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ORIGINAL ARTICLE

Predicting gestational diabetes mellitus during the first trimester using anthropometric measurements and HOMA-IR

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Abstract
Purpose To determine the predictability of gestational diabetes mellitus (GDM) during the first trimester using the degree of insulin resistance and anthropometric measurements and to assign the risk of developing GDM by weight gained during pregnancy (WGDP).
Methods A total of 250 singleton pregnancies at 7–12 gestational weeks were studied. Body mass index (BMI), waist/hip ratio (WHR), quantitative insulin sensitivity check index (QUICKI), homeostasis model assessment-insulin resistance (HOMA-IR) scores and WGDP were determined. The backward stepwise method was applied to estimate possible associations with GDM. Cutoff points were estimated using receiver operating characteristic curve analysis.
Results GDM was found in 20 of 227 singleton pregnancies (8.8 %). The calculated HOMA-IR, QUICKI, BMI, WHR, WGDP, and parity were significantly associated with GDM. Logistic regression analyses showed that three covariates (HOMA-IR, BMI, WGDP) remained independently associated with GDM. It was calculated as OR 1.254 (95 % CI 1.006–1.563), AUC 0.809, sensitivity 90 %, specificity 61 % with cutoff = 2.08 for HOMA-IR; OR 1.157 (CI 1.045–1.281), AUC 0.723, sensitivity 80 %, specificity 58 % with cutoff = 25.95 for BMI; OR 1.221, (CI 1.085–1.374), AUC 0.654, sensitivity 80 %, specificity 46 % with cutoff = 4.7 for WGDP. Despite a HOMA-IR score of >3.1 in pregnant women, GDM was detected in only three of 29 patients (10.3 %) if WGDP was <4.7 kg at weeks 24–28.
Conclusions First trimester screening for GDM can be achieved based on maternal anthropometric measurements and HOMA-IR. In particular, if BMI is >25.95 kg/m^2 and the HOMA-IR score >2.08, controlling weight gain may protect against GDM.

Keywords First trimester pregnancy · Gestational diabetes mellitus · Insulin resistance · Body mass index · Waist/hip ratio · Weight gain

Introduction

Gestational diabetes mellitus (GDM) is glucose intolerance that is recognized during pregnancy and is the most frequently encountered gestational metabolic complication [1]. Approximately 90 % of pregnancies complicated by diabetes are GDM. GDM is found in approximately 7 % (range 1–14 %) of pregnancies [1, 2] and causes many complications for both the mother and baby during and beyond delivery [3]. Increasing physical activity, controlling weight gain, and following a suitable diet program can reduce the risk of GDM [4]. Thus, it is important to detect GDM during early pregnancy and to take precautions to reduce the risk. Insulin resistance (IR) is an important pathogenic mechanism for the development of GDM. Maternal hyperinsulinemia and IR are characteristic patterns during a normal pregnancy to meet the needs of the fetus [5]. However, more IR occurs in the peripheral tissues in women with GDM [6]. Lapolla et al. stated that the

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impairment of beta-cell function is prominent when GDM manifests, which is characterized with inadequate adaptation to the increase in insulin resistance during pregnancy [7]. The homeostasis model assessment-insulin resistance (HOMA-IR), which is a fasting glucose and insulin measurement, is an excellent parameter to detect IR [8]. An overweight status before pregnancy and weight gain during pregnancy (WGDP) are associated with the development of GDM [9]. Patients with a high BMI and IR run a greater risk for developing GDM. A diagnosis of GDM at weeks 24–28 indicates that patients have not tried to prevent GDM. The aim of this study was to determine the predictability of GDM during the first trimester using the HOMA-IR, BMI, and waist/hip ratio (WHR). Also, the effect of gaining weight until the end of the second trimester was assessed for the risk of developing GDM.

Materials and methods

Study design and subjects

This prospective observational study was conducted at Mevlana University Faculty of Medicine, Department of Obstetrics and Gynecology, Konya, Turkey from December 2014 through May 2015. The study protocol was approved by the Mevlana University Clinical Research Ethics Committee (Ref. No. 26857650/006/04/05.12.2013). Written informed consent was obtained from all participants prior to enrolling in the study.

