Psychiatria Danubina, 2021; Vol. 33, Suppl. 10, pp S30-36
Medicina Academica Mostariensia, 2021; Vol. 9, No. 1, pp 30-36 *Original paper*
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PREVALENCE OF GESTATIONAL DIABETES MELLITUS AND PERINATAL OUTCOMES ACCORDING TO THE OLD WHO CRITERIA AND IADPSG CRITERIA

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received: 8.4.2021; revised: 20.5.2021; accepted: 7.6.2021

SUMMARY

Background: *Gestational diabetes mellitus (GDM) is the most common metabolic disorder in pregnancy. Pregnancies with GDM have worse outcomes compared to pregnancies with normal glucose tolerance. The objectives of the study were to determine the prevalence of GDM and perinatal outcomes according to the old WHO criteria and IADPSG criteria.*

Subjects and methods*: A retrospective study included 2,405 pregnant women who delivered between January 2009 and December 2010. According to the OGTT results, pregnant women were divided into 4 groups. We analyzed the prevalence of GDM, characteristics of pregnant women and their newborns and perinatal outcomes.*

Results: *We found significantly higher prevalence of GDM according to the IADPSG criteria compared to the WHO criteria. Pregnant women with GDM were significantly older, had higher pre-pregnancy BMI, fasting and 2-h plasma glucose. Pregnant women with GDM had worse pregnancy outcomes compared to control group. The overall proportion of overweight and obese pregnant women was the highest in the group of untreated pregnant women with GDM according to the IADPSG criteria. In this group we found significantly higher rate of fetal macrosomia and LGA. The rate of caesarean section was significantly higher in comparison to control group. Pre-eclampsia was significantly more common in groups of pregnant women with GDM compared to control group.*

Conclusion: *IADPSG diagnostic criteria reveals more women with hyperglycemic disorders in pregnancy. A group of pregnant women who were normoglycemic according to the WHO criteria, but according to the IADPSG were diagnosed GDM, had adverse pregnancy outcomes. Lower values of glycemia, than those defined for diabetes in pregnancy, are associated with adverse pregnancy outcomes.*

Key words: *GDM - WHO – IADPSG - pregnancy outcome*

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INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy (Metzger & Coustan 1998). It is the most common metabolic disorder in pregnancy. Gestational diabetes mellitus increases the risk of fetal and neonatal complications (HAPO Study Cooperative Research Group et al. 2008, Athukorala et al. 2007, Jones 2001). Maternal complications of GDM include more frequent hypertensive disorders in pregnancy and termination of pregnancy by cesarean section (Casey et al. 1997, Joffe et al. 1998, Yogev et al. 2004, Negrato et al. 2009). The long-term consequences of GDM on health of mothers and their offsprings include development of obesity, diabetes mellitus and metabolic syndrome (Verma et al. 2002, Cheung & Byth 2003, Lee et al. 2007, Vohr & Boney 2008).

Given the lack of unique criteria in the diagnosis of GDM, it is difficult to speak of the exact incidence of gestational diabetes. The incidence of gestational diabetes ranges widely from <1% to 28% (Jiwani et al. 2012). Over the last 50 years, a number of studies have been published discussing different criteria for diagnosing GDM. O'Sullivan's 3-hours oral glucose tolerance test (OGTT) criteria with a load of 100 g of glucose are the basis of numerous studies (O'Sullivan & Mahan 1964). According to World Health Organisation (WHO) criteria from 1999, GDM is diagnosed if the two-hour glucose concentration in OGTT is ≥ 7.8 mmol / L, because fasting glucose concentration ≥ 7.0 mmol / L indicates diabetes in pregnancy (Report of a WHO Consultation 1999).

