	3.01	*0.0367*	0.3627
$IRI_{Belfiore}$	1.14	1.01	1.09	0.13	1.318	1.36	0.31	0.09	1.448	1.53	0.26	0.08	*0.0034*	*0.0005*
QUICKI	0.348	0.345	0.048	0.005	0.324	0.333	0.045	0.012	0.336	0.337	0.051	0.017	*0.0366*	0.3628
Matsuda	9.196	6.67	9.60	1.05	5.033	3.552	5.064	1.46	3.91	2.69	3.04	1.01	*0.0157*	*0.0107*
$Stumvoll_{0,120}$	0.068	0.094	0.079	0.008	0.021	0.056	0.107	0.03	0.009	0.033	0.095	0.032	*0.0147*	*0.0008*
$Stumvoll_{Demographics}$	0.105	0.111	0.045	0.005	0.091	0.095	0.059	0.017	0.065	0.059	0.056	0.019	0.3382	*0.0414*

Mann-Whitney U-test; BMI — body mass index