Among a total of 250 volunteer pregnant women at gestational weeks 7–12, nine who did not tolerate the oral glucose tolerance test (OGTT) and 14 who did not continue the control visits were excluded. Thus, the remaining 227 patients were included in this study. A detailed history, BMI, body weight at pregnancy onset, WHR, and fasting glucose and insulin levels were recorded for all patients at the first visit. Pregnant women who had previous type 1 or 2 diabetes, with fasting plasma glucose level above 95 mg/dL, multiple pregnancies, untreated endocrine disturbances, chronic hypertension, preeclampsia, or medication that affected fasting glucose or insulin levels were excluded from the study. BMI was determined using the formula: BMI = weight/height^2 (kg/m^2). The patients were divided into five groups based on their BMI: underweight (<18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), fat (30.0–39.9 kg/m^2), and obese (≥40.0 kg/m^2) [10]. The WHR was calculated for each patient, and the cutoff was determined as 0.8 according to previous study [11]. Plasma glucose was measured using an enzymatic reference method with hexokinase. Serum insulin levels were measured using commercial kits and a chemiluminescence device (Elicsys 2010; Roche Diagnostics, Manheim, Germany). HOMA-IR was used to determine IR during the first trimester. The HOMA-IR score was calculated as [fasting plasma insulin (μIU/mL) × fasting plasma glucose (mg/L) × 0.05]/22.5. The quantitative insulin sensitivity check index (QUICKI) was calculated as 1/[log(FPI) + log(FPG)] [12] where FPG and FPI are the fasting glucose and insulin concentrations. All pregnant women were followed prospectively. In the week of 24–28, their bi-level GDM scannings were done. On the first stage 50 g oral glucose tolerance (OGT) was applied. Results below 140 mg/dL were accepted as negative. Second level 100 g OGT was applied whose results are above 140 mg/dL. GDM was diagnosed in those women whose two or more glucose concentrations were higher than the following thresholds (fasting 95 mg/dL, after 100 g glucose was applied on the first hour 180 mg/dL, on the second hour 155 mg/dL and on the third hour 140 mg/dL) [13]. In addition, weight gain was recorded from the beginning of pregnancy until the week the OGTT was conducted.

Statistical analysis

Statistical analyses were performed using SPSS ver. 20 for Windows software (SPSS Inc., Chicago, IL, USA). Student's *t* test was used to compare independent sampled parametric data, and the Mann–Whitney *U*-test was used when the variances were extremely heterogeneous. Fisher's exact test or the Chi-square test was used for categorical variables. Variables related to GDM were identified using the backward likelihood ratio method and logistic regression. The HOMA-IR score, BMI, WHR, parity, and WGDP variables were added to the logistic regression model to estimate the occurrence of GDM. p values <0.05 were considered significant.

Results

A total of 227 singleton pregnancies with first trimester data and an OGTT performed at weeks 24–28 of pregnancy were included. Among them, the incidence of GDM was detected as 8.8 % in cohort. The characteristics and biochemical parameters of the pregnant women with and without GDM are summarized in Table 1. WGDP, WHR, BMI, and HOMA-IR were significantly higher in GDM group ($p < 0.05$). QUICKI was significantly decreased in GDM group ($p < 0.001$).

Logistic regression

BMI, WHR, parity, WGDP, and the HOMA-IR variables that were significantly different according to Student's *t* test and Pearson's Chi-square test were included in the logistic