The current criteria for gestational diabetes detect pregnant women at increased risk of developing diabetes mellitus after pregnancy but do not detect pregnan-

cies with an increased risk of adverse pregnancy outcomes. A large, multicentre HAPO (Hyperglycemia Adverse Pregnancy Outcome - HAPO) study was initiated to determine the more precise limit of intervention in GDM (HAPO Study Cooperative Research Group et al. 2008). According to the results of the HAPO study, the International Association of Diabetes and Pregnancy Study Group (IADPSG) proposed new criteria for GDM (International Association of Diabetes and Pregnancy Study Groups Consensus Panel et al. 2010). According to the IADPSG criteria, at least one maternal plasma glucose concentration should be equal to or above the upper limit - set at 5.1 mmol/L for fasting measurements, 10 mmol/L for 1-hour measurements, and 8.5 mmol/L for 2-hour measurements - for GDM to be diagnosed (International Association of Diabetes and Pregnancy Study Groups Consensus Panel et al. 2010). One of the goals of the new IADPSG criteria was to standardize the approach in the diagnosis of GDM. Numerous countries around the world have adopted the new IADPSG criteria for GDM. The World Health Organization and the American Diabetes Association (ADA) have adopted the new criteria for GDM (World Health Organization Guideline 2014, American Diabetes Association 2014). However, some professional societies did not accept the new IADPSG criteria for GDM (National Institute for Health and Care Excellence. NICE guideline 3 2015).

The aim of this study is to determine the difference in the prevalence of GDM according to WHO (1999) and IADPSG criteria. The second goal is to investigate the additional proportion of pregnant women with hyperglycemic disorders and the association with pregnancy outcomes detected using IADPSG criteria that were not detected by current WHO criteria.

We hypothesized that the IADPSG criteria for GDM are more sensitive than the old WHO criteria, so the diagnosis of GDM will include more pregnant women. It is to be expected that pregnant women who do not have GDM according to old WHO criteria, but have an adverse course and pregnancy outcome, are likely to have GDM according to IADPSG criteria.

SUBJECTS AND METHODS

In this retrospective study data collected from the medical history of 2 405 pregnant women who underwent 2-hour oGTT with 75 g glucose between 24 and 28 weeks of gestation and visited Department of Obstetrics and Gynecology, Clinical Hospital Center, Zagreb, Croatia, between January 2009 and December 2010. Pregnant women with spontaneous singleton pregnancies were included in the study. Excluded are multiple pregnancy, in vitro fertilization pregnancy, pregnant women who treated with corticosteroids before OGTT, who treated with intravenous tocolysis (beta-sympathomimetic) and insulin therapy, and pregnant women with overt diabetes.

Data of pregnant women and the pregnancy outcomes were collected and analyzed from the medical history. The body mass index was calculated as the ratio of the weight in kilograms before pregnancy and the square of the height expressed in meters. The calculated pre-pregnancy body mass index was classified as malnutrition (BMI <18.5 kg/m^2), normal body weight (BMI 18.5-24.9 kg/m^2), overweight (BMI 25.0-29.9 kg/m^2) and obesity (BMI ≥ 30 kg/m^2 (Report of a WHO Expert Committee 1995). Weight gain in pregnancy was calculated as the difference between pre-pregnancy weight and birth weight. The age of gestation was determined on the first day of the last menstrual period, and was confirmed by ultrasound examination in the first trimester of pregnancy. Preterm delivery is defined as delivery before 37 weeks of gestation.

Ponderal index was calculated as birth weight (g) / birth length (cm^3) x 100. Macrosomia was defined as a birth weight ≥ 4000 g. Large for gestational age (LGA) was defined when the birth weight is > 90. growth percentiles depending on gender, gestational age and parity (Kolčić et al. 2006). Small for gestational age (SGA) was defined when the birth weight is <10th percentile of growth depending on gender, gestational age and parity (Battaglia & Lubchenco 1967).

Chronic hypertension was diagnosed if blood pressure exceeded ≥ 140/90 mmHg before pregnancy or in the first 20 weeks of pregnancy. Gestational hypertension is defined as the onset of hypertension after the 20th week of gestation without proteinuria. The diagnosis of pre-eclampsia was diagnosed after the 20th week of gestation if the value of systolic blood pressure is ≥ 140 mmHg or diastolic ≥ 90 mmHg in previously normotensive women with proteinuria. Proteinuria is defined as urinary protein excretion ≥ 300 mg / 24 hours.