Table 1 Characteristics and biochemical data of the pregnant women

Variables	GDM negative ($n = 207$), Mean ± SD	GDM positive ($n = 20$), Mean ± SD	p value
Maternal age (years)	26.9 ± 5.2	28.8 ± 4.8	0.113
Parity [n (%)]			
Nulliparous	79 (38.2 %)	6 (30.0 %)	0.471*
Multiparous	128 (61.8 %)	14 (70.0 %)	
Weight (kg) (at 6–12 weeks)	67.8 ± 14.7	78.1 ± 15.4	0.003
WGDP	5.0 ± 3.9	7.5 ± 4.1	0.010
Waist circumference (cm)	80.8 ± 10.5	89.7 ± 11.9	<0.001
Hip circumference (cm)	99.4 ± 10.3	105.8 ± 14.2	0.011
WHR	0.81 ± 0.05	0.84 ± 0.04	0.004
BMI (kg/m^2)	25.6 ± 5.01	29.5 ± 5.3	0.001
HOMA-IR	2.2 ± 1.7	3.8 ± 1.6	<0.001
QUCKI	0.349 ± 0.03	0.317 ± 0.01	<0.001**

WGDP weight gain during pregnancy, *QUCKI* quantitative insulin sensitivity check index, *WHR* waist/hip ratio, *BMI* body mass index (kg/m^2), *SD* standard deviation, *HOMA-IR*, homeostasis model assessment-insulin resistance index

* Pearson's Chi-square test

** Mann–Whitney *U* test

regression model to estimate the occurrence of GDM during the first trimester.

WHR was dropped from the model at step 1, and parity was dropped at step 2. WGDP, HOMA-IR, and BMI were significant predictors of GDM in the first trimester. Logistic regression analyses showed that only these three covariates remained independently associated with GDM. BMI ≥25.95 increased GDM risk (OR 1.157; 95 % CI 1.045–1.281, $p < 0.005$). HOMA-IR and WGDP were also related with increased risk of GDM (for HOMA-IR OR 1.254, CI 1.006–1.563, $p = 0.045$; for WGDP OR 1.221, CI 1.085–1.374, $p = 0.001$).

A receiver operating characteristics (ROC) curve analysis was applied to the high BMI cases in the first trimester and to the HOMA-IR with WGDP cases until the end of the second trimester, which were significant according to the backward stepwise (likelihood ratio) method used to estimate GDM, and the cutoff values were determined for each of them (Fig. 1; Table 2). From the positive GDM patients, 80 % for BMI and WGDP and 90 % for HOMA-IR were estimated by the cutoff value (Table 3).

In the decision tree model, which is made for predicting GDM in the first trimester, none of the GDM-positive patients' HOMA-IR score were not below 1.47. While 8 of (40 %) the GDM-positive patients' HOMA-IR scores were in the range of 1.47–3.1, 12 of (60 %) remaining GDM-positive patients' HOMA-IR scores were above 3.1. Despite a HOMA-IR score of >3.1 in pregnant women, GDM was detectedin only three of 29 patients (10.3 %) if WGDP was <4.7 kg at weeks 24–28. On the other hand, if HOMA-IR is above 3.1 and WGDP is above 4.7 kg, GDM

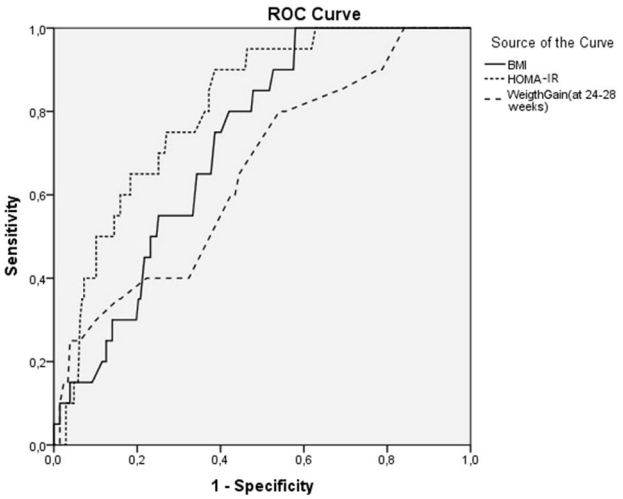

Fig. 1 Receiver operating characteristics curve (ROC) analysis for body mass index (BMI), homeostasis model assessment-insulin resistance (HOMA-IR), and weight gained during pregnancy (WGDP) at weeks 24–28 of gestation

was detected 56.2 % of the patients. From the stand point of GDM, the most risky patient group was those whose HOMA-IR score is above 3.1 and WGDP is above 4.7 kg. Nine of 20 (45 %) patients were in this high-risk group in our study (Fig. 2).

Discussion

This prospective study showed that a high BMI, higher HOMA-IR, decreased QUICKI at the first prenatal visit,

Table 2 Area under the curve, cutoff points, sensitivity, specificity, and predictive values of WGDP, BMI, and HOMA-IR

Variables	AUC	Std. error[a]	Asymptotic sig[b]	95 % CI		Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
				LB	UB					
WGDP	0.654	0.062	0.023	0.532	0.777	4.7	80	46	12	96
BMI	0.723	0.045	0.001	0.635	0.812	25.95	80	58	15	96
HOMA-IR	0.809	0.041	0.000	0.729	0.889	2.08	90	61	18	98

WGDP weight gain during pregnancy, *BMI* body mass index, *HOMA-IR* homeostasis model assessment-insulin resistance, *CI* confidence interval, *LB* lower bound, *UB* upper bound, *PPV* positive predictive value, *NPV* negative predictive value, *AUC* area under the curve

[a] Under the nonparametric assumption

[b] Null hypothesis: true area = 0.5

Table 3 Distributions of GDM-positive/negative patients according to the cutoff values predicted by HOMA-IR, BMI, and WGDP at weeks 24–28 of gestation

	Cut-off value	GDM negative, $n = 207$ (%)	GDM positive, $n = 20$ (%)	Total, $n = 227$ (%)
HOMA-IR	<2.08	127 (61.4)	2 (10.0)	129 (56.8)
	≥2.08	80 (38.6)	18 (90.0)	98 (43.2)
BMI	<25.95	120 (58.0)	4 (20.0)	124 (54.6)
	≥25.95	87 (42.0)	16 (80.0)	103 (45.4)
WGDP	<4.7	95 (45.9)	4 (20.0)	99 (43.6)
	≥4.7	112 (54.1)	16 (80.0)	128 (56.4)

HOMA-IR homeostasis model assessment-insulin resistance index, *BMI* body mass index (kg/m^2), *WGDP* weight gain during pregnancy, *GDM* gestational diabetes mellitus

and excess WGDP increased the risk of GDM significantly. It is important to apply suitable therapies after diagnosing GDM to decrease morbidity of the mother and fetus. Creating a model to estimate GDM during the first trimester allows for therapy to continue and provides preventive medical services for pregnant women.

Pregnancy is a diabetogenic state, and IR often increases during the third trimester. GDM will occur when pancreatic functions do not compensate for IR. It has been thought that diabetogenic hormones (growth hormone, corticotropin-releasing hormone, human placental lactogen, and progesterone) secreted from the placenta cause overt diabetes. Placental growth hormone increases IR for fetal nutrition. In addition, human placental lactogen and prolactin improve the mother's appetite by increasing leptin resistance and promote maternal beta-cell expansion and insulin production to defend against the development of GDM [14]. The International Association of Diabetes and Pregnancy study group (IADPSG) and the American Diabetes Association recommend that pregnant women with no prior diabetic profile take the OGTT test at weeks 24–28 of gestation [15, 16]. However, performing a GDM scan at that time may prevent interventions, such as diet, medication prescriptions, exercise, and blood glucose monitoring. It is ideal to detect pregnancies at high risk for diabetes early during gestation.

Screening or testing for diabetes can be performed earlier in the first prenatal visit if the pregnant woman has a history of GDM, a BMI >30 kg/m^2, or impaired glucose metabolism [17]. There is no rule as to when to detect GDM during a pregnancy, but all tools used to detect diabetes risk during pregnancy are applicable in healthy nonpregnant women as well [18]. It is useful to detect GDM early during gestation to prevent complications, such as retinopathy and nephropathy, and to reduce fetal morbidities [19]. Despite that the 2014 United States Preventive Services Task Force guidelines do not explain the benefits and harm of screening tests before gestational week 24 [20], the IADPSG recommends performing these tests at the first prenatal visit according to the patient's history [15]. In addition, the American Diabetes Association suggests screening tests in pregnant women with a risk of GDM, such as those who are obese, have impaired glucose metabolism, or have a history of GDM [21].