All pregnant women underwent an oral glucose tolerance test with a standard load of 75 g glucose between the 24th and 28th week of pregnancy, as recommended by the World Health Organization. Pregnant women were fasted for at least 8 hours before loading. Glucose concentration in venous plasma was measured 0 and 2 h after load using the hexokinase method. The diagnosis of GDM was made according to the WHO and IADPSG criteria. All pregnant women diagnosed with GDM according to WHO criteria were treated with a diabetic diet (daily caloric intake was calculated based on body mass index, gestational age, and ideal body weight). Pregnant women, who were diagnosed with GDM according to IADPSG criteria, were without therapy since these pregnancies were managed as normal.

According to the OGTT results, pregnant women were divided into 4 groups:

- *1. group* GDM according to WHO criteria, according to IADPSG criteria normal glucose tolerance - WHO + / IADPSG - (N=150);

- *2. group* GDM according to IADPSG criteria, according to WHO normal glucose tolerance - WHO - / IADPSG + (N=521);
- *3. group* GDM according to IADPSG and WHO criteria (overlapping group) - WHO + / IADPSG + (N=404);
- *4. group* normal glucose tolerance according to both criteria - WHO - / IADPSG - (N=1330) (Table 1).

Pregnant women with a glycemic value 2 hours after load ≥ 7.8 mmol / L and ≥ 8.5 mmol / L, were excluded from the second group because they were included in group 3 (overlapping group).

The study was approved by Ethics Committee of the Department of Obstetrics and Gynecology. Informed consent was not obtained from the respondents as it is a retrospective study.

The data were analyzed with the SPSS version 20. (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). Data are presented tabularly and graphically by descriptive statistics methods. Nominal and categorical values are shown through frequencies and proportions, while quantitative values are shown through arithmetic means and standard deviation. The distribution of quantitative variables was tested by the Kolmogorov-Smirnov test. Comparisons between the values of continuous variables were made using the ANOVA test using Scheffe's post-hoc test, i.e. using the Kruskal-Wallis test and the post-hoc Mann-Whitney test with adjusting the level of statistical significance. Differences in categorical variables were analyzed by χ^2 test. P<0.05 was considered as statistically significant.

RESULTS

The Venn diagram shows data on the diagnosis of GDM in the examined sample. In the examined sample, GDM was diagnosed according to WHO criteria in 150 pregnant women, according to IADPSG criteria in 521 pregnant women, 404 pregnant women had GDM according to both criteria. The prevalence of GDM according to WHO criteria was 6.2%, while according to IADPSG criteria it was 21.7%. The prevalence of GDM according to IADPSG criteria was statistically significantly higher compared to WHO criteria (p<0.001). According to the IADPSG criteria, an additional 15.5% of pregnant women were diagnosed with GDM (Figure 1).

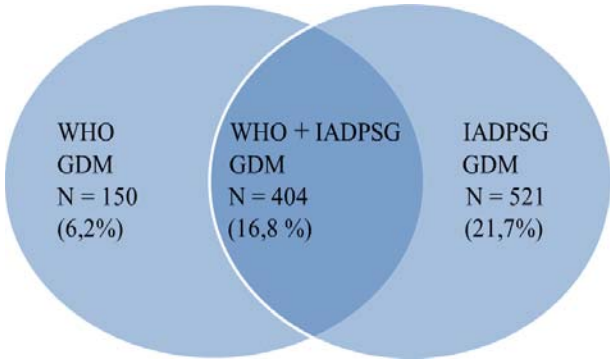

Figure 1. Distribution of pregnant women according to GDM diagnosis (GDM – gestational diabetes mellitus)

Pregnant women with GDM were significantly older, had higher pre-pregnancy BMI, fasting and 2-h plasma glucose (p<0.001). Pregnant women with GDM had lower weight gain in pregnancy and shorter gestation duration compared to the control group (p<0.001). The proportion of primiparous was the lowest in the second group. The proportion of overweight and obese pregnant women was highest in groups with GDM compared to the control group (p<0.001). There was no significant difference in adverse obstetric history between groups (Table 2).

Birth weight was significantly higher in group 2 (without diabetic diet) compared to the control group (p<0.001). The Apgar score at 1 minute was significantly lower in newborns of mothers with GDM. However, post-hoc testing did not prove statistically significant differences between groups. There were no significant differences in Apgar score at 5 minute, Ponderal index, and congenital anomalies between groups (Table 3).