Ozcimen et al. reported that GDM can be predicted during the first trimester if the HOMA-IR score is >2.60 [22]. In our prospective study, the predictability for developing GDM increased when BMI, WHR, and WGDP were added and combined with HOMA-IR. Controlling weight gain reduces the incidence of GDM in pregnant women who have a high BMI and HOMA-IR at their first prenatal visit. Excess WGDP [10, 23, 24], a BMI >30 kg/m^2, marked weight gain before and between pregnancies [25] can increase the risk for GDM. In our study, GDM was predicted during the first trimester with 80 % sensitivity and 58 % specificity in pregnant women with a BMI >25.95 kg/m^2 at the first prenatal visit, which is compatible with other

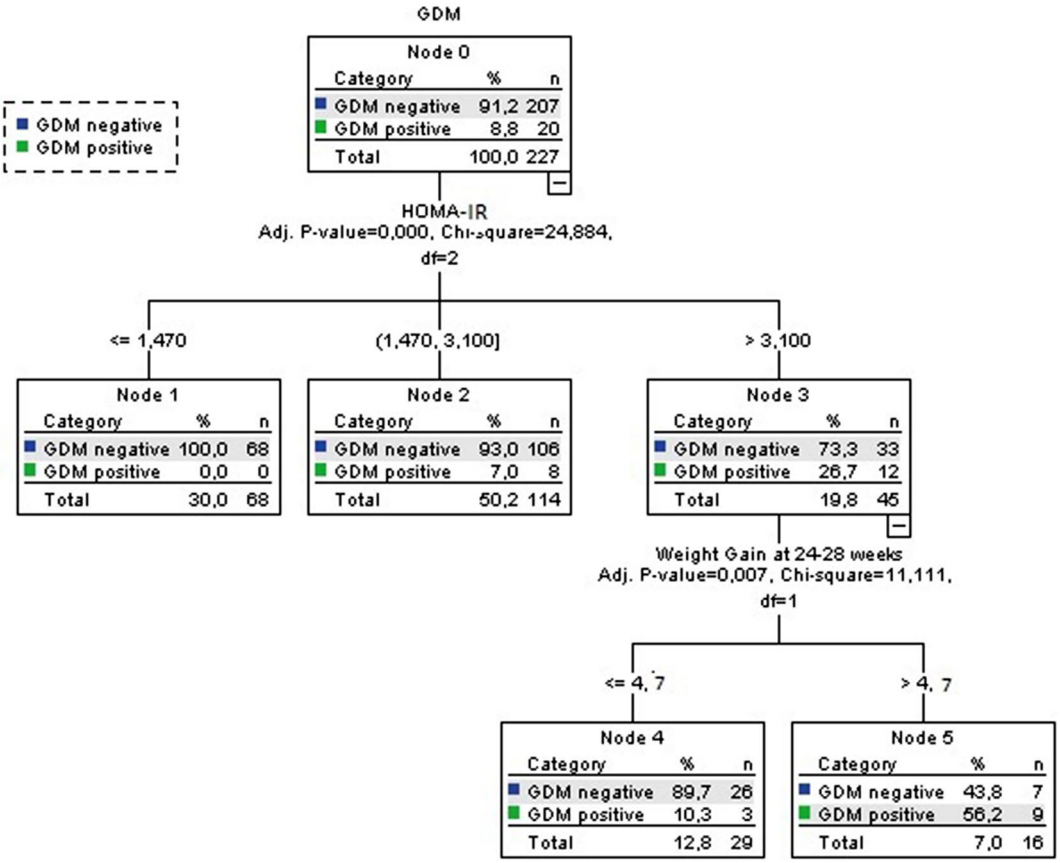

Fig. 2 Decision tree for the homeostasis model assessment-insulin resistance index (HOMA-IR) scores during the first trimester and distribution of gestational diabetes mellitus (GDM)-positive/negative patients according to weight gain by weeks 24–28 of pregnancy

studies. Besides, the risk for developing GDM was higher in pregnant women who gained >4.7 kg by weeks 24–28 of gestation (80 % sensitivity and 58 % specificity).

Women with the potential to become pregnant should be followed before gestation, as both high BMI and WGDP increase the risk for GDM. We have seen women with a high BMI who lost the excess weight prior to becoming pregnant and did not gain much weight during pregnancy.

In simple terms, IR is an atypical response of tissues to normal insulin levels. Since regulating blood sugar is not the only task of insulin, differences in subnormal levels can be observed in many tissues. However, IR usually induces a subnormal glucose response in clinical practice [26]. The pathological pathway of IR has not been identified. A link between insulin and insulin-like growth factor-1 receptors is believed to exist [27].

Normal pregnancy is characterized by increased insulin levels at gestational weeks 16–18. Catalano et al. showed progressive impairment in insulin sensitivity in obese women (47 %) and in normal-weight pregnant women (56 %) during the third trimester [28]. Before these gestational weeks, the hyperinsulinemia as an independent state of pregnancy may indicate a risk of GDM.

The commonly used techniques to diagnose IR are the euglycemic insulin clamp, insulin tolerance test/insulin suppression test, and intravenous glucose tolerance test [29, 30]. However, these techniques are not applicable for clinical use. Thus, IR cannot be measured by a registered test. Many studies have used the HOMA-IR or HOMA, based on the glucose to insulin ratio. However, because no standardized insulin assay is available, changes in beta-cell function and these ratios are used typically as indicators of IR. In conclusion, HOMA-IR and the quantitative insulin sensitivity check index have been recommended [31], but there is no commonly accepted HOMA-IR cutoff value. We determined the predictability of GDM with a 90 % sensitivity and 61 % specificity by ROC analysis in patients whose HOMA-IR scores were >2.08 in the first trimester.

Some studies have used insulin levels to predict GDM, such as Grewal et al. They used first trimester insulin levels to estimate IR or GDM later in pregnancy. GDM was predicted with 80 % sensitivity and 57.4 % specificity in their study if the insulin level was >7.45 μU/mL [32].

It has shown that the QUICKI for the GDM women decreased much more than the normoglycemic women, which means a faster decrease in the liver's sensitivity as they neared their term [7]. In our study we also find that the mean QUICKI levels were significantly lower than the levels of the healthy women.

The WHR was significantly different ($p < 0.005$) between the groups with and without GDM (0.84 ± 0.04 vs. 0.81 ± 0.05). However, it was not a predictor of GDM in the logistic regression analysis using the backward stepwise (likelihood ratio) method.

Although our study had some limitations, we showed that GDM may be predicted using first trimester data, such as high BMI and HOMA-IR values. The sensitivity and specificity of BMI and HOMA-IR values were modest in our study, as few of the enrolled patients had GDM. We did not evaluate dynamic insulin sensitivity using the OGTT insulin sensitivity (OGIS) model. However, we determined QUICKI and HOMA-IR for insulin sensitivity. Moreover, the strength of this study is that increased first trimester body mass index and higher HOMA-IR levels together with increased weight gain during second and third trimester simply may show the increased risk for GDM. On the other hand, in our country the calculation of HOMA-IR is cost-benefit. Because the total cost of FPG and FPI is only 2.5 dollars. However, OGTT costs 7 dollars. So testing HOMA-IR or QUICKI is more cost-effective. Larger-scaled studies should be conducted to determine the utility of the parameters tested here.

In conclusion, this study showed that GDM can be screened in the first trimester using anthropometric measurements and HOMA-IR. To the best of our knowledge, this study is the first study suggesting cutoff values of HOMA-IR, BMI, and WGDP for GDM. The main finding of this study is that the pregnant women with BMI >25.95 kg/m^2, HOMA-IR >2.08, and WGDP >4.7 kg are found as high risk for GDM. Therefore, controlling WGDP with diet and exercise programs can be suggested to these women.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards, and the study was approved by the local ethics committee at Karolinska Institutet.

Informed consent Informed consent was obtained from all individual participants included in the study.

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