The frequency of macrosomia differed significantly by groups, with the highest frequency of 23.2% in group 2 (p=0.001). The frequency of LGA newborns was significantly highest in groups with GDM compared to the control, with the highest frequency in group 2 (p=0.002). There were no significant differences between groups in the frequency of preterm delivery, SGA newborns, chronic hypertension and gestational hypertension. Pre-eclampsia was significantly more common in groups of pregnant women with GDM compared to the control group (p<0.001) (Table 4).

Table 1. Study groups according to OGTT results

Group	Fasting glucose, mmol/L	1 h OGTT, mmol/L	2 h OGTT, mmol/L
WHO+/IADPSG-	<5.1	<10.0	≥7.8-8.4
WHO-/IADPSG+	≥5.1-6.9	≥10.0	<7.8
WHO+/IADPSG+	≥5.1-6.9	≥10.0	≥7.8-11.0
WHO-/IADPSG-	<5.1	<10.0	<7.8

OGTT – oral glucose tolerance test; WHO - World Health Organization; IADPSG - International Association of Diabetes and Pregnancy Study Group

Table 2. Characteristics of pregnant women in groups

	WHO+IADPSG- N=150	WHO-IADPSG+ N=521	WHO+IADPSG+ N=404	WHO-IADPSG- N=1330	p[a]
Diabetc diet	Yes	No	Yes	No	
Age, y, (mean ± SD)	31.81±5.09	31.47±4.83	32.61±4.86	30.31±4.84	*<0.001*
Pre-pregnancy BMI, kg/m^2 (mean ± SD)	23.43±4.31	25.46±5.33	25.27±5.04	23.40±4.04	*<0.001*
Gestation weight gain, kg (mean ± SD)	14.99±4.69	14.55±5.92	12.93±5.56	15.56±5.27	*<0.001*
Weight at birth, kg (mean ± SD)	79.69±2.94	86.65±4.89	82.80±14.43	81.93±2.47	*<0.001*
Parity (mean ± SD)	0.67±0.92	0.86±1.06	0.71±0.96	0.61±0.88	*<0.001*
Fasting plasma glucose, mmol/L (mean ± SD)	4.52±0.33	5.36±0.28	5.00±0.55	4.42±0.37	*<0.001*
2-h plasma glucose, mmol/L (mean ± SD)	8.01±0.20	6.27±1.03	9.26±0.63	5.73±0.96	*<0.001*
Length of pregnancy at delivery, wk (mean ± SD)	39.67±0.96	39.69±1.00	39.34±1.24	39.70±1.06	*<0.001*
Primiparous N (%)	88 (58.7)	235 (45.1)	205 (50.7)	746 (56.1)	*<0.001*
Burdened obstetric history, N (%)	37 (24.7)	118 (22.6)	105 (26.0)	309 (23.2)	0.631
BMI - malnutrition, kg/m$_2$, N (%)	8 (5.3)	16 (3.1)	13 (3.2)	55 (4.1)	*<0.001*
BMI - normal body weight, kg/m^2, N (%)	96 (64.0)	276 (53.0)	217 (53.7)	930 (69.9)	
BMI - overweight, kg/m^2, N (%)	33 (22.0)	141 (27.1)	103 (25.5)	246 (18.5)	
BMI - obesity, kg/m^2, N (%)	13 (8.7)	88 (16.9)	71 (17.6)	99 (7.4)	

BMI – body mass index; SD – standard deviation; N (%) – number (percentage); p[a] – Fisher's exact test or χ^2 test

Table 3. Characteristics of newborns in groups

	WHO+IADPSG- N=150	WHO-IADPSG+ N=521	WHO+IADPSG+ N=404	WHO-IADPSG- N=1330	p[a]
Diabetc diet	Yes	No	Yes	No	
Birth weight, g, (mean ± SD)	3537.3±429	3657.5±493	3517.1±488	3530.6±442	*<0.001*
1-min Apgar score, (mean ± SD)	9.77±0.83	9.84±0.59	9.80±0.72	9.88±0.58	*0.031*
5-min Apgar score, (mean ± SD)	9.92±0.32	9.94±0.32	9.95±0.27	9.96±0.32	0.469
Ponderal index, g/cm^3, (mean ± SD)	2.70±0.21	2.73±0.24	2.71±0.25	2.70±0.22	0.261
Congenital anomalies, N (%)	1 (0.7)	5 (1.0)	6 (1.5)	11 (0.8)	0.645

SD – standard deviation; N (%) – number (percentage); p[a] – Fisher's exact test or χ^2 test

Table 4. Pregnancy outcomes

	WHO+IADPSG- N=150	WHO-IADPSG+ N=521	WHO+IADPSG+ N=404	WHO-IADPSG- N=1330	p[a]
Diabetc diet	Yes	No	Yes	No	
Macrosomia, N (%)	21 (14.0)	121 (23.2)	65 (16.1)	209 (15.7)	*0.001*
LGA, N (%)	28 (18.7)	131 (25.1)	85 (21.0)	232 (17.4)	*0.002*
Vaginal birth, N (%)	113 (75.3)	415 (79.7)	292 (72.3)	1141 (85.8)	*<0.001*
Ceasarean section, N (%)	36 (24.0)	104 (20.0)	111 (27.5)	184 (13.8)	
Vacuum extraction, N (%)	1 (0.7)	2 (0.4)	1 (0.2)	5 (0.4)	
Preterm delivery, N (%)	0 (0)	8 (1.5)	8 (2.0)	18 (1.4)	0.369
SGA, N (%)	1 (0.7)	7 (1.3)	11 (2.7)	39 (2.9)	0.103
Chronic hypertension, N (%)	3 (2.0)	3 (0.6)	4 (1.0)	6 (0.5)	0.105
Gestational hypertension, N (%)	4 (2.7)	31 (6.0)	29 (7.2)	61 (4.6)	0.084
Pre-eclampsia, N (%)	2 (1.3)	2 (0.4)	7 (1.7)	1 (0.1)	*<0.001*

LGA - Large for gestational age newborn; SGA - Small for gestational age newborn; p[a] – Fisher's exact test or χ^2 test

DISCUSSION

If we compare groups of pregnant women with GDM only according to WHO and IADPSG criteria, it can be seen that prevalence of GDM is 3.5 times higher according to IADPSG criteria. If we add to these groups a group with overlapping criteria (WHO + IADPSG +), the overall prevalence of GDM according to WHO criteria was 23% and according to IADPSG criteria 38.5%. With the new IADPSG criteria, we detected a

new 15.5% of pregnant women with GDM. The results of other studies also showed a higher prevalence of GDM according to IADPSG criteria compared to WHO criteria (O'Sullivan et al. 2011, Leng et al. 2015).

In addition, the fact that more and more women of reproductive age are overweight and obese contributes to the increasing prevalence of GDM. This is particularly present in developed countries, where the rate of overweight and obese women of reproductive age is estimated at around 60% (Flegal et al. 2010). This partly explains our results regarding the prevalence of GDM according to IADPSG and WHO criteria if we know that the total proportion of overweight and obese pregnant women in groups 1 and 2 was 30.7% and 44.0%.

Jenum et al. showed that prevalence of GDM according to WHO and IADSPG criteria was 13.0% and 31.5%, respectively (Jenum et al. 2012). Arora et al. found the prevalence of GDM according to IADPSG 34.9% and 9% according to WHO criteria (Arora et al. 2015). Larger or minor differences in the prevalence of GDM are probably due to demographic and socioeconomic differences in the examined population of pregnant women.

Chu et al. showed that the risk of developing GDM increases with increasing body mass index. This risk is 2.14 times higher in overweight pregnant women, 3.56 times higher in obese pregnant women, and 8.56 times higher in severe forms of obesity compared to normal weight pregnant women (Chu et al. 2007).

On average, pregnant women with GDM according to IADPSG criteria had the highest pre-pregnancy body mass index and average fasting glucose concentrations (group 2). The proportion of overweight and obese pregnant women was the highest in this group (27.1% and 16.9%). Retrospective application of the IADPSG criteria revealed pregnant women with risk factors for adverse pregnancy outcomes.

Harreiter et al. showed that pregnant women with an early diagnosis of GDM according to IADPSG criteria had the highest pre-pregnancy body mass index (Harreiter et al. 2016). Laafira et al. showed in their retrospective study that the mean body mass index at the beginning of pregnancy was the highest in the group of pregnant women with GDM according to IADPSG criteria (Laafira et al. 2016).

Analyzing pregnancy outcomes between the examined groups, it can be seen that pregnant women who were retrospectively diagnosed GDM (group 2) had worse pregnancy outcomes compared to treated pregnant women and pregnant women with normal glucose tolerance. These pregnant women delivered, in average, newborns with the highest birth weight and the highest ponderal index. The rate of fetal macrosmia and LGA were the highest in this group. The rate of cesarean section was statistically significantly higher compared to the pregnant women with normal glucose tolerance. This group of pregnant women had, on average, the highest fasting plasma glucose concentrations. The importance of fasting plasma glucose concentration in the diagnosis of GDM according to IADPSG criteria is known (International Association of Diabetes and Pregnancy Study Groups Consensus Panel et al. 2010).

Crowther et al. reported the effects of GDM treatment on pregnancy outcomes. Similar to the results of our study, they showed that the rate of LGA and macrosomia was significantly higher in the group of pregnant women with untreated GDM compared to the treated group. Newborns from pregnant women with untreated GDM had the highest birth weight (Crowther et al. 2005).

Landon et al. showed that treating "mild" forms of GDM defined by the Carpenter-Coustan criteria (1998), but with a fasting blood glucose of less than 5.3 mmol / L, reduces the rate of some adverse pregnancy outcomes (overgrowth, shoulder dystocia, cesarean delivery, and hypertensive disorders) (Landon et al. 2009).

O'Sullivan et al. reported poorer perinatal outcomes of pregnant women diagnosed with GDM according to IADPSG criteria, who had normal glucose tolerance according to WHO criteria (O'Sullivan et al. 2011).

Similar to our study, there was no statistically significant difference in the rate of congenital anomalies and hypotrophic children. The rate of fetal macrosomia and hypertrophic children was similar to rate in our study. They found significantly higher rate of gestational hypertension and pre-eclampsia in the group with untreated GDM according to IADPSG criteria compared to pregnant women with normal glucose tolerance. The higher proportion of hypertensive disorders found by O'Sullivan et al. compared to our study is probably due to the higher average body mass index, higher average age of pregnant women as well as due to the fact that were also included respondents of noneuropean origin. The proportion of pregnancies completed by cesarean section was significantly higher than in our study. The lower rate of cesarean section in our study, in contrast to O'Sullivan study, can also be explained by the lower rate of hypertensive disorders and premature birth (O'Sullivan et al. 2011).

It is known that the diagnosis of gestational diabetes increases the risk for termination of pregnancy by cesarean section. When a pregnancy with GDM is also burdened with a hypertensive disorder, the risk for termination of pregnancy by caesarean section becomes even higher (Stella et al. 2008).

This study has some limitations. Pregnant women from the third group (404 pregnant women) were diagnosed GDM according to both WHO and IADPSG criteria. This means that some results overlap. In addition, the study was conducted in one center.

CONCLUSION

The introduction of the IADPSG criteria in the diagnosis of GDM increases the prevalence of GDM, but also reveals a new, high-risk group of pregnant women whose pregnancies are burdened with an adverse outcomes. The IADPSG diagnostic criteria have further emphasized the preconception problem of obesity and hyperglycemic disorders, and direct us to the prevention and treatment of obesity much earlier, not just in pregnancy. With this approach, we can expect more favorable pregnancy outcomes, a lower rate of long-term and harmful consequences that hyperglycemic disorders can leave on the mother and offspring.

Acknowledgements: None.

Conflict of interest: None to declare.

Contribution of individual authors:

Mato Pavic, Ana Zovak Pavic, Milenko Bevanda & Slavko Oreskovic made conception of the study, performed literature search, interpretation of data, wrote initial draft of publication.

Vedran Premuzic made conception of the study, performed literature search, wrote initial draft of publication and approved final version of manuscript; made conception of the study, performed literature search, wrote initial draft of publication; performed statystical analysis.

Slobodan Mihaljevic made conception of the study, performed literature search, interpretation of data and approved final version of manuscript.

All authors approved final version of manuscript.